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Review

Developmental programming of adult haematopoiesis system

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ABSTRACT

The Barker hypothesis of '*foetal origin of adult diseases*' has led to emphasize the concept of 'developmental programming', based on the crucial role of epigenetic factors. Accordingly, it has been demonstrated that parental adversity (before conception and during pregnancy) and foetal factors (i.e., hypoxia, malnutrition and placental insufficiency) permanently modify the physiological systems of the progeny, predisposing them to premature ageing and chronic disease during adulthood. Thus, an altered functionality of the endocrine, immune, nervous and cardiovascular systems is observed in the progeny. However, it remains to be understood whether the haematopoietic system itself also represents a portrait of foetal programming. Here, we provide evidence, reporting and discussing related theories, and results of studies described in the literature. In addition, we have outlined our opinions and suggest how it is possible to intervene to correct foetal mal-programming. Some pro-health interventions and recommendations are proposed, with the hope of guarantee the health of future generations and trying to combat the continuous increase in age-related diseases in human populations.

1. Introduction

During the life of complex organisms, including humans, some their organs and systems are specifically targeted to preserve homeostasis, and guarantee health by providing protection against potential pathogens and by counteracting various environmental and endogenous stressors. One such system is the haematopoietic system (HS). HS is an active system, which has evolved in vertebrates (including humans) for the production and renewal of a wide range of terminally differentiated cells and corpuscles, involved in essential functions for the health of the organism, ranging from oxygenation, coagulation, angiogenesis, to cardiovascular repair and immunity (Doulato et al., 2012, Eaves, 2015). Therefore, alterations in its homeostasis, structure, and function can induce, with advancing age, the onset and progression of several age-related diseases (ARDs) (Denkinger et al., 2015; Doron et al., 2018). HS-related ARDs comprise immune disorders (i.e. autoimmune diseases, recurrent bacterial infections, influenza virus infections, etc.) linked to immunosenescence (Ciaffoni et al., 2015; Denkinger et al., 2015; Akunuru and Geiger, 2016), anaemia linked to the effects of ageing on red blood cells (Röhrig, 2016; Taimeh et al., 2017), and haematologic malignancies (i.e. acute myeloid leukaemia, the incidence of which increases dramatically in the elderly, due to intrinsic and extrinsic age-related changes in both haematopoietic stem cells (HSC)/progenitors (HSPCs) and components (i.e. endothelial cells (EC) of their niches; see

Abbreviations: AGM, aorta-gonad-mesonephros; ARDs, age-related diseases; BM, bone marrow; CVDs, cardiovascular diseases; EC, endothelial cells; EPC, endothelial progenitor cells; EHT, endothelial-to-haematopoietic transition; GM, gut microbiota; HFD, high-fat-diet; HPA, hypothalamic–pituitary–adrenal axis; HS, haematopoietic system; HSC, haematopoietic stem cells; HSPCs, haematopoietic progenitor cells; iPCS, induced pluripotent stem cells; IUGR, intrauterine growth restriction; MSCs, mesenchymal stem cells; NO, nitric oxide; RA, retinoic acid; RAS, renin-angiotensin system; RARs, retinoic acid receptors; ROS, reactive oxygen species; TFs, transcription factors; TLR, Toll-like receptor; VEGF-A, vascular endothelial growth factor A

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Box 1

HS features and components and a brief description of the niches of HSC: a natural ecosystem where the EC cells play a key role (see Nagai et al., 2006; Mendez-Ferrer et al., 2008; Haznedaroglu and Beyazit, 2010; Clements and Traver, 2013; Benites et al., 2014; Yao et al., 2014; Klamer and Voermans, 2014, Denkinger et al., 2015; Long and Huang, 2015; Vaidya and Kale, 2015; Zhao and Li, 2015; Akunuru and Geiger, 2016; Sasine et al., 2016; Beerman et al., 2017; Finn et al., 2017; Perlin et al., 2017; Ramalingam et al., 2017; Tamma and Ribatti, 2017).

The HS explicates its crucial role through the process of 'haematopoiesis', which occurs in the bone marrow (BM), during the adult life of a vertebrate, and is orchestrated by HSC. However, other anatomic districts, during the early stages of HS development, are involved in the initial phases of haematopoiesis (*see* Boxes 4 and 5). HSC, as multi-potent stem cells, give rise to different branches of more lineage-restricted progenitors (HSPCs). In turn, HSPCs can differentiate in the diverse populations of mature blood and immune cells. Furthermore, HSC play another crucial role-provision for self-renewal, proliferation, and maintenance of their alert and quiescent states, typical of adult stem cells (ASCs). However, for performing their functions in a physiological manner, HSC require a specialized habitat and appropriate resources, which, in turn, contribute to the control of their fate and roles. Accordingly, HSC (like any other ASCs) are localized in specialized tissue micro-environments, "the niches", more precisely "the endosteal and perivascular niches" (*see their structures and composition illustrated* Fig. 1*S A and B*).The niches of HSC consist of a stromal cellular component, defined support cells, vessels (mainly sinusoids: small blood vessels consisting of a fenestrated endothelium) and elements of the extracellular matrix (ECM). The support cells include a wide variety of cells: cells derived from HSC themselves (macrophages), endothelial cells (EC), perivascular stromal cells, osteoblasts and osteoclasts, adipocytes, mesenchymal stem cells (MSCs), and other cell types. The molecular and cellular elements of HS niches show a fine interplay with HSC, that preserves HSC homeostasis and influences their fate and biological age. Cotemporally, it is modulated by the systemic conditions and mediated by a sophisticated crosstalk between different molecular pathways (i.e. Notch, Toll-like receptor (TLR; particularly TLR-4), Wnt pathways and others, *see* Table 1). The pathways are activated by several stimuli, including growth factors, cytokines, chemokines, regulatory factors, hypoxia, danger molecules, and pathogens. In addition, they habitually create specific networks, which differ in dependence on the conditions of niche's micro-environment and the pressure of systemic stressors. Systemic stressors and conditions of niche's micro-environment modulate the genetic expression, protein levels and crosstalk between pathways. This highlights a crucial feature of the HS, that is 'the dynamic character' of both HSC niches and HSC cell populations related to biological effects of local and systemic stressors. Thus, the niches of HSC are a typical example of a natural ecosystem, where HSC represent the organisms living in a specific geographic area: "the endosteal and perivascular niches" (*see* Fig. 1*S A and B*). In such ecosystem, HSC receive their principal nutriments, including oxygen, nutrients, growth factors, cytokines, chemokines, and regulatory factors. The maintenance of these resources and the structural and physiological features of HSC's niches guarantees the physiological HSC functions during the entire existence of an individual, as abovementioned. Consequently, the loss of the physiological state of the HSC's ecosystem related to any changes of niches themselves and/ or not accompanied by systemic alterations and/or by action the various stressors can result in an altered HSC's destiny, and, in turn, in modified HSC's activities. For example, it has been demonstrated that obesity and systemic inflammation modulate HSC functions, as recently reported by Benites's group. This occurs through oscillations of the circadian rhythm, which influence the HSC's mobilization by reducing the CXCL12 expression via norepinephrine mediated activation of β3-adrenergic signaling. Norepinephrine is released from sympathetic nerves of the BM under photic signals, which affect nerves of the suprachiasmatic nucleus. Moreover, Gram-negative bacteria infections can stress the HSC activities via the activation of TLR-4 signaling pathway expressed on both HSC themselves and support cells of the niches, such as EC. This determines alterations in niche's micro-environment (e.g. activation of an inflammatory response), which influence, in turn, HSC functions and destiny, as suggested by the experimental evidence of recent

Box 1 and Fig. 1S, Nagai et al., 2006; Mendez-Ferrer et al., 2008; Haznedaroglu and Beyazit, 2010; Clements and Traver, 2013; Benites et al., 2014; Yao et al., 2014; Klamer and Voermans, 2014; Denkinger et al., 2015; Long and Huang, 2015; Vaidya and Kale, 2015; Zhao and Li, 2015; Akunuru and Geiger, 2016; Sasine et al., 2016; Beerman et al., 2017; Finn et al., 2017; Perlin et al., 2017; Ramalingam et al., 2017; Tamma and Ribatti, 2017. HS ageing is also associated with other ARDs, including other forms of cancer, cardiovascular diseases (CVD), type 2 diabetes and neurodegenerative disorders (like Alzheimer's disease), significantly related to senescence of endothelium component (excessive angiogenesis, compromised repair and abnormal damage) (Balistreri, 2016a; Balistreri et al., 2016b; Murphy and Tall, 2016; Balistreri, 2017a).

These observations underline that the maintenance of an optimal functional performance of systems during the life (particularly in adult and old age) is vital for an individual, and, thereby, an exhaustive knowledge of mechanisms and pathways involved in their functional decline is imperative for counteracting ARDs. The HS provides an example of such maintenance. Nevertheless, it remains to understood if its aging and the related ARDs may be programmed during the development, as currently recognized for other systems, such as nervous, endocrine, immune and cardiovascular systems (Fisher et al., 2012; Bateson et al., 2014; Faa et al., 2014; Alexander et al., 2015; Bateson, 2015; Projecto-Garcia et al., 2017; Kwon and Kim, 2017; Miranda et al., 2017; McGowan and Matthews, 2018; Walker and Spencer, 2018). Numerous findings demonstrate that the degree of functional decline (senescence) of human systems, as well as the related-ARD onset, can originate in the early life's stages of an individual (Phillippe and Phillippe, 2017; Wells, 2017; Vaiserman, 2018). The foetal period (and particularly the embryonal phases; "critical windows") is highly susceptible to numerous environmental stressors with the consequence to impact the adult period and its health status (Wells, 2017). Thus, it represents a critical period of development, characterized by a high rate of cellular proliferation and plasticity in the developing systems (47). These remarks are in accordance with the innovative concepts on the high susceptibility of our systems to maternal, environmental and intrauterine stressors, during their embryonic development (Fisher et al., 2012; Bateson et al., 2014; Faa et al., 2014; Alexander et al., 2015; Bateson, 2015; Projecto-Garcia et al., 2017; Kwon and Kim, 2017; Miranda et al., 2017; McGowan and Matthews, 2018; Walker and Spencer, 2018; Vaiserman, 2018). Adverse developmental conditions can impact the (epi)genetic and physiological processes of foetal development, thereby permanently modifying the architecture and functionality of hypothalamic-pituitary-adrenal (HPA) axis and systems of the progeny (Fisher et al., 2012; Bateson et al., 2014; Faa et al., 2014; Alexander et al., 2015; Bateson, 2015; Projecto-Garcia et al., 2017; Kwon and Kim, 2017; Miranda et al., 2017; McGowan and Matthews, 2018; Walker and Spencer, 2018; Vaiserman, 2018), predisposing them to disease development during adulthood.

Here, we report, for the first time, experimental evidence and related theories that demonstrate how adult destiny of HS and blood cells may be developmentally programmed. In addition, we describe mechanisms and pathways underlying these associations. Finally, we also outline our views and propose pro-health interventions and therapeutic approaches, that might be the key for the health of future generations and delaying/retarding the continuous increase of ARDs incidence in modern populations (Balistreri, 2017b; Balistreri, 2018a).

1.1. Developmental programming: conceptual background and underlying mechanisms

The concept of developmental programming of an organism is well-established. It is the result of the evolution of intrauterine development (*vivipary and placentation* in Eutherian mammals, including humans). For facilitating its comprehension and role in programming HS, it reports a brief description, and evidences the mechanisms involved.

Since the pioneering works of David Barker and colleagues (Barker et al., 1989; Barker, 2004; Barker et al., 2009), the causal links between poor environmental conditions early in life and development of life-long pathological phenotypes, such as autoimmune, physical (i.e. cardiovascular) and mental disorders, have been well established in several cohort studies. Among the aetiological factors acting during the critical windows in prenatal and/or neonatal life, there are poor or unbalanced nutrient intake, unhealthy lifestyle (substance abuse, smoking, alcohol, sedentariness, etc.), and maternal exposures to stress and xenobiotics (Preston et al., 2018). Based on data from these studies, the Developmental Origins of Health and Disease (DOHaD) hypothesis was proposed as early as three decades ago (Jazwiec and Sloboda, 2019; Hanson et al., 2011; Hanson and Gluckman, 2014). According to this hypothesis, the developing organism may adapt to unfavourable growth conditions, both structurally and functionally, thereby predisposing to development of various pathological conditions in later life. The theoretical basis for the DOHaD concept has been thoroughly discussed over the last decades (Hanson et al., 2011; Hanson and Gluckman, 2014; Vaiserman, 2018). A variety of hypotheses emphasizing different aspects of the developmental programming phenomenon such as the “thrifty phenotype” hypothesis (Vaiserman, 2018), the “catch-up growth” hypothesis (Hales and Barker, 2013) have been further propounded to explain causal relationships between early-life adversities and later-life health outcomes. A more recent “predictive adaptive response” hypothesis (Bateson et al., 2014) proposes an evolutionary basis for the developmental programming. According to this hypothesis, early-life environmental cues might be used by the organism to search optimal phenotypic strategy with which the greatest future dividends will be gained. If the resulting phenotype is optimally matched to the developmentally predicted life-course conditions, it may subsequently promote its fitness and viability. If a mismatch, however, exists between the developmentally programmed phenotype and actual environmental conditions, it may lead to its decreased adaptability and, thereby, to the enhanced disease susceptibility in adult life.

