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The peculiar aging of human liver: A geroscience perspective within transplant context

Cristina Morsiani[a,*], Maria Giulia Bacalini[b], Aurelia Santoro[a,c], Paolo Garagnani[a,c,d,e,f,g], Salvatore Collura[a], Antonia D'Errico[h], Magda de Eguileor[i], Gian Luca Grazi[j], Matteo Cescon[k], Claudio Franceschi[a,l], Miriam Capri[a,c,m]

[a] Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Bologna, Italy
[b] IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy
[c] CIG-Interdepartmental Center "Galvani", University of Bologna, Bologna, Italy
[d] Clinical Chemistry Department of Laboratory Medicine, Karolinska Institutet at Huddinge University Hospital, Stockholm, Sweden
[e] Laboratory of Cell Biology, Rizzoli Orthopaedic Institute, Bologna, Italy
[f] CNR Institute of Molecular Genetics, Unit of Bologna, Bologna, Italy
[g] Center for Applied Biomedical Research (CRBA), St. Orsola-Malpighi University Hospital, Bologna, Italy
[h] Pathology Unit, Department of Experimental, Diagnostic and Specialty Medicine (DIMES), S. Orsola-Malpighi Hospital, University of Bologna, Bologna 40138, Italy
[i] DBSV-Dipartimento di Biotecnologie e Scienze della Vita, Università degli Studi dell'Insubria, Varese, Italy
[j] IRCCS-Regina Elena National Cancer Institute, Roma, Italy
[k] DIMEC-Department of Medical and Surgical Sciences, S. Orsola-Malpighi Hospital, Bologna, Italy
[l] Department of Applied Mathematics of the Institute of ITMM, National Research Lobachevsky State University of Nizhny Novgorod, Russian Federation
[m] CSR-Centro di Studio per la Ricerca dell'Invecchiamento, University of Bologna, Bologna, Italy

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ABSTRACT

An appraisal of recent data highlighting aspects inspired by the new Geroscience perspective are here discussed. The main findings are summarized as follows: i) liver has to be considered an immunological organ, and new studies suggest a role for the recently described cells named telocytes; ii) the liver-gut axis represents a crucial connection with environment and life style habits and may influence liver diseases onset; iii) the physiological aging of liver shows relatively modest alterations. Nevertheless, several molecular changes appear to be relevant: a) an increase of microRNA-31-5p; -141-3p; -200c-3p expressions after 60 years of age; b) a remodeling of genome-wide DNA methylation profile evident until 60 years of age and then plateauing; c) changes in transcriptome including the metabolic zones of hepatocyte lobules; d) liver undergoes an accelerated aging in presence of chronic inflammation/liver diseases in a sort of continuum, largely as a consequence of unhealthy life styles and exposure to environmental noxious agents. We argue that chronic liver inflammation has all the major characteristics of "inflammaging" and likely sustains the onset and progression of liver diseases. Finally, we propose to use a combination of parameters, mostly obtained by omics such as transcriptomics and epigenomics, to evaluate in deep both the biological age of liver (in comparison with the chronological age) and the effects of donor-recipient age-mismatches in the context of liver transplant.

1. Minutes of medicine history

The study of liver anatomy began on the earliest period of Babylonian history, about 3000 years before the birth of Christ, due to Babylonian rituals of divination and the use of sheep liver (Cavalcanti de et al., 2013). Galen (about 160 A.D.) proposed the centrality of liver as source of all veins and Leonardo da Vinci conducted first relevant studies of liver anatomy in the early 1500s (Jones, 2012). The centrality of liver as metabolic and endocrine organ and its age-related dysfunction have been recognized since the middle of last century when parenchyma morphology, key metabolic enzymes and mitochondria role started to be investigated in deep (Tauchi and Sato, 1968; Vink, 1959). In particular, founding father of hepatology is considered to be Hans Popper who also wrote seminal papers on liver and aging (Popper, 1985).

Currently, the total amount of complex functions, including

* Corresponding author at: DIMES- Department of Experimental, Diagnostic and Specialty Medicine, Alma Mater Studiorum, University of Bologna, Via San Giacomo, 12, 40126 Bologna, Italy.
E-mail address: cristina.morsiani2@unibo.it (C. Morsiani).