Over the past three decades, many experimental studies have been performed to investigate mechanisms contributing to DOHaD phenomenon (for recent reviews, see, e.g., Fleming et al., 2018; Fall and Kumaran, 2019). The impaired organ development is ordinarily mediated by the reduction in cell numbers and by disturbed balance of typical cell types within different tissues. Such changes within certain body organs and systems inevitably impair their functioning long after the developmental processes are completed (Fisher et al., 2012; Bateson et al., 2014; Faa et al., 2014; Zohdi et al., 2014; Alexander et al., 2015; Bateson, 2015; Projecto-Garcia et al., 2017; Kwon and Kim, 2017; Miranda et al., 2017; McGowan and Matthews, 2018; Walker and Spencer, 2018). Specifically, it is now evident that adverse early-life exposures may induce life-long changes in functional identity of immune cells (known as *immune reprogramming*), thereby leading to enhanced susceptibility to immune and inflammatory disorders later in life (Chen et al., 2016). The innate immune cells, and particularly foetal and adult tissue-resident macrophages (i.e. microglia) constitute a typical example of immune reprogramming process, as stressed in this review. This is important for the aging process, since it is well established that all ARDs, HS-related ARDs included, have a clear inflammatory basis (Franceschi et al., 2018). Furthermore, all the developmentally programmed structural/functional changes are evidently accompanied by corresponding epigenetic modifications (heritable modifications in gene expression occurring without changes in DNA sequence), which present a key link between the genes, environment and phenotype (Vukic et al., 2019). These epigenetic modifications play a crucial role in the orchestration of temporal, and cell- and tissue-specific gene expression profiles during the development, as well as in adapting the organism to its actual environment. Among the basic mechanisms of epigenetic control, DNA methylation is the most intensely studied epigenetic mark. DNA methylation is a covalent modification of DNA involving the addition of a methyl group to the 5-position of the cytosine ring in CpG dinucleotides in the promoter gene regions. This modification typically leads to transcriptional silencing. One more key mechanism of epigenetic regulation is post-translational modification of core histone proteins. The histone acetylation generally causes to transcriptional activation (Block and El–Osta, 2017). Regulation by non-coding RNAs governing gene expression at either transcriptional or post-transcriptional levels is another crucial component of the epigenetic control (Wei et al., 2017). Importantly, all these mechanisms are interrelated, so, feedback loops can operate as self-regulatory mechanisms in epigenetic regulation (Jablonka and Lamm, 2012). One important point in the context of the role of epigenetics in developmental programming is that the epigenome (a complex network of epigenetic marks regulating both the chromatin structure and the genome function) seems to be most plastic during early development, especially throughout establishing differentiation-dependent and cell lineage-specific gene expression profiles (Burns et al., 2018). In mammalian development, the periods of high environmental vulnerability are related to the processes of epigenetic reprogramming occurring during two waves of genome-wide demethylation and subsequent *de novo* methylation in primordial germ cells, early embryos, and also in embryonic stem cells (Lee et al., 2014; Zeng and Chen, 2019). These waves of demethylation and subsequent re-methylation are generally believed now to be designed to erasing epigenetic memory and restoring naïve pluripotency, and to preventing the transmission of acquired abnormal epigenetic marks (epimutations) to the next generations. After establishing in early development, majority of epigenetic marks are stably transmitted across the mitotic cell divisions and contribute to the determination and differentiation of certain cell lineages. In mammalian species, including humans, windows of enhanced epigenetic plasticity were found to extend from periconception through weaning (Hochberg et al., 2011).

2. From the developmental programming to HS (re)programming and its destiny in adult life

All the described concepts suggest that HS function, destiny and disease in adult life are strongly dependent on the developmental programming processes. In Fig. 1, we present the risk factors involved, the consequent mechanisms and effects induced, object of description and discussion in the various sections of our review. In addition, we propose a model on HS programming represented in Fig. 2, described and discussed of follows.

2.1. A model on HS programming based on the key role of epigenetic, endothelium and HPA axis re-programming

Parental adversity (both maternal and paternal, see factors listed in Figs. 1, and 2), before conception and during gestation, alters the functionality and causes damages in parental endothelium, the essential component of stroma of all tissues/organs/systems and the hub of HS niches (see Box 1 and Fig. 1S), safeguarding their homeostasis and function. Cotemporally, it determines a growing activation of HPA axis accompanied by a parallel augment in a low systemic inflammatory grade, and concomitant metabolic disorders. These stress conditions may permanently reset: 1) the HPA axis of developing foetal hypothalamus and 2) the structure and function of foetal endothelium, with profound effects on their subsequent functioning (amply quoted in Vaiserman, 2018 and Vaiserman et al., 2018). The complete knowledge

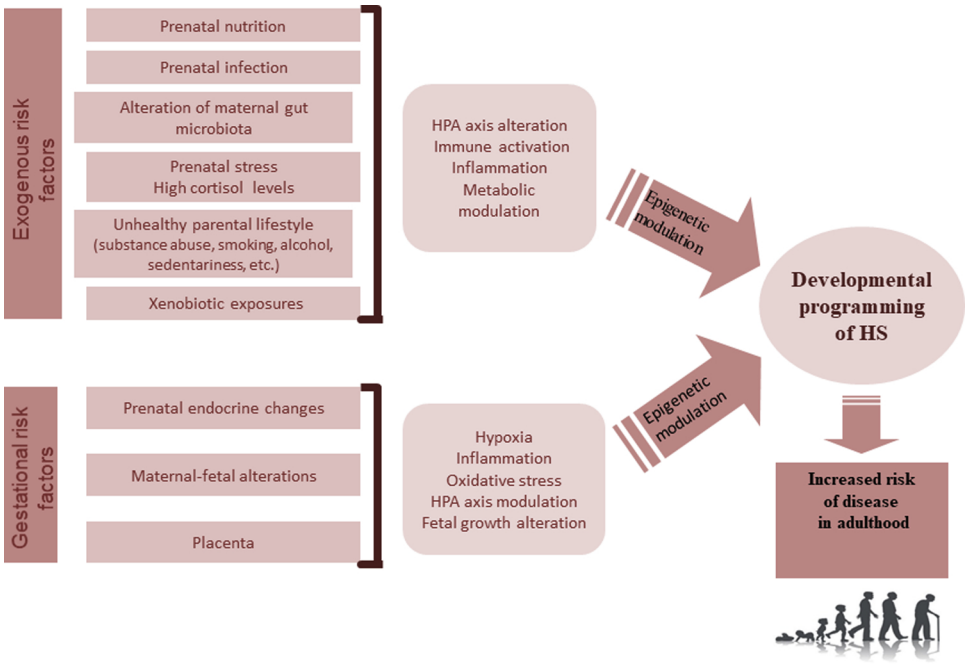

Fig. 1. The endogenous and gestational risk factors, and the related mechanisms and effects. It summarizes the endogenous and gestational risk factors influencing this process, and the related mechanisms and effects induced on HPA axis, immune, endocrine and metabolic systems, influencing HS developmental programming, and the outcomes in adult life.

about the related mechanisms is crucial, given the key role of HPA axis activity in any stress conditions and ARD pathogenesis (Gupta and Morley, 2014), on one hand, and the crucial relevance of endothelium, in physiological development, homeostasis, function and disease of all the human systems, HS included. Epigenetic (re)programming orchestrates these developmental programming events, through firstly a close interaction between maternal endothelium and developing placenta. In turn, developing placenta and hypothalamus influence the expression of foetal genome. In particular, the developing foetal hypothalamus regulates the release of hormones, modulating its functions and those of maternal hypothalamus. This results in the secretion of various hormones, that are crucial for the foetus itself, and able to exacerbate the maternal stress condition. Maternal and foetal changes in hormonal levels, such as insulin, growth hormone (GH), insulin-like growth factors (IGFs), glucocorticoids, catecholamines, leptin and thyroid hormones have been, indeed, detected (Fowden et al., 2006, 2016). Such variations influence, from one hand, the foetal development and have long-lasting outcomes for metabolic, cardiovascular and reproductive functioning (Fowden et al., 2006, 2016). From another hand, they contribute to the onset of pathological conditions during pregnancy,

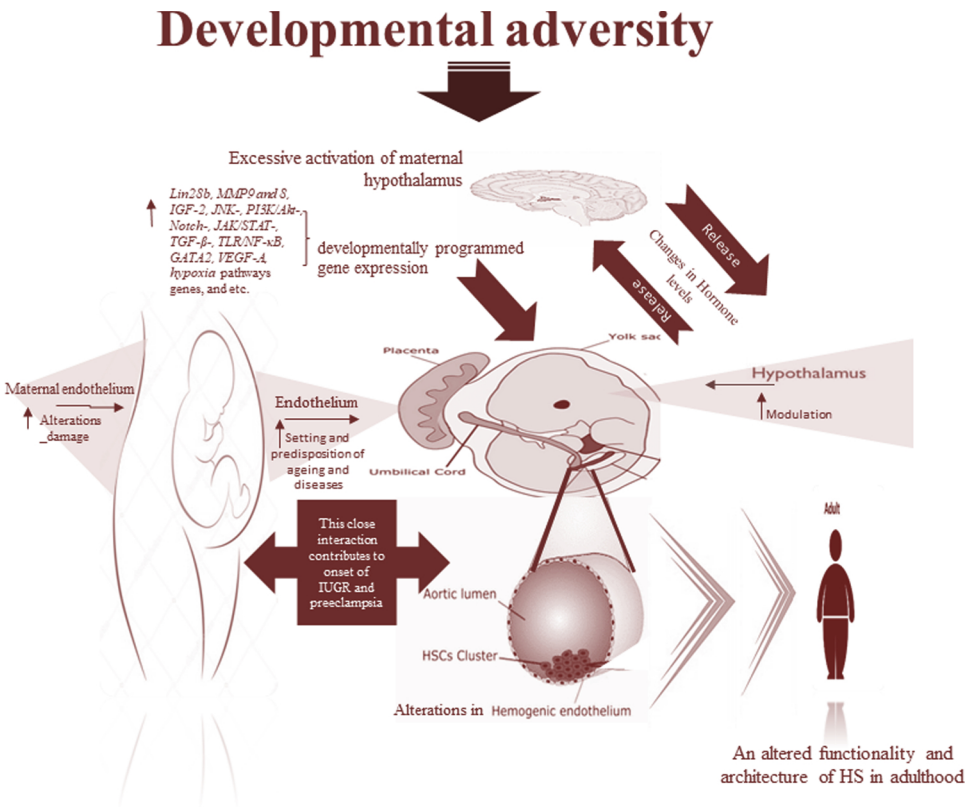

Fig. 2. A model on HS programming. HS programming appears to be the result of key programmed events, such epigenetic, HPA and endothelium reprogramming. Specifically, developmental adversity (of both maternal and paternal) permanently resets the HPA axis and endothelium with profound effects on their subsequent functioning (amply quoted in Vaiserman, 2018 and Vaiserman et al., 2018). This is the consequence of epigenetic (re)programming, that induces these effects through a strong interaction between maternal endothelium and developing placenta, and after with foetal hypothalamus. Developing placenta and hypothalamus influence the expression of foetal genome. In particular, the developing foetal hypothalamus regulates the release of hormones, modulating its functions and those of maternal hypothalamus. This determines the secretion of various hormones, that are crucial for the foetus itself, but responsible of pregnancy conditions, such as IUGR and pre-eclampsia (Fowden et al., 2006, 2016). All such changes influence the structure and function of hemogenic endothelium and, thereby, impact the architecture and functionality of HS in adulthood, that might be associated with the onset of CHIP, as stressed in the text (Park and Bejar, 2018), as well as with high risk of ARDs.

such as intrauterine growth restriction (IUGR) and preeclampsia (amply quoted in Vaiserman, 2018 and Vaiserman et al., 2018), having not fully clear mechanisms. Nevertheless, recent evidence suggests that abnormalities in "maternal-foetal circulation" can be a main cause. For example, changes in the Doppler velocity of uterine and umbilical arteries, determined by an increase of impedance to blood flow in circulation of placenta and spiral arteries of mother, have been detected (Unterscheider et al., 2013). This suggests the key role of "(re)programmed" endothelium. The "(re)programmed" endothelium also evidences alterations in both architecture and function of hemogenic endothelium and, in turn, in HS programmed development and destine in adulthood (*see* Fig. 2, and *for further clarification it remands to paragraphs 3.1 and 4,* and Boxes 4 and 5).

In addition, it has been shown that maternal pathological conditions, including IUGR, are significantly associated with the appearance of several pathologies in neonates (Kesavan and Devaskar, 2019). IUGR neonates show prematurity and related immediate medical problems, and a notable susceptibility to hypertension, CVDs, type 2 diabetes, and neurodegenerative diseases in adult age. Based on these concepts, several theories and models on brain and cardiovascular systems have been developed (see Box 2, Balistreri, 2016a; Balistreri et al., 2017; Barker et al., 1989; Barker, 2004; Barker et al., 2009). In addition, crucial appear the mechanisms evidenced by some groups, and particularly by Tain's group (Chen et al., 2013; Lanoix et al., 2012; Serón-Ferré et al., 2012; Landgraf et al., 2015; Tain et al., 2017) (see Box 3).

In in the next sections, we report experimental data and recent evidence in order to support our suggestions.

2.2. Experimental data

Increasing experimental data support HS (re)programming process. Marks and co-workers investigated whether the HS is modulated by epigenetic reprogramming (Kamimae-Lanning et al., 2015). They focused their study on the effect of maternal high-fat-diet (HFD) on the HS foetal compartment. Furthermore, they used C57BL/6 mice and performed several cellular and molecular investigations to test the effects of gestational HFD and maternal obesity on day 14.5 foetal HS liver. Thus, they show that an adverse maternal metabolic micro-environment can induce a reduction in self-renewal of HSPCs through maternal adipocytokines, and result in an increase in their differentiation in both lymphoid and myeloid lineages in the foetal liver (Kamimae-Lanning et al., 2015). Furthermore, they found in adult HFD mice elevated blood levels of leptin correlated with HFD status and alterations in lymphoid and myeloid lineages. However, no investigations into the role of leptin signaling in changing foetal haematopoiesis under HFD were performed by Marks's group (Kamimae-Lanning et al., 2015). Data obtained in this study were also corroborated by gene expression assays, which showed an up-regulation in *Lin28b* and *Metalloproteinase 8 and 9 (MMP-8 and 9)* genes. This suggested an increased release of the HSPC pool from foetal liver niches and the sensitivity of HSPC pool to HFD conditioned inflammatory micro-environment, particularly in male mice. In female mice, the researchers observed that oestrogens have a protective effect against HFD condition (Kamimae-Lanning et al., 2015).

In another recent study, Harris and co-workers (Harris et al., 2013) discovered that an increased glucose metabolism preferentially impacts haematopoietic and vascular targets in zebrafish embryos, using gene expression analysis and mitochondria-derived Reactive Oxygen Species (ROS)-mediated stimulation of hypoxia-inducible factor 1α (HIF-1α).

Interestingly, the results of the Kono group emphasise the effects of epigenetic reprogramming on foetal liver haematopoiesis by using bi-maternal mouse, embryos containing two haploid sets of genomes from non-growing and fully-grown oocytes developed at embryonic day 13.5 (Wu et al., 2008). Similar data were previously obtained by Morrison and co-workers in humans (Adkins et al., 2007). They observed that in bone-marrow (BM) *Insulin-like growth factor 2 (IGF-2)* gene is bi-allelically expressed and investigated whether IGF-2 is imprinted in peripheral blood of children and adults. This suggests that allelic expression of *IGF-2* is modulated during haematopoietic development (Adkins et al., 2007).

Recently, another research group (Cañete et al., 2017) underlines the importance of Vitamin A-rich diet in HS foetal development. Vitamin A is an essential micronutrient during life of an individual and is physiologically active as a metabolite of retinoic acid (RA), acting through nuclear retinoic acid receptors (RARs). In addition, it acts as a powerful patterning regulator of embryonic development of all organs and systems, but especially of vascular and haematopoietic systems, as well as of their homeostasis in adult life (Cañete et al., 2017). The relevance of vitamin A during pregnancy has been confirmed by the adverse effects that its deficit induces, including not only the increased risk for maternal night blindness and anaemia, but also congenital malformations (i.e. xerophthalmia, lower resistance to infections) and

Box 2

Theories related to foetal programming and well recognized brain and cardiovascular models (see Balistreri, 2016; Balistreri et al., 2017; Barker et al., 1989; Barker, 2004; Barker et al., 2009).

Various theories have been presented on foetal programming. Of note are those that describe the developmental programming of brain and the cardiovascular system, yet are still underestimated, and should therefore be adequately re-evaluated by the research community. Thus, it begins to give true weight to *placental, matrilineal, and epigenetic mechanisms,* promoting the adaptive development of the mammalian brain to the environment and its related pathologies during the adult period (i.e. neurodegenerative diseases, such as Alzheimer's and Parkinson's syndromes) as now underlined by several research groups. Of great importance is also the theory proposed by Barker based on the concept that the human diseases in adult age are determined by causes linked to foetal development. Barker suggests that a sustained interplay, during the crucial foetal development, between the environment of the mother and the foetus (primarily influenced by maternal genome and intrauterine state, and subsequently by epigenetic factors as a result of action of insults or stressors) can affect the gene expression in the foetus causing the development of definitive foetal phenotypes that increase the susceptibility of onset of pathologies in adult age. For example, it has been demonstrated that neonates having a low weight at birth, which is considered as a biomarker of an altered foetal development and an inadequate maternal diet, show a high risk for several age-related diseases in adults. Concepts from Barker's theory have been supported by data obtained in investigations performed in both different human groups and diverse organisms. However, they continue to be demonstrated by a growing number of studies, and their importance is also suggested in preventive programmes proposed by institutions and organizations, such as the World Health Organization. Additionally, they are also encouraging the formulation of other theories, including the one recently put forth by Pitale and Sahasrabuddhe based on the concept of ageing of the cardiovascular system related to foetal development, subsequently proposed by other groups. It supposes that the insults or stressors of maternal origin can influence the development of the cardiovascular system of the foetus in a definitive manner, determining the onset of phenotypes related to the ageing process, such as altered development, high maternal levels of triglycerides, cholesterol, and glycaemia. All these factors are able to mediate endothelial cell injury, as supported by animal investigations and are able to determine the onset of endothelial dysfunction in the progeny, known to be associated with the onset of CVDs and other pathological conditions, such as the endothelium, the fundamental stroma element of all tissues (HS niches included), as emphasized in our recent reports. However, the mechanisms involved are not completely known.

Box 3
The mechanisms involved in developmental programming identified by Tain group (Tain et al., 2017) and Landgraf et al. (2015).

Among these mechanisms, the effects mediated by high reactive oxygen species (ROS) levels have been considered first. High ROS levels have been demonstrated to be the result of stress conditions, that lead to a) a sustained activation of hypothalamus-pituitary-adrenal axis responsible for high levels of glucocorticoids, b) a high activation of immune system, and c) alterations in the system involved in the regulation of blood volume and systemic vascular resistance, that is the renin-angiotensin-aldosterone system (RAAS). In addition, the action of melatonin (N-acetyl-5-methoxytryptamine), a key molecule of developmental programming, has been proposed to be involved. This evidence agrees with the following functions of melatonin: 1) circadian rhythm modulator, 2) free radical scavenger, 3) antioxidant molecule, and 4) immunomodulator. Based on these biological effects, Tain and co-workers have proposed that melatonin is able to contribute to a successful pregnancy and a physiological foetal development, but its alterations are significantly associated with an altered developmental program. During pregnancy, melatonin mediates its expression and increases its release, achieving levels like those in maternal plasma, with a peak at terminal pregnancy and basal levels immediately after delivery. In addition, it is also produced by placenta, as well as the expression of its receptors and clock genes. Melatonin deficit induces an alteration in circadian rhythm, which is significantly associated with an altered activity of placentas. A similar condition, characterized by low levels of melatonin, has been observed for preeclampsia. Moreover, maternal melatonin has been demonstrated to influence foetal circadian system by crossing the placenta and entering the foetal circulation. In the foetal pituitary gland from rodents, melatonin-binding sites have been detected at a gestational age of 15 days. Mouse studies suggest the role of maternal melatonin in the development of the foetal circadian system. Furthermore, Landgraf and co-workers in 2015 have demonstrated that alterations in the maternal circadian system induced by genetic manipulations lead to an altered development of foetal organs. Consistent with this evidence, melatonin is consequently suggested as a potential drug for facilitating a normal foetal programming, as well as a drug acting on RAAS.

increased risk of foetal mortality. RA signaling has been also demonstrated to be essential for imprinting the expression of genes involved in foetal haematopoiesis (Cañete et al., 2017).

Furthermore, recent studies report that several inflammatory mediators, including chemokines, cytokines, adipocytokines, and eicosanoids, are involved in HS programming (Balistreri, 2015; Rogers and Velten, 2011). Their increased expression and release in circulation has been suggested to be induced by the activation of maternal hypothalamic-endocrine-immune response evocated by endogenous or exogenous insults and stressors, that, through maternal-foetal circulation, determine epigenetic effects on the placenta, foetal hypothalamus and specific tissues, such as endothelium. For instance, maternal systemic infections of the periodontal and respiratory tracts induce the release of the above-mentioned inflammatory molecules, that act on the development of the foetal systems, including HS. However, this is underestimated by physicians because they do not consider foetal tracts (Rogers and Velten, 2011).

Overall, the data provided above suggest the crucial relevance of the close relationship between the maternal and foetal micro-environment and its significant contribution in HS developmental programming and susceptibility to adult diseases, such as ARDs (Fisher et al., 2012; Bateson et al., 2014; Faa et al., 2014; Zohdi et al., 2014; Alexander et al., 2015; Bateson, 2015; Projecto-Garcia et al., 2017; Kwon and Kim, 2017; Miranda et al., 2017; McGowan and Matthews, 2018; Walker and Spencer, 2018). Accordingly, some studies have reported that the prematurity at birth and IUGR may be the major risk factors for alterations in adult HS, contributing to HS ageing and the increased susceptibility to HS diseases and ARDs (Fisher et al., 2012; Bateson et al., 2014; Faa et al., 2014; Zohdi et al., 2014; Alexander et al., 2015; Bateson, 2015; Projecto-Garcia et al., 2017; Kwon and Kim, 2017; Miranda et al., 2017; McGowan and Matthews, 2018; Walker and Spencer, 2018). In the next section, these observations are briefly reported and discussed.

2.3. Closed maternal-foetal relationship as a relevant risk factor for adult HS health and diseases

Among the diseases related to foetal development programming, CVDs seem to be the first pathology (Zohdi et al., 2014; Alexander et al., 2015; Miranda et al., 2017), particularly the IUGR condition linked to placental insufficiency or maternal malnutrition as mentioned earlier, which affects proliferation of heart cells, quantity, dimension and maturation, as demonstrated in prenatal hearts from rats and sheep (Agah et al., 2000; Bubb et al., 2007; Louey et al., 2007; Drenckhahn, 2009; Xiong et al., 2016). Similarly, placental alterations such as insufficiency have also been observed in rats, with a restoration during the post-birth period after the consumption of a normal diet. Although the effects of IUGR on the cardiovascular system are well known, its impact on the HS is poorly studied and the mechanisms of haematopoietic diseases are beginning to be clarified (Gupta et al., 2004; Ravishankar et al., 2007). However, several research groups demonstrated that premature birth and IUGR may contribute to the pathogenesis of adult haematopoietic diseases through increased oxidative stress (Saker et al., 2008; Howlader et al., 2009; Negi et al., 2012). In turn, oxidative stress leads to lipid peroxidation, protein and DNA damage in various tissues in the body, including the heart, aorta, pancreas, small intestine and kidneys, and particularly in cells with high proliferative activity such as stem cells, leading them to apoptosis (Beerman, 2017). Stem cell compartments in the haematopoietic and non- haematopoietic tissues and germ cells, that are characterized by long telomeres and high telomerase activity, are mostly affected by the effects of oxidative stress (Madonna et al., 2011; Balistreri et al., 2014; Liu et al., 2019; Poz et al., 2019). Telomeres are tandemly repeated DNA sequences (TTAGGG) localized at the end of chromosomes and maintained through the telomerase which is constituted by a protein component (Telomerase Reverse Transcriptase (TERT) and an RNA component (TERC). Telomerase functions to protect chromosomal DNA from breaking or from formation of unsuitable base pairs, by forming a protective cap together with the telomeres binding proteins, including TRF1, TRF2, and shelterin (widely quoted in Liu et al., 2019). TERT synthesis is closely controlled and occurs only in some cells in a physiological manner, such as stem cells, but also in neoplastic cells (Madonna et al., 2011; Balistreri et al., 2014; Liu et al., 2019; Poz et al., 2019). With each cell division, telomeres undergo a significant shortening. Without functional telomerase, telomeres show progressive shortening, which will determine replicative senescence and cellular senescence (Belgiovine et al., 2008; O'Sullivan and Karlseder, 2010; Whiteman et al., 2017). In 2017, the group of Goswami has suggested that telomeres can represent an optimal biomarker for foetal developmental programming (Whiteman et al., 2017). On the other hand, growing evidence is showing shortening of telomeres during foetal development, caused by many factors (i.e. maternal genetic background, epigenetic factors, lifestyle, clinical conditions, etc.). However, Goswami and co-workers (Whiteman et al., 2017) emphasized that the relationship between all these factors and shortening of telomeres, as well as the pathways and mechanisms involved are not clear. Certainly, further studies are necessary, which could help in their discovery, and consequently, in the development of personalized treatments.