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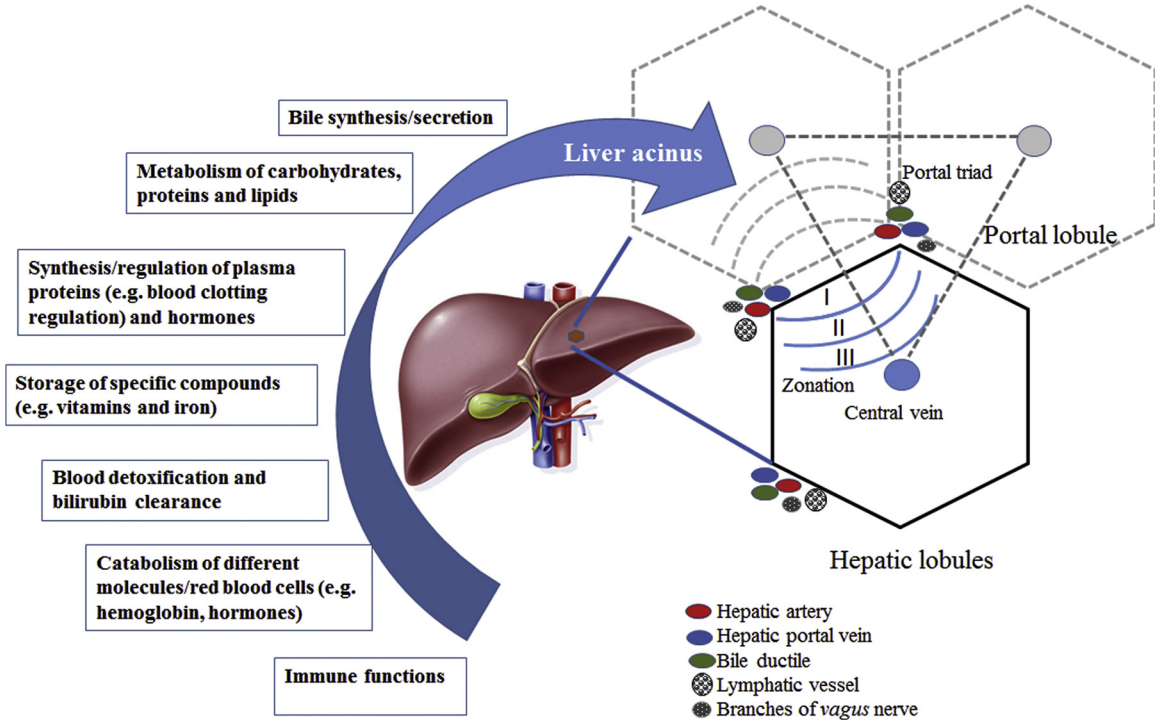

Fig. 1. Liver functions and structures.
The complex functions of liver are mentioned highlighting hepatic lobule, portal lobule (triad includes proper hepatic artery, hepatic portal vein, bile ductile together with lymphatic vessel and branches of *vagus* nerve) and liver acinus with the three metabolic zones. Zone 1 rings the portal tracts, where the oxygenated blood from hepatic arteries enters and mixes in the sinusoids with blood from the portal vein. Zone 3 is located around the central vein, where oxygenation is much lower, and zone 2 is located between zone 1 and zone 3.

enzymatic activities along with liver physiology, has intensely been documented and Fig. 1 summarizes this knowledge together with the peculiar architecture of hepatic and portal lobules. In particular, portal triad (proper hepatic artery, hepatic portal vein, one/two bile ductules, lymphatic vessel and branches of *Vagus* nerve are represented in the scheme) and the three characteristics metabolic zones (hepatic acinus) based upon oxygen tension, are shown (Gebhardt, 1992; Hijmans et al., 2014). Parenchymal cells (hepatocytes and bile ducts cells or cholangiocytes) and non-parenchymal cells (sinusoidal endothelial cells, mast cells, Kupffer cells/KCs, and hepatic stellate cells/HSC) together synchronize the vital functions in liver homeostasis and further, make possible the regeneration of the organ itself (Michalopoulos, 2017).

In the post-genomic era, the study of human liver has reached a profound knowledge in term of genomic regulation. The number of genes that are usually expressed makes evident the complexity of liver function and activity. The transcriptome analysis shows that 59% (n = 11553) of all human gene/transcripts (n = 19613) are expressed in the liver and 426 of these genes show an elevated expression in liver compared to other tissue types (https://www.proteinatlas.org/humanproteome/liver).