As mentioned earlier, prenatal insults, such as pregnancy

complications, can trigger cellular senescence by increasing oxidative stress. Oxidative stress causes lipid peroxidation and protein and DNA damage to the telomeric ends of actively proliferating cells, such as the stem cell compartment of haematopoietic tissues, leading them to apoptosis (Beerman and Rossi, 2014). Oxidative stress may also alter chromatin remodelling enzymes and may result in changes in histones, which in turn control gene expression (Sebert et al., 2011; Beerman and Rossi, 2014). This evidence is supported by experimental studies in animals with low weight at birth, which indicates high expression of molecules with anti-proliferative activities. In humans, increased maternal weight, pregnancy complications, including IUGR and pre-eclampsia (Al-Sweedan et al., 2013) and gestational age (Chandra et al., 2012) have been shown to negatively influence the number and functionality of circulating CD34 + HSC through telomere shortening, which decreases their self-renewal along with their ability to proliferate and differentiate. These effects are crucial, given the importance of number and functionality of HSC in new-borns. In fact, reduced circulating levels of HSC are significantly associated with complications in foetal development (Bui et al., 2013). In addition, it has been revealed that maternal age affects circulating levels of HSC progenitors, such as EPC in neonates (Balistreri, 2016a, a). Accordingly, Kotowski and collaborators demonstrated that elevated circulating levels of HSC in neonates are significantly associated with a reduced susceptibility of developing several diseases, ranging from ventricular alterations, anaemia, syndrome of respiratory distress and infections (Kotowski et al., 2012). In new-borns from pregnancies with complications, an altered development in the anatomic structure (i.e. mineral composition and quantity) of HSC niches, which can influence the normal HS development and likely contribute to onset haematopoietic pathologies and other ARDs, has been observed (Kotowski et al., 2012). On the other hand, the analysis of DNA samples from leukocytes of these new-borns showed significant methylation of CpG sequences in genes encoding molecules expressed in the HS, as well as in the cells of the cardiovascular, immune, and metabolic systems (Parets et al., 2015; Bhavnani et al., 2018).

3. From HS programming to programming of microglia and other adult tissue-resident macrophages

Another important confirmation on the relevance of the biological effects of HS developmental (re)programming in adult life and susceptibility to multiple ARDs derives from the intense research on foetal monocytes and origins of adult tissue-resident macrophages. It has currently led to abandon the old concept on the monocyte-macrophage cells, that considers them only as scavenger cells of pathogens, dead cells and exogenous/endogenous molecules (Tauber, 2003; Cavaillon, 2011). Today, it has well recognized that tissue resident macrophages significantly contribute to the development and maintenance of homeostasis of all the tissues and organs (Ginhoux et al., 2015). Furthermore, their dysfunction has been associated with onset and progression of all the ARDs (Wynn et al., 2013; Moore et al., 2013; Noy and Pollard, 2014; Prinz and Priller, 2014). The diverse role of macrophages in tissues/organs health and ARD diseases is based on their plastic and dynamic change in the phenotypical polarization between two extremes, identified as pro-inflammatory M1 and reparative M2 macrophages (Prinz and Priller, 2014; Zhou et al., 2014), characterized by the expression of specific cell surface markers and the secretion of different cytokines, even if it is recently discussing about a third phenotype, M3 as intermediate of two traditional phenotypes (Malyshev and Malyshev, 2015). The macrophage's plasticity depends on the microenvironment's conditions. These last can reprogram their phenotype toward the proinflammatory M1 phenotype or toward the anti-inflammatory M2 phenotype, or M3. In the macrophage reprogramming, it is crucial the well-controlled and coordinate activity of signaling pathways, including some of those involved in HS development and listed in Table 1, such as JNK-, PI3K/Akt-, Notch-, JAK/STAT-, TGF-β-, TLR/NF-κB-, and hypoxia-dependent pathways. In addition, a post-transcriptional regulation based on micro-mRNA also happens.

These observations suggest that the diverse tissue macrophage populations and their pathways may represent promising targets for developing appropriate ARD's treatments and modulating/reprogramming the fate of tissues/organs. In order to achieve this goal, it is necessary an exhaustive knowledge of both mechanisms and pathways involved in their origin and development, specialized tissue roles and preservation of their number and functionality during their life in the resident tissues and organs. Of remarkable relevance in this research area are the discoveries made by Ginhoux and co-workers on the ontogeny of microglia (Ginhoux et al., 2010). Specifically, they have revealed (Ginhoux et al., 2010), by using fate mapping analysis, that adult microglia, associated with the pathogenesis of brain ARDs, including neurodegenerative and brain inflammatory diseases (Nasello et al., 2018), constitute an exclusive macrophage population of central nervous system (CSN) for two reasons: 1) their origin from primitive macrophages, and precisely from yolk sac (YS) myeloid progenitors (at embryonic day 8.5–9 in mice, *see reference* Ginhoux et al., 2010); 2) their maintenance in CSN residence, that differs by that of other tissue resident macrophage cells. In fact, they can continuously self-renew throughout adulthood. These results evidence microglia as an ontogenically distinct population in the mononuclear phagocyte system (MPS). In addition to their unique origin, microglia show a large heterogeneity at several levels in everyone, from stages of development, site of residency to functional stages in health and disease (Silvin and Ginhoux, 2018).

In agreement to these findings, Ginhoux and co-workers, Palis and others (De Kleer et al., 2014; Hoeffel and Ginhoux, 2015; Ginhoux and Guilliams, 2016; Palis, 2016; Hoeffel and Ginhoux, 2018) have also evidenced that HSC-independent haematopoiesis provides long-lived tissue-resident macrophage populations having key roles in multiple adult organs. Their evidence has been confirmed by other groups as summarized in diverse recent elegant reports (Ginhoux and Guilliams, 2016; Buchrieser et al., 2017; Hassnain Waqas et al., 2017; Munro and Hughes, 2017; Guilliams and Scott, 2017; Honold and Nahrendorf, 2018; Joshi et al., 2018; Mukaida et al., 2018). For better understanding the importance of this evidence, we briefly summarize how HSC-independent haematopoiesis occurs and ontogeny of tissue resident macrophages cells. In addition, it reports the data of recent investigations that demonstrated the origin from YS haematopoiesis of other innate immune cells involved in diverse inflammatory pathologies, such as ARDs. Moreover, a focus has been given to the description on effects induced by systemic inflammation evocated by diverse stressor factors during pregnancy that appears to impact both microglia and CNS development of new-born.

3.1. Haematopoiesis ontogeny and a focus on HSC-independent haematopoiesis

Haematopoiesis emerges in three sequential waves or programs (*remand to concepts stressed* in Box 4 and Box 5; see Fig. 3A–C). The first wave, called primitive program, starts at E7.25 in the yolk ac (YS) blood islands and forms erythroid (Ery), megakaryocytes (MK) and macrophage progenitors (Mac). Ery, MK and Mac rapidly give rise to maturing blood cells of all the three lineages. In addition, Mac form pre-Mac and then YS or "*primitive*" macrophages at the origin of microglia in the brain. The second wave occurs in the hemogenic endothelium (HE) of the YS forming vasculature at E8.25, and then erythromyeloid progenitors (EMPs). These two waves of progenitors (called *HSC-independent haematopoiesis*) that arise in the YS are necessary and even adequate to sustain the survival of the embryo until birth in the absence of HSC. They provide key signals to support HSC emergence. Furthermore, HSC-independent haematopoiesis also provides long-lived tissue-resident macrophage populations that function in multiple adult organs. Indeed, from EMPs, the first fetal monocytes generate. In turn,

Table 1
Signalling pathways involved in Haematopoietic Stem Cell homeostasis and disease (see Long and Huang, 2015; Sasine et al., 2016).

Signalling Pathways	Features and Functions
BMP signalling	It represents a member of the transforming growth factor-β (TGFβ) super-family. Its function is to control several mechanisms of cells, as well as their destiny. In fact, it is an essential pathway in foetal growth, as well as that of the HS.
Hedgehog (Hh) signalling	It plays a key role in vascular development during foetal growth particularly in the onset of formation of haemogenic endothelium.
Notch signalling	It is a pathway with relevant functions in both foetal and adult life. It has multiple functions and is expressed in all adult tissues, for regulating homeostasis and diseases. There are four components of this family of receptors (Notch1, Notch2, Notch3, and Notch4 in mammals), and five ligands. Its activities are based on crosstalk with other conserved pathways.
Wnt Signalling	It is expressed in both foetal and adult cells and it mediates several actions, such as homeostasis of tissues. It plays a key role in in HSC cells and in cardiovascular cells.
TLR signalling	It is the notorious innate immune pathway involved in both, PAMPS and DAMPS immune responses. In addition, it also represents the key inductor of clonotypical immune responses. In mammals, 11 to 13 members exist. They show a typical structure with a toll/interleukin-1 (TIR) intracellular domain, which, allows activation of downstream signalling culminating in the activation of NF-kB transcription factor. Data indicate that TLR4, a member of TLR family, cooperates with the other pathways listed, particularly with the Notch pathway to regulate the fate of HSC, as well as homeostasis and diseases of tissues, organs and systems, such as the cardiovascular system.
Blood flow, shear force and nitric oxide signalling	They are fundamental for the development of the cardiovascular system, and for the destiny, quantity, and function of HSC.
Retinoic acid (RA) pathway	RRA pathway is involved in controlling the development and functions of haemogenic EC during definitive haematopoiesis.
Catecholamines and GATA3	In the development and specification of HSC, several signalling pathways from the sympathetic nervous system to the dorsal aorta are involved. Among these, Gata3 has been observed to be up-regulated, even though evidence concerning its functions still remains unclear. However, it plays a fundamental role in the development of sympathetic nervous system and consequently in the production and release of HSC

fetal monocytes insinuate in every tissue, to exception of the brain, where they differentiate into most adult resident macrophage populations (*see* Fig. 3B and C). These fetal monocyte-derived macrophages maintain the capacity to self-renew throughout adulthood in certain tissues, such as the liver or the lung, where they will not be replaced by adult BM-derived monocytes. This second wave also creates lympho-

Box 4
A brief description of HS ontogenesis and the relevance of endothelium in HSC origin (Kanji et al., 2011; Medvinsky and Rybtsov, 2011; Ciau-Uitz et al., 2014; Ciau-Uitz and Patient, 2016; Slukvin II, 2016).

During foetal life, haematopoiesis occurs in various anatomic districts, ranging from the yolk sac, aorta-gonad-mesonephros region, placenta, to the foetal spleen and liver (*see* Fig. 3*A–C*). Despite this evidence, how, HSC are generated in the embryo, remains "theme" of intense investigation. Currently, several studies, principally in animal models (*see* Table 2), are, indeed, performed for this aim. The experimental evidence, until now obtained, converges on a crucial point. Specifically, it stresses the associated origin of mature blood cells with vascular development, and the initial development of HSC within the major arteries of embryo. Accordingly, it has been reported that mature blood cells are created in three different "waves".The first haematopoiesis wave starts during the early steps of embryogenesis, and specifically when the supply of oxygen and nutrients is inadequate to sustain the development. It consents to create erythroid progenitors in a manner and time, that are strictly associated with vascular onset. On one hand, this guarantees the development of HS, and on the other hand, the onset of the cardiovascular system, essential for the life of the embryo. Precisely, around embryonic day 7.5, also called E7.5, the emergence of blood development occurs in the yolk sac, where the extra-embryonic mesoderm differentiates, creating blood islands. This step signs the origin of erythroid precursors and erythroid cells, that may be considered "primitive". As a result, this step plays a relevant role, because it consents the distribution of oxygen, and consequently the embryonic development. Macrophage and megakaryocyte progenitors are also formed in this step. The second wave initiates around day E8.25, at which the erythro-myeloid progenitors originate within the yolk sac. In turn, the erythro-myeloid progenitors give rise to definitive erythrocytes and most myeloid lineages. Lymphoid lineages originate during the time ranging from E9.0 to E9.5 in the yolk sac and intra-embryonic para-aortic splanchnopleura region. All subsets of T foetal and adult cells arise from these progenitor cells. Contrarily, for B cells, these progenitors create only B1 and marginal zone B cells. Regarding tissue-resident monocyte-macrophage cells, including those of the brain (i.e. microglia cells), lung and liver, they originate during these early steps of haematopoiesis waves, and persist for the entire life of an adult individual. This supports the well-recognized role of these cells in the pathophysiology of the multiple ARDs, which develop in these tissue districts during adult life, as well as altered responsiveness, in this period of life, of both macrophage and lymphocyte subsets, themselves exclusively produced during foetal development. Such as result, these observations agree the fundamental hypothesis of Dr Barker. HSC, that have the potential of long-term self-renewal (which has been detected after transplantation into lethally irradiated hosts and used for defining HSC cells), originate by E10.5 within the major arteries, including the dorsal aorta, the vitelline and umbilical arteries. By E11.5, HSC are also observed in the yolk sac and placenta; details regarding their production and whether they are the result of a *de novo* generation or are formed due to HSC circulating in these anatomic districts remains to be clarified. However, as newly produced cells, HSC migrate to the foetal liver, and by E16.5 to the BM (*see* Fig. 3*A–C*), their definitive location during the adult life of an individual. Some groups sustain that following the origin of B2 cells might facilitate the identification of the definitive BM-HSC emergence *in vitro* studies, since these last represent a unique immune lineage specifically created from adult-populating BM- HSC cells. However, currently, there is a limited number of studies in this regard, and the data on B2 emergence are confounding. Further studies are necessary for additionally clearing the emergence of HSC and their progenitors during their ontogenesis. However, several uncertain questions particularly concern the first haematopoietic wave in the E7.5 step, related to the development of primitive erythrocytes, macrophages, and megakaryocytes. The first wave is defined as primitive haematopoiesis to be able to distinguish it from the other two subsequent waves, which occur from E8.5 on, and consequently it is called as definitive haematopoiesis.

Box 5

Experimental evidence on the key role of Endothelium on HSC origin and the relevance of specific pathways and transcription factors in setting and modulating EC and HSC in a temporally and spatially specific manner, obligated by environmental conditions (Carpenter et al., 2011; Carroll and North, 2014; Letourneau et al., 2016; McMullen and Mostyn, 2009; Bertrand et al., 2010; Mizuochi et al., 2012; Ciau-Uitz et al., 2010; Rafii et al., 2013; Imanirad et al., 2014; Sandler et al., 2014; Poulos et al., 2016; Lis et al., 2017, Balistreri, 2016, Balistreri et al., 2016; Ciau-Uitz et al., 2013; Gritz and Hirschi, 2016; Kosan and Godmann, 2016; Balistreri, 2017b; Balistreri et al., 2017).

From the brief description on HS ontogenesis in Box 4, a close relationship between the blood progenitors, HSC themselves, and a specialized endothelium cell population, termed "hemogenic endothelium" (that is *an endothelial cell population that has the potential to become a blood cell, is characterized by an endothelial-specific gene expression signature and endothelial-specific cell morphology, and is localized within the endothelial layer of a blood vessel*) does emerge. Hemogenic endothelium is supposed to give rise to haematopoietic cells through a process defined "endothelial-to-haematopoietic transition" (EHT). Investigations on zebrafish embryos and *in vitro* cultured mouse aorta/gonad/mesonephros explants have supported this evidence, and have validated the simple speculation, proposed by some groups around the first decades of 20th century. Findings from these studies have evidenced that EHT happens through gradual morphological and phenotypic changes of EC for achieving haematopoietic competence and give rise to haematopoietic cells. Furthermore, they have demonstrated that EHT appears to be driven by the action of specific transcription factors (TFs), and particularly by members of the ETS and Gata families. Gata2, Scl, and Runt-related transcription factor 1 (Runx1) have been found to play a crucial role and appear to have important actions during blood development. Consistent with this, these TFs exhibit multiple functions depending on micro-environment conditions in both embryonic and adult blood lineages. Deletions in genes encoding these TFs or their control elements have demonstrated their key role in EHT. In addition, the elegant studies by Rafii group provide a significant experimental evidence on their crucial role, and cotemporally underline the relevance of endothelial origin of HSC. Precisely, they demonstrate the decisive role of four TFs, such as FOSB, GFI1, RUNX1 and SPI1, transduced in adult EC cells or purified non-haemogenic human umbilical vein EC, in providing to these cells the capacity of trans-differentiating directly into HSC-like cells. This might represent an optimal treatment for counteracting HS diseases in adult life. An ulterior experimental evidence on effective molecular mechanisms related to EHT derives from the studies, that have examined how and where the major embryo vessels (such as the dorsal aorta (DA)) arise, even if of limited number and essentially performed in human, mouse, and chick embryos. They have demonstrated that DA originates from the fusion of the earlier paired DAs, and the process appears to be mediated by midline/notochord bone morphogenetic protein (BMP), Wnt16, and Notch pathways, and regulated by genes involved in tissue specification, including *Gata2*, *Vascular endothelial growth factor A* (*VEGFA*) and *VEGFA*-independent pathway genes. Furthermore, studies in animal models performed by embryologists on yolk sac blood islands, (where the internal cells differentiate into erythrocytes, and the external cells give rise to EC), have demonstrated the co-expression of specific TFs for blood and EC polarization, including Gata2, Etv2, Fli1, Lmo2, and Tal1/Scl, suggesting the presence of a bipotential common progenitor cell, "the haemangioblast*",* for blood and EC cells. In addition, they confirm that HS development is temporally and spatially specific, with HSC lineage trajectories obligated by environmental conditions. However, a limited number of *in vivo* investigations on *haemangioblasts,* performed in some animal species, reports contrasting data. This discrepancy might be due to difficulty to identify these progenitor cells *in vivo by* using some experimental methods, or the incapacity to reproduce the appropriate environmental conditions. Thus, additional studies are necessary for confirming this relationship, as well as for demonstrating the close association between EC and HSC. In this field, recent advances in biotechnology might help in clarifying the association. Among these innovative methods, such as genome editing proposed in 2013 by Charpentier and Doudna, might be encouraged for investigations in animal models. Despite the gaps evidenced in the studies performed until now and the necessity to clear and identify the molecular mechanisms involved in EHT process, it is possible to underline a relevant evidence. It is represented by the discovery of the pathways and TFs, their sophisticated crosstalk and their networks involved in this process. In addition, their relevance stays in being expressed on both embryo and adult HSC and niche's EC, and in regulating their functions in both the two life (embryo and adult) periods of an individual. Among these pathways, the RAS pathway mediates diverse control actions on haemogenic EC during definitive haematopoiesis, including the control of their physiological growth, functions, and specification, as largely evidenced by Gritz and Hirschi in a recent review. Another important pathway is the Notch pathway, a key regulator of cardiovascular progenitor and mature cell development (as mentioned above), and of blood cell development, by acting downstream of angiokines, i.e. VEGF, sonic hedgehog (Shh), and gridlock (Grl), as recently found in several investigations particularly performed in zebrafish. Four members of the Notch pathway and five ligands have been detected in mammals. The Notch pathway is also involved in the fate of blood cells. Mouse and zebrafish embryos without Notch 1 and 4 receptors show abnormal alterations in vascular and haematopoietic development (10). The same results have been also demonstrated in humans, where they appear to be involved in the production and differentiation of CD45-positive cells. Thus, the Notch pathway mediates several pleiotropic effects. We have recently reviewed the related mechanisms involved. Among these, the different tissue levels of its ligands or Notch itself, tissue micro-environment conditions, and its ability to constitute a network with other pathways have been underlined. During the various phases of HSC ontogenesis, the Notch pathway interacts with other pathways, mediating different effects, due to the active participation of different downstream signalling molecules and TFs. Particularly, in the phase of haemogenic EC development, the Notch pathway constitutes a complex network with RA and c-Kit pathways, where c-kit (also called CD117) represents a growth factor receptor binding the stem cell factor (SCF). This axis mediates the upregulation of p27, a cell cycle inhibitor of G1 phase, and in turn determines haemogenic specifications. In its fundamental role to regulate the onset of formation of HSC and their progenitors, the Notch pathway also interacts with Wnt, Hedgehog, and the TGFβ/BMP pathways, as shown by data obtained from zebrafish embryos. Recently, other pathways have been demonstrated to interact with the Notch signalling pathway and to contribute to HSPC formation in zebrafish embryos. They include some G protein–coupled receptors (GPCRs), such as eicosanoid and chemokine receptors (e.g. PGE2, CXCR4, and CNR2 receptors), as well as nuclear oestrogen receptors and the vitamin D pathway. Interestingly, some researchers have also shown that inflammation, hypoxia, and metabolic factors can also modulate several effects of the Notch signalling pathway. Studies in both mice and zebrafish embryos have underlined an interesting link between prominent evolutionary innate immunity pathways, that is the TLR-4/NF-κB pathway, and the Notch pathway. This interaction has been found to regulate HSPC development from the haemogenic endothelium, as well as the optimal function of haemogenic endothelium itself. This evidence allows to complement relevant data from other recent studies on the role of sterile inflammation in HSPC and endothelium development, and their physiological function in both zebrafish and mice. These results propose that a low-grade of inflammation is necessary in the two processes mentioned earlier. In other words, a low activation of the TLR-4/NF-κB pathway evocated by pathogens or danger molecules results in the efficient formation and function of both endothelium and HSPCs, allowing primarily to counteract eventual infections or limited tissue injuries and to guarantee normal cell turnover, and consequently to contribute to maintenance of the homeostatic status of the micro-environments. Furthermore, maternal stressors, such as metabolic factors (e.g. hyperglycaemia), have been shown to promote the release of ROS, which appear to regulate Notch levels and those of its different ligands, and consequently to mediate activation of the TLR-4/NF-κB pathway. The different effects of the two pathways, namely the TLR-4/NF-κB and Notch pathways, have been also demonstrated to regulate the function and homeostasis of other tissues and systems, and to contribute to disease onset. Among these, it primarily includes the cardiovascular system. Moreover, as mentioned earlier, the hypoxia status, which

characterizes intrauterine environment, has also been demonstrated to be involved in the crosstalk of the two abovementioned pathways. Mouse studies have revealed that the stress and stretch pathways activated by blood flow influence the Notch and TLR4/NF-κB pathways. Of relevance is the study from Adamo and co-workers in mouse embryos, which demonstrated the importance of mechanical forces in promoting haematopoiesis and haemogenic endothelium development via nitric oxide (NO) and Notch activation. Other studies underline that the context-dependent specific roles of the Notch pathway (via the formation of diverse networks and axes) are regulated in a sophisticated manner by regulatory molecules. The best-characterized regulator molecules are represented by TFs, primarily including Runx1 and Gata2. Overall, the evidence reported shows the involvement of key sophisticated mechanisms driven by complex molecular networks, which mediate the intricate interplay between the two cell types, EC and HSPCs. This picture is additionally complicated by maternal imprinting during developmental programming.

myeloid progenitors (LMPs) that provide T and B lymphoid precursors (see Boxes 4 and 5). The third wave starts at E10.5 with the emergence of the first HSC (see Boxes 4 and 5) from the embryo proper HE of the aorta-gonads-mesonephros (AGM) region. Beyond E10.5, HSC are also produced in HE situated in umbilical and vitelline arteries, as well as in the placenta and YS. EMPs, LMPs and HSC rapidly infiltrate fetal liver, that becomes the principal hematopoietic organ until late gestation. In the perinatal period, HSC can also generate fetal monocytes, contributing to a limited population of resident macrophages (widely quoted in De Kleer et al., 2014; Hoeffel and Ginhoux, 2015; Palis, 2016; Buchrieser et al., 2017; Mukaida et al., 2018).

3.2. Other innate immune cells from YS haematopoiesis: γδ T cells?

Recently, the group of Ginhoux in collaboration with French researchers (Gentek et al., 2018) have provided another important discovery. They have demonstrated that epidermal γδ T cells originate from YS haematopoiesis and clonally self-renew in the adult. This suggests that they resemble Langerhans cells, the epidermal resident macrophages, for origin and maintenance. Consequently, epidermal microenvironment applies a lineage-independent influence on the initial seeding and homeostatic preservation of its resident immune cells. Further studies on γδ T cells of other tissue districts (i.e. gut) might provide important insights in the understanding of the increased susceptibility to autoimmune disorders and metabolic syndrome in later ages.