Concomitantly, the progress of surgery science has allowed the prolongation of life to patients with end-stage liver. This review will highlight the aging mechanisms in the framework of the new Geroscience (Kennedy et al., 2014) with a specific focus on life style/environment and age effects on liver disease onset. Further, the use of old liver (> 70 years of age) into younger recipients with successful orthotopic transplantation will be discussed, thus underlining the peculiar characteristic of human liver and its role in the immune system (IS).

2. Immune cells inhabit liver and sentinel the liver-gut axis

The role of liver as hemopoiesis site during fetal development, i.e. at third trimester of gestation, has clearly been recognized since some decades (Gale, 1987). As well, the liver as organ belonging to IS has already been defined (Bogdanos et al., 2013) even if the central role of liver as first barrier for gut antigens is not yet completely grasped. In fact, the liver is the first organ with an unique anatomical and immunological site which antigen-rich blood from the gastrointestinal tract is forced in through a network of sinusoids and skimmed by antigen presenting cells and lymphocytes (Racanelli and Rehermann, 2006). The liver is a site not only of resident innate cells, such as KCs, mast cells, dendritic cells, but also of lymphocytes (T and B cells) and of innate lymphocyte populations. In particular, natural killer cells, CD56 + T cells, NKT cells, γδT cells, and mucosal-associated invariant T cells play a critical role in first line immune defense against invading pathogens, in modulation of liver injury and in recruitment of circulating lymphocytes (Freitas-Lopes et al., 2017). In fact, circulating lymphocytes come in close contact to antigens displayed by endothelial cells, mast cells, KCs and liver resident dendritic cells in the sinusoids, thus acting as antigen presenting cells. Further, circulating lymphocytes can also contact hepatocytes directly, because the sinusoidal endothelium is fenestrated and lacks a basement membrane. This structure allows for the rapid exchange of molecules from blood into hepatocytes and facilitates the removal and degradation of immunogenic molecules (e.g., LPS or bacterial endotoxin) in the liver (Robinson et al., 2016).

Thus, liver unique anatomy may enable direct or indirect priming of lymphocytes, modulates the immune response to hepatotropic pathogens and allows some of the exceptional immunological properties of this organ. In particular, KCs exhibit a remarkable plasticity tightly depending on the local metabolic zones and immune-cytokine environment. They can express a range of polarized phenotypes, from the pro-inflammatory/M1 phenotype to the alternative/M2 phenotype, having a relevant role also in liver diseases (Dixon et al., 2013). Additionally, liver sinusoidal endothelial cells and KCs appear to be

central for the maintenance of immune tolerance, by promoting T cell anergy/deletion and by the generation of regulatory cell subsets (Grant and Liberal, 2017).

Close to sinusoids, a peculiar type of cells, named telocytes (TCs), has been recently discovered. Liver TCs, localized in the space of Disse, are different from other interstitial cells (KCs and HSC) due to their morphology and immuno-phenotypes. TCs are stromal cells described in all human organs (Bei et al., 2015b; Ceafalan et al., 2014; Ibba-Manneschi et al., 2016; Luesma et al., 2013; Sheng et al., 2014; Xiao et al., 2013; Zheng et al., 2014) and characterized by a very small spindle-shaped cell body which very long convoluted cytoplasmic processes, or telopods, originate from. Thanks to these thread-like telopods, TCs communicate among themselves and with any other type of cells and interact with collagenic bundles, forming an extensive homo and hetero cellular network, likely involved in the maintenance of tissue homeostasis (Pulze et al., 2017).

Apart specific markers (co-expressed CD34/vimentin and Oct-4/c-kit), TCs express markers of the immune-surveillance such as Toll-like receptors 4 and 5, allograft inflammatory factor-1 (Aif-1), adrenocorticotropic hormone (ACTH) as well as endogenous pro-inflammatory cytokines such as IL-18 (Pulze et al., 2017) and temporarily, may also express c-kit, Sca-1 and Oct-4 being stem cell markers (Dawidowicz et al., 2015; Edelstein et al., 2016; Pulze et al., 2017). TC network is able to integrate many different functions initiating innate immune