3.3. The weight of maternal fetal environment in the distinct functional properties of myeloid cells in early and adult life

The observations abovementioned suggest that lineage specification and the function of adult tissues resident macrophages are influenced by both the origin of the progenitors and the maternal-fetal environmental factors. For example, it has been reported that high local or systemic levels of immunomodulatory cytokines, such as IL-10, TGFβ, or adenosine, produced by several maternal populations with immunosuppressive functions and involved in maternal fetal tolerance, can impact the functional activity of myeloid cells during fetal life or early post-natal life (Sun et al., 2005; Mold et al., 2008; Elahi et al., 2013; Rieber et al., 2013; Abt et al., 2012) Another important factor influencing the proprieties of myeloid cells after birth is represented by the direct or indirect epigenetic effects of microbial-derived signals resulting from the initial colonization of the gastrointestinal tract by the microbiota *(remand to paragraph 5 for detailed description)*. Overall these effects lead new-borns and young infants to have a diverse susceptibility to infections and a different response to vaccination, and other clinically relevant implications, such as the development of allergies. Another support for these suggestions comes from investigations that additionally demonstrate how the maternal fetal microenvironment is relevant in the setting of all systems, HS included. They tested the effects of human cytomegalovirus (CMV) infection in utero, by evidencing their influence on the function of fetal myeloid cells through the activation and expansion of fetal innate lymphocytes, such as NK or γδ T cells (Vermijlen et al., 2010). Likewise, it has been reported that the exposure to cigarette smoke of pregnant mice resulted in a clastogenic damage in maternal and fetal BM cells, and in the tissue macrophages and other tissue specific cells of liver and peripheral blood of their foetuses (Balansky et al., 2016). Lastly, interesting are the recent data obtained in rats about the effects of intrauterine maternal hyperglycemia on myeloid cells of progeny. They showed an increase of BM cellularity and myeloid progenitors in offspring, that intensified with age and preceded the onset of neutrophilia in old ages. Neutrophilia resulted significantly augmented in old offspring endangered to a high fat diet, contributing to onset of chronic morbidities, such as ARDs (Blue et al., 2015).

Of note, also are the studies that revealed how maternal systemic inflammation can impact the development of microglia and CSN, briefly described in the next paragraph.

3.4. System inflammation during pregnancy and its effects on microglial and CNS development

It has been recognized that maternal systemic inflammation is significantly related to an altered development of CSN, and epidemiological and animal studies support this evidence. Specifically, it has been observed that systemic inflammation, related to bacterial or viral infections during the first and second trimesters of pregnancy is significantly associated with an increased risk in new-borns of developing schizophrenia or autism (Estes and McAllister, 2016), because of activation of microglia induced by viral or bacterial molecules, as shown in studies in pregnant animals after injections of polyI:C (a synthetic analog of double-stranded RNA present in some viruses) or lipopolysaccharide (a component of the membrane of Gram-negative bacteria) (Smith et al., 2007a). Elevated levels of IL-6 and IL-17 have been assessed in pregnant animals. These cytokines have been demonstrated to mediate dangerous effects on embryonic wiring of mouse brain. Likewise, elevated levels of IL-6 in human pregnant mothers have been correlated with brain connectivity and working memories in new-borns (Smith et al., 2007b; Rudolph et al., 2018). In addition, direct action of these cytokines on neurons has been demonstrated, or indirect action on microglia activation that contributes to CNS degeneration. It has been also evidenced that the action of inflammation on the microglia can determine not only immediate effects on the fetal brain, but also long-term alterations in brain development and in the structure and function of the adult, related to the increased risk of dysfunction and neurodegeneration, being the microglia a long-lived-tissue-macrophages.

4. A key driver of HS (re)programming: endothelium and potential interventions

Foetal endothelium has a fundamental role in immune cells (i.e. macrophages) and HS ontogeny, as abovementioned (*see for details paragraph 3.1 and* Boxes 4 and 5), as well as in the development of other systems. A close relationship between the blood progenitors, the HSC themselves, and a specialized endothelium cell population, termed “hemogenic endothelium”, HE, does exist. Torres and co-workers (Padrón-Barthe et al., 2014) have defined HE as an endothelial cell population, generated by mesodermal precursors, and characterized by an endothelial-specific gene expression signature and endothelial-specific cell morphology, which appears for the first time in the YS, and produces blood precursors with markers related to definitive

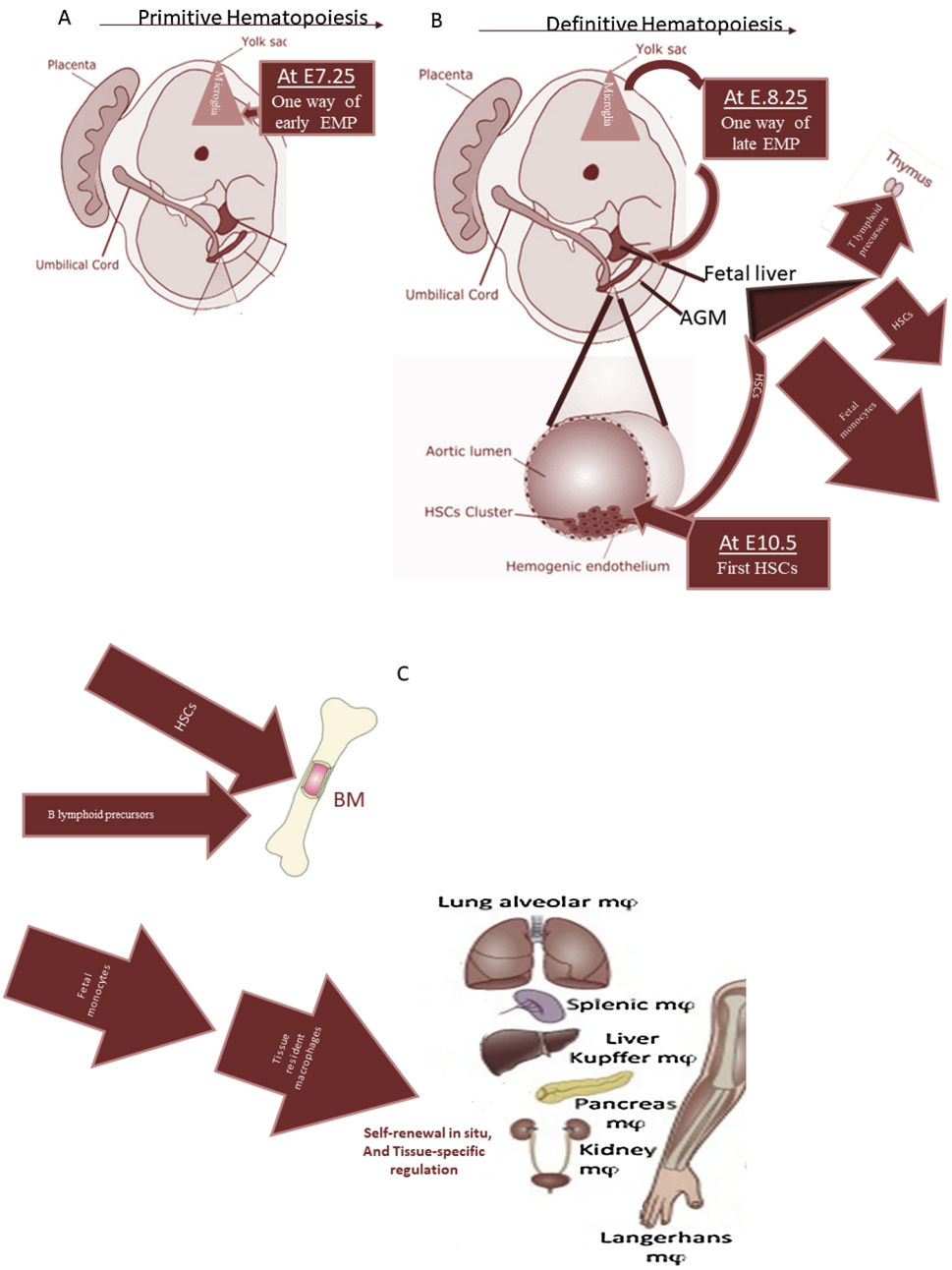

Fig. 3. A-C: HSC ontogeny and origin of the tissue resident macrophages. **In A**, representation of primitive haematopoiesis, that begins in the yolk sac (YS) at E7.25, giving rise to early erythroid (Ery), megakaryocytes (MK) and macrophage progenitors (Mac) (early EMP). Ery, MK and Mac progenitors rapidly generate maturing blood cells of all three lineages. In addition, Mac form pre-Mac and then YS or "*primitive*" macrophages at the origin of microglia in the brain. **In B,** definitive haematopoiesis that origins from second wave. It occurs in the hemogenic endothelium (HE) of the YS forming vasculature at E8.25, and then late erythromyeloid progenitors (late EMPs). Late EMPs seed fetal liver, originating fetal monocytes. In turn, fetal monocytes infiltrate every tissue (except for the brain) and differentiate into most adult resident macrophage populations (**in C**). This second wave also generates lympho-myeloid progenitors (LMPs) that provide T and B lymphoid precursors (**in B**). The third wave is starting at E10.5 with the emergence of the first HSC from the embryo proper HE of the aorta-gonads-mesonephros (AGM) region. Beyond E10.5, HSC are also produced in HE situated in umbilical and vitelline arteries as well as in the placenta and YS. EMPs, LMPs and HSC rapidly seed the fetal liver that becomes the main hematopoietic organ until late gestation. After, HSC migrate into BM (**see C**).

haematopoiesis, through a process defined "endothelial-to-haematopoietic transition" (see Box 4 and Table 2*, references* Kanji et al., 2011; Medvinsky and Rybtsov, 2011; Ciau-Uitz et al., 2014; Ciau-Uitz and Patient, 2016; Slukvin II, 2016; and Box 5, *references* Carpenter et al., 2011; Carroll and North, 2014; Letourneau et al., 2016; McMullen and Mostyn, 2009; Bertrand et al., 2010; Mizuochi et al., 2012; Ciau-Uitz et al., 2010; Rafii et al., 2013; Imanirad et al., 2014; Sandler et al., 2014; Poulos et al., 2016; Lis et al., 2017; Balistreri, 2016; Ciau-Uitz et al., 2013; Gritz and Hirschi, 2016; Kosan and Godmann, 2016; Balistreri et al., 2017). Increasing evidence supports its remarkable role in this process, and studies on animal models have provided interesting results (see Box 5). In according to the crucial role of foetal endothelium, it has ben also demonstrated that it is the fundamental target of HS programming (Fig. 2). This correlates with the well-recognized role of endothelium of being the key component of the HSC niches, and particularly of perivascular niches (see Box 1 and Fig. 1S), and the tissue stroma, and, thereby, the key driver for diverse ARDs in adult life, as demonstrated by our and other groups (Balistreri, 2016a, 2017a, Adamo et al., 2009; Regina et al., 2016; Madonna and De Caterina, 2011). A growing body of evidence demonstrates how developmental programming seats and predisposes the foetal endothelium to ageing and disease. Of note is the study of Pearce and Khorram (2013). It shows how the maturation and differentiation of foetal vasculature is influenced by Vascular endothelial growth factor (VEGF) levels, depending on VEGF expression itself, its receptors and Transcription Factors (TFs), which are, in turn, modulated by chronic hypoxia, maternal food restriction, glucocorticoids, and miRNA. Thus, they conclude that this altered process predisposes neonates to a risk of cardiovascular deregulation. Other more recent investigations demonstrate how chronic hypoxia and altered maternal clinical conditions can affect the maturation and differentiation of endothelium and the vasculature of all the tissue districts, ranging from foetal-placental arteries, carotid arteries, myocardium, to cerebrovascular systems, renal, liver, and pulmonary arteries (Pearce and Khorram, 2013; Silpanisong et al., 2017; Yzydorczyk et al., 2017; Muñoz-Muñoz et al., 2018). In addition, Franco's group highlights that the IUGR condition in rats alters the

Table 2
Animal models[a] in the study of HSC ontogenesis (see McMullen and Mostyn, 2009; Letourneau et al., 2016).

Animal models	Features, Specifies and a summary of relevant data
Zebrafish 	*An ideal animal model for the study of haematopoiesis. Its external fertilization allows for observation and experimentation of embryos. Data from zebrafish embryos studies have demonstrated that perturbations in many of the major developmental signals that control haematopoiesis are significantly associated with haematologic disorders and disease, including anaemia, bone marrow failure syndromes, and leukaemia. Thus, the knowledge of regulatory pathways controlling HSPC production and function has important clinical implications.*  *Embryos*
Drosophila melanogaster 	*In the last 20 years, evidence has established an important relationship of the development of blood cells in vertebrates with that of Drosophila melanogaster. In fact, it represents an optimal model for performing several types of investigations,* .
Mouse 	*The mouse is the most common mammalian model for the study of haematopoiesis and has allowed us, indeed, to achieve and facilitate our understanding of haematopoietic biology. Several discoveries have been made in mouse studies, including the discovery of self-renewing multipotent stem cells, the identity and function of HSC and HSC progenitors, and related mechanisms*

[a] Animal models are preferentially used for two reasons: 1) HS development is evolutionarily conserved, and 2) the investigation's complexity of the HSC ontogenesis process in mammalian embryos is elevated, essentially because of the intrauterine development.

functions of EC and their progenitors, the endothelial progenitor cells (EPC). Precisely, they report that IUGR decreases vasodilatation through the acetylcholine pathway, Nitric oxide (NO) levels, and reduces the functionality of EPC, by significantly inducing senescence in BM EPC (Oliveira et al., 2017). Hartner's group summarizes in a review published in 2018 that IUGR conditions also induce several metabolic alterations, which also contribute to endothelium dysfunction (Menendez-Castro et al., 2018). Furthermore, Grove's group demonstrates that maternal HFD also affects endothelium functioning (Fan et al., 2013). Of notable relevance also is the paper of Musa and coworkers (Musa et al., 2014), which summarizes data from over 230 articles on the crucial influence of maternal conditions and intrauterine conditions on endothelium structural and function of progeny, describing all the modifications, related mechanisms and pathways involved. The substantial review shows that a large array of maternal and foetal factors permanently affects the vascular developmental programming, determining structural and functional alterations, which in turn impact the development and the fate of adult tissues and systems, such as HS, cardiovascular system and their disease risk. Furthermore, they emphasize the key role of epigenetic factors in this complex scenario. The same scenario could influence HSC emergence. HSC originate from the endothelium of foetal macro-vessels and signals from the vascular microenvironment are critical for HSC development and adult fate (see Boxes 4 and 5, and Fig. 3A–C).

Taken together, these observations demonstrate that the maturation and differentiation of foetal endothelium and its dysfunction are strictly dependent on developmental programming events and intrauterine/foetal micro-environments. In addition, they suggest how endothelium programming is crucial in influencing HS and immune developmental programming. This results not only in an increased risk for several ARDs, such as CVDs, but also in an altered functionality and architecture of HS in adulthood. Such HS alterations might be, during ageing, the cause of the expansion of HSPC clones, harbouring specific, disruptive, and recurrent genetic variants, in individuals without clear diagnosis of haematological malignancies, defined as clonal hematopoiesis of indeterminate potential (CHIP) (Park and Bejar, 2018). Some CHIP-related mutations can increase the risk for leukemia, but also of other diseases, such as CVD and type 2 diabetes (Park and Bejar, 2018). Recently, Ebert's group demonstrated an association between CHIP and atherosclerotic CVDs, and suggested the potential mechanisms involved (Jaiswal et al., 2017). This evidence emphasizes the remarkable EC role in regulating the HSC lifecycle, as demonstrated by the Butler group (Hadland et al., 2015; Ramalingam et al., 2017). HSC have a close relationship with EC in their perivascular niches during their life (see Boxes 4 and 5 and Fig. 1S). EC assume this relevant function as HSC hub from the early origin HSC phases (i.e. from HSC embryonic specification and emergence from the HE; see Boxes 4 and 5), by regulating a large range of biological processes, which are fundamental for HSC preservation during the lifespan of an organism.

4.1. Pharmacological targets/targeting as potential therapeutic approach to endothelium programming

The close relationship between endothelium and HS suggests a therapeutic approach, that is the use of agonists, antagonists and inhibitors of molecular pathway networks related to their crosstalk (see Table 1 and Boxes 1, 4 and 5). This might be an optimal strategy for improving HSC function during their altered development, or in ageing, or for developing better regenerative approaches. On the other hand, an emerging class of anti-ageing/disease treatments (i.e. anti-ARDs treatments with anti-HS diseases included) is represented by the pharmacological targets/targeting. In the specific case, typical examples are the pathways described in Table 1. They appear to be similar in the two crucial periods of life (embryo and adult) of HSC and niche's EC and regulate their functions (see Boxes 1, 4 and 5; Long and Huang, 2015; Sasine et al., 2016).

Other approaches, intervention measures and recommendations might be used for modulating HS programming, primarily acting on the mother's (parental) clinical conditions. Among these, the intervention measures on maternal (parental) microbiota might be an appropriate approach. Another possibility might be to modulate the HSC of newborns by using experimental methods of regenerative medicine, such as

cellular or tissue reprogramming. These are described and discussed in the subsequent sections.

5. Intervention measures on maternal (parental) microbiota as another potential therapeutic approach vs. HS programming

Currently, the interest in research investigations of microbiota is increasing because of their key role in modulating several mechanisms and processes linked to human health and disease. Microbiota forms an important component of our body and is constituted by many microorganisms (i.e. bacteria, viruses, and mycetes) (Kamada et al., 2012). A recent estimation has quoted the average abundance of microbial cells to be about 3.8×10^{13} (Bashan et al., 2016). The microbiota resides in various anatomical structures of our body and is organized in niches. However, it is mainly found in the gut (Kamada et al., 2012; Bashan et al., 2016), and is defined as the gut microbiota (GM). The major bacterial species found here include the phyla Firmicutes and Bacteroidetes (Eckburg et al., 2005; Rodríguez et al., 2015).

In the context of this review, our attention on GM is related to the emerging close relationship between the microbiome, its metabolites and haematopoiesis. It has been demonstrated by the Balmer group that the composition and quantity of the myeloid cell lineage is strongly influenced by the diversity of microbiota (Balmer et al., 2014). On the other hand, Taur and co-workers have observed that the microbiota with fewer microorganism types is not a favourable factor for the success of an allogenic stem cell transplantation. In fact, this unfavourable condition has been demonstrated to be significantly correlated with an increase in mortality and a consequent reduced survival of transplant patients (Taur et al., 2014). Similar results have been obtained in mice treated with antibiotic therapy (Espinoza et al., 2016). In addition, it has been demonstrated in mice that some aliments, influencing the microbiota, can indirectly modulate HS function, such as aliments rich in fibres, which specifically modulate the function of some bacteria, which are able to transform these aliments into short-chain fatty acids (SCFAs). Accordingly, mice subjected to aliments rich in fibres showed high BM levels of myeloid precursors (Trompette et al., 2014). In addition, elevated systemic lipopolysaccharide levels related to the dysbiosis of GM have been demonstrated to have myelosuppressive effects via chronic activation of TLR-4 expressed in HSC (Trompette et al., 2014). These results agree that the relationship between alteration of microbiota and the onset of several immune disorders, are linked with the development of ARDs (Zapata and Quagliarello, 2015).

As reported above, malnutrition or overnutrition in pregnancy is involved in influencing foetal programming. In addition, there is an increasing evidence on the role of environmental experiences to affect intestinal microbiota, in early life, emphasizing a “microbial programming phenomenon (widely quoted in Vaiserman et al., 2018). In this context, obesity has been shown to be a key challenge for the health of both mothers and children. In children, obesity causes alterations in development of both microbiota and immune responses. Despite its significance, weight during pregnancy, the composition and functional quality of maternal microbiota, and whether it mediates negative effects in progeny is unknown. Recently, Kozyrskyj and colleagues (Kozyrskyj et al., 2016) reviewed literature from human studies and found that maternal obesity can modulate the composition and function of gut microbiota in new-borns. Vertical transport of microbiota and the release or inhibition of release of their metabolic products have been hypothesized as possible mechanisms (Weissman, 1994).

In the next section, the effects of GM on haematopoiesis are mainly described.

5.1. Experimental evidence for the effects of microbiota on haematopoiesis

Research in the GM field is still in its initial stage; however, some interesting results concerning the relationship between GM and haematopoiesis are available. In this context, it can be highlighted that several GM products influence haematopoiesis, and that the BM cellular pool composition is correlated with GM structure and heterogeneity (Khosravi et al., 2014).

Mouse studies have made a significant contribution to understanding GM effects on HS. Studies in germ-free mice revealed that their immune system and immunological functions are impaired. This altered phenotype is consequently associated with their increased susceptibility towards intestinal and systemic infections (Smith et al., 2007a). This underlines the importance of GM functions. In fact, GM can realize a broad number of specific biochemical and molecular reactions and consequently of synthesizing a wide spectrum of molecules and metabolites that human cells are not able to produce. Some of these specific bacterial compounds exert an effect on the haematopoietic function. For example, SCFAs interact with the immune system, through the GPR receptors, which are expressed in many immunological cells. In many cases, SCFAs exert an anti-inflammatory effect through the inactivation of the NF-κB pathway. From a haematopoietic point of view, SCFAs promote the generation of specific subsets of T cells (Singh et al., 2010; Kurita-Ochiai et al., 1995).

In another study in mice, the effects of using fermentable fibres as dietary supplementation on the immune system have been analysed. The results showed that increase in fibre bioavailability leads to the expansion of members from the phylum Bacteroidetes. In turn, this results in a significant local (intestinal) and systemic increment of SCFA. Increased SCFA concentration boosts the proliferation of dendritic cell precursors in the BM through the activation of GPR41. An interesting observation is that changes in the GM are accompanied by changes in the lung microbiota, even though they do not lead to an increase of SCFA levels, possibly due to the lack of suitable substrates (Zimmerman et al., 2012).

Neutrophil aging and turnover also seem to be influenced by GM. A study from Zhang and co-workers in mice demonstrated that neutrophil aging is influenced by GM through the activation of TLRs and myeloid differentiation factor-88 network. In the study, the authors showed that GM depletion resulted in a decrease in the circulating aged neutrophils and increase the susceptibility of mice to inflammatory pathologies (Zhang et al., 2015).

As mentioned earlier, antibiotic treatments often lead to severe haematopoietic impairments through BM suppression. Such a condition is not caused due to the direct effect of antibiotic drugs. Accordingly, relevant data have been reported from a recent study by Josefdottir and co-workers (Josefsdottir et al., 2017). They investigated the adverse effect of antibiotics by depleting mouse GM by antibiotic treatment. GM depletion in mice caused a massive impairment of the haematopoietic function, in terms of reduced cell count in the blood stream paired with reduced cellularity in the BM. In the study, they demonstrated that this acquired haematopoietic phenotype was due to the GM depletion and not due the antibiotic treatment. In fact, GM transplant restored physiological haematopoiesis. They observed that the immunological impairment was caused by the suppression of GM by antibiotics led to an immune-phenotype identical to the one of Stat-1 deficient mice. This suggests that the suppression of the Stat-1 signaling induced by GM suppression is systemic and not limited to the intestinal area (Baldridge et al., 2015).

All these results are extremely far-reaching when we consider the GM plasticity and variability. GM is extremely susceptible to environmental factors and nutritional factors, as showed in twin studies, (Chow et al., 2010; Biagi et al., 2011). Moreover, GM changes with age, in the older subjects, some specific features of the centenarians GM have been linked to the longevity phenotype (Franceschi et al., 2000; Biagi et al., 2011; Rampelli et al., 2013; Biagi et al., 2016; Grignolio et al., 2014). Taken together, the strong link between microbiota and haematopoiesis represents a new critical factor that may determine the fate of the individual immune-biography traits, such as inflammaging (Franceschi et al., 2000), in health and disease (Grignolio et al., 2014).

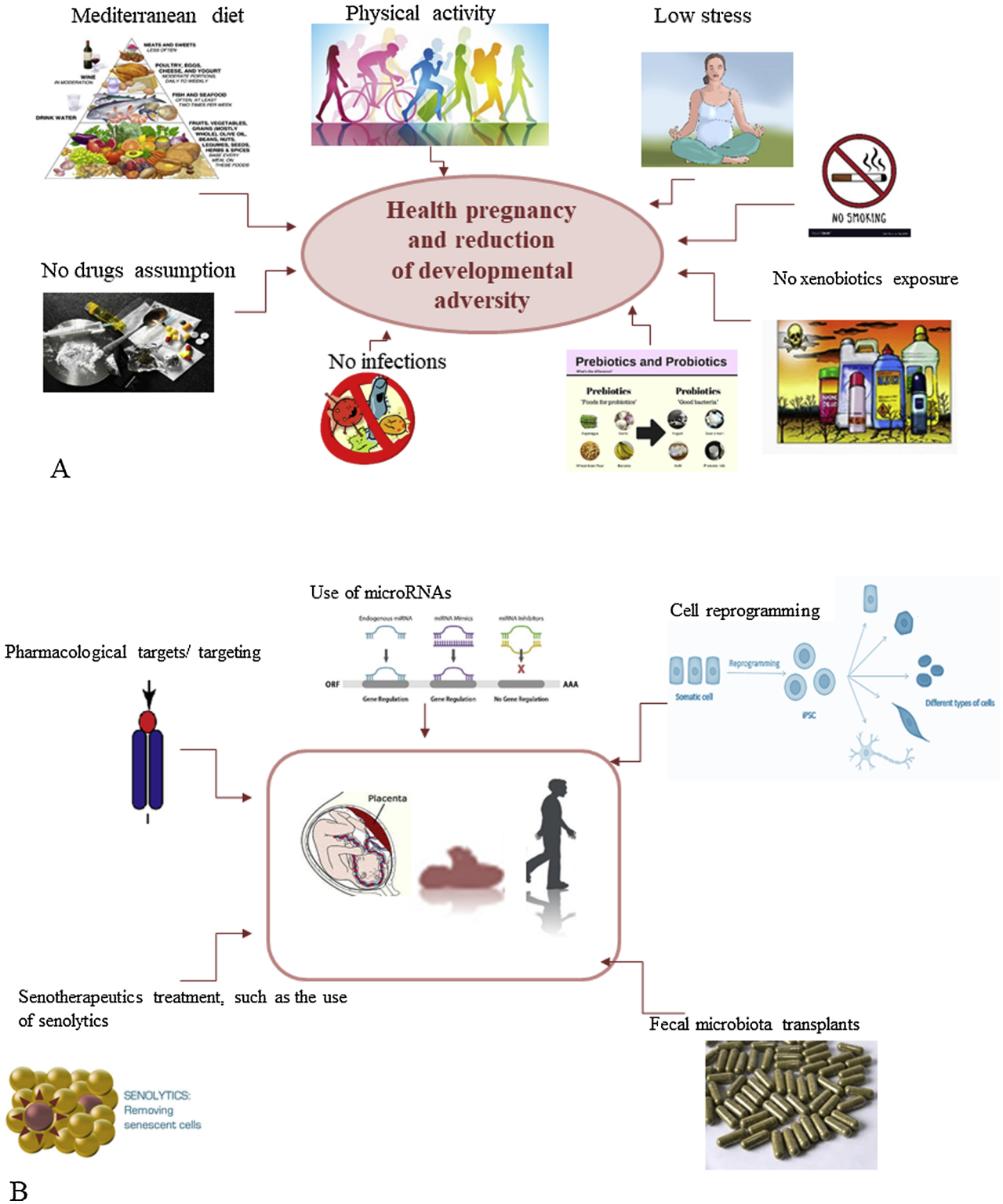

Fig. 4. A-B: Suggested interventions, recommendations and therapeutic approaches of first and second level. **In A,** all the interventions and measures to recommend of both parents, who wants to have kids. **In B,** the potential therapeutic approaches as measures to apply during prenatal, neonatal and adult periods of life cycle of an individual (*see for details the conclusions section*).

6. Cellular or tissue reprogramming as another potential solution

Studies on HSC have been and are the objects of relevant investigations of generations of researchers primarily for their clinical relevance and biological properties, and today particularly for new advances on their origin and development. However, many aspects in this field remain to be discovered and clarified. The role of developmental programming in HS, its destiny and consequences in adult life emphasizes the necessity of performing underlying investigations. This might also facilitate the application of HSC in cell therapy, potentially obtaining more HSC, or progenitors. Presently, *de novo* generation of these cells may be achieved by converting adult somatic cells to a

pluripotent state and termed as induced pluripotent stem cells (iPSCs) *in vitro*. This technology has been defined as *cellular reprogramming* (Gurdon, 1962), which has provided a new method for performing investigations on pathologies, development of treatments and translational approaches. Currently, a new form of this methodology has been proposed, which is essentially based on the use of specific transcription factors for a cellular lineage, suggested for the first time by Takahashi and Yamanaka in 2006 and consequently called Yamanaka factors (Takahashi and Yamanaka, 2006). Alternately, the use of microRNAs can allow reorganization of the genetic expression of one somatic cell to assume a different cellular phenotype and fate (Srivastava and DeWitt, 2016). Thus, it appears to function like direct reprogramming. This can permit, as its principal advantage, control of the resident support cells of niches within eventual damaged organs or old tissues. As a result, it can facilitate the regeneration or repair of the lost or old cells by transforming them directly in the cellular type, which is required by the conditions of a specific tissue. Accordingly, it seems to be promising and might become a strategy for counteracting eventual damage or ageing of HSC, and particularly of EC cells. In fact, the endothelium (as highlighted above) represents not only the *"essential element"* for the physiological development or its inhibition and that for adult destiny of HSC, but also for the physiological or diseased conditions of all tissues and organs, being the essential component of their stroma. The injury of the endothelium as a long-term effect, leads to the onset of the pathological condition that is known as *endothelial dysfunction* (Balistreri, 2016a, 2017a, Adamo et al., 2009; Regina et al., 2016; Madonna and De Caterina, 2011). In turn, endothelium dysfunction precedes the onset of not only CVDs, but also other pathologies related to age (Balistreri, 2016, 2017a, Adamo et al., 2009; Regina et al., 2016; Madonna and De Caterina, 2011). Thus, direct reprogramming might present a hope for retarding or delaying these illnesses. Interesting results on the use of direct reprogramming *in vivo* have been obtained in mice, as demonstrated by the Abad group (Abad et al., 2013). Thus, reprogramming can be achieved *in vivo*. Support for this evidence presented may be obtained from experiments on mouse BM transplantation followed by identification of iPSCs in circulation, that emphasises the possibility to directly reprogram HS *in vivo* (Abad et al., 2013). However, Abad and colleagues also demonstrated that Yamanaka factors induce a high grade of morality in mice, principally linked to the development of teratoma in multiple tissues (Abad et al., 2013). Certainly, this can limit its applications as a regenerative or an anti-ageing strategy (Abad et al., 2013). Alternatively, it might help to use this methodology for reprogramming only a specific organ or tissue, regulating the time of its application and considering the conditions of a tissue or organ in order to modulate it. Thus, the results until now obtained do not allow experimentation for clinical uses. Several questions remain unanswered and require attention. Thus, further investigations are necessary. The subsequent paragraph emphasizes the use of iPSCs to allow the reprogramming of tissue resident macrophages, given their fundamental role in both homeostasis and diseases of tissues and organs, as noted above. However, this approach is still in a childish status, but it certainly provides new possibilities.

6.1. iPSCs as source for modulating tissue macrophage differentiation and function

Recent evidence has shown the possibility to undergo iPSCs to a reminiscent process of YS-haematopoiesis *in vitro*. This consents to obtain iPSC-derived primitive macrophages (iMacs) able to terminally differentiate into specific tissue macrophages, by using specific growth factors and organ-specific cues. This approach has consented of co-culturing human or murine iMacs with iPSC-derived neurons and to induce their differentiation into microglia-like cells *in vitro*. Furthermore, it has been demonstrated that murine iMacs can differentiate *in vivo* into microglia after injection into the brain, and into functional alveolar macrophages after engraftment in the lung. Additionally, iPSCs obtained from a patient with familial Mediterranean fever have been induced to differentiate into iMacs with pro-inflammatory characteristics, mimicking the disease phenotype. In the complex, these investigations suggest the possibility of using iMacs as source of tissue-resident macrophage precursors, that can be the targets for biological, pathophysiological, and therapeutic studies (Takata et al., 2017; McQuade et al., 2018).

7. Conclusions and perspectives

HS is crucial for the life of an individual (Doulato et al., 2012, Eaves, 2015), but, as all the human systems, it shows a functional decline with ageing responsible of onset of several ARDs (Balistreri, 2018b). In addition, comparably to other systems, it shows an interindividual variation not only in disease risk, but also in ageing rate (de Haan and Lazare, 2018). Today, the growing evidence suggests that these variations originate not in later stages of life cycle of an individual, but rather in the early periods. These represent critical windows of rapid growth and epigenetic remodeling, and, thereby, of high phenotypical dynamicity and plasticity during which an organism is particularly vulnerable to environmental conditions that adversely impact tissue, organ and system development and disease propensity later in life (widely quoted in Vaiserman, 2018 and Vaiserman et al., 2018). Evidence, here reported, shows that HS is developmentally programmed, as other systems, and, thereby, in adulthood, it is the portrait of developmental programming, and particularly the result of several developmental programming events, primarily including endothelium (re) programming, being the hub of the HS origin, homeostasis and function (Pinho and Frenette, 2019), as well as of other human systems (Balistreri, 2016a, 2017a,b). In turn, endothelium (re)programming impacts HS and immune programming with the cooperation of hormonal and metabolic alterations (altered HPA axis and increased release of cortisol, but also of other crucial hormones) and epigenetic and microbial programming (Fig. 2). The combination of all these programming conditions leads HS to assume long-term structural and functional alterations, that permanently modulate its functions, increase risk of disease and speed of ageing. However, their prevention may become a reality. Since evidence supports the positive effects of a healthful diet (Hillier and Olander, 2017) (i.e. Mediterranean diet; Biagi et al., 2019), physical activity (Thompson et al., 2017), low stress (Ng et al., 2019), non-usage of smoking, alcohol and drugs (Hill et al., 2019) during pregnancy, we suggest to recommend them to both parents who want to have kids, before and during pregnancy (see Fig. 4A). McGowan and Matthews (2018) supports this concept, suggesting the role of both parents and their lifestyle in developmental programming. They state that parental adversity (not only maternal, but also paternal), linked to stress and/or to their altered clinical status due to onset of diseases, such as hypertension, type 2 diabetes, or an unhealthy lifestyle, including smoking, alcohol, use of drugs, diet, and sedentariness, exercise profound biological effects on both foetal development and subsequent functionality of HPA axis and specific systems. Furthermore, these effects appear to be species-, gender-, and age-specific, and depend on the timing and duration of exposure, as emphasized by McGowan and Matthews (2018). In addition to the first level healthspan-promoting interventions, we also propose to apply some second-level therapeutic approaches during prenatal and neonatal periods or in adult life (see Fig. 4B). Among these, emphasis has been given to the pharmacological targets/targeting of pathways involved in the crosstalk of endothelium-HS, cellular/tissue reprogramming, use of miRNAs, and modulation of microbiota of both parents and new-borns through the innovative method of fecal microbiota transplantation (FMT) (Wang et al., 2019). FMT consents to directly modify the recipient's gut microbiota in order to normalize the composition and to provide a therapeutic advantage. Thanks, the positive consensus of United States Food and Drug Administration, occurred in 2013, FMT has been applied for treating recurrent and refractory *Clostridium difficile* infection. Since

2013, its application is only restricted to gastrointestinal disorders, but it is also administrating to patients affected by other diseases, such as ARDs (Wang et al., 2019). Thus, FMT might be considered as a beneficial therapeutic treatment for HS-ARDs. Evidence shows few adverse effects, even if the long-term outcomes of FMT have not been completely elucidated (Wang et al., 2019). Consequently, it is imperative to fix regular follow-up for both identifying the periodicity and length of FMT treatment and monitoring the clinical efficacy and long-term adverse events. In addition, further studies are needed for developing personalized FMT treatments for everyone and his clinical conditions according to diverse features of hosts and diseases/conditions to treat, such as adverse HS programming.

Another treatment might be the senotherapeutics, that includes three therapeutic approaches: (i) molecules able to selectively kill senescent cells (SCs), that is, senolytics; (ii) compounds with the capacity to attenuate the proinflammatory program of SCs, or that modify the senescent phenotype, that is, senomorphics; and (iii) prevention of the accumulation of senescent cells (Baumann, 2018; Olivieri et al., 2018; Gurău et al., 2018; Xu et al., 2018).

All these measures may consent: a) to reduce the effects of developmental adversity, b) to favour a well-matched HS development programming principally acting on endothelium, and 3) to delay/retard the onset of ARDs (HS diseases included) in adulthood (see Fig. 4A–B). Furthermore, the development of treatment options specifically aimed at recovering disturbed epigenetic profiles is increasingly regarded now as one more promising interventional approach to mitigating unfavourable outcomes of early-life epigenetic mal-programming and reducing risks for development of pathological conditions later in life. The disadvantageous epigenetic modifications are known to be potentially reversible; therefore, they may likely be corrected by certain lifestyle factors such as diet, physical activity, etc. (Abdul et al., 2017; Wallace et al., 2018; Ferioli et al., 2019) as well as by pharmacological interventions (Pasyukova and Vaiserman, 2017) specifically targeted at epigenome. If these therapeutic strategies will be established, then such an approach would provide a way to slow down the epigenetic clock (Vaiserman, 2018; Fransquet et al., 2019) and to modify the dynamics of epigenetic age (Xiao et al., 2019) during the life course and, thus, to slowing down and/or delaying age-related processes.

The lack of specific biomarkers for monitoring developmental programming makes difficult to test and verify the biological effects of eventual interventions and treatments. The group of Goswami has suggested the telomere length as optimal biomarker for developmental programming (Whiteman et al., 2017). The epigenetic age indices such as DNA methylation-based biomarkers are also considered now as another promising option (Horvath and Raj, 2018).

These difficulties, as well as the need to identify the unknown long-term outcomes of the described interventions and therapeutic approaches, reflect several gaps and the need of performing further studies. These might firstly consent of discovering all the mechanisms and pathways of HS programming and facilitate the identification of appropriate targets for effective treatments, such as personalized treatments. Multidisciplinary investigations are particularly suggested, being everyone the result of the sophisticated interplay of environmental factors with its genome, trascriptome, proteome, metabolome, microbiome, epigenome, exposome, as evidenced in describing and discussing on HS programming.

Author's contributions

CRB was involved in design, wrote and edited the paper. RM wrote the section 'Closed maternal-foetal relationship as a relevant risk factor for adult HS health and diseases. PG wrote the section 'experimental evidence for the effects of microbiota on haematopoiesis'. AV wrote the section on developmental programming and related mechanisms, and proposed suggestions and considerations underlying in editing of text and figures. CRB, RM, AV and GM revised the manuscript. All authors participated in the study, and they read and approved the final version of the paper.

Declaration of Competing Interest

The authors declare that there are not conflicts of interests.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.arr.2019.100918.

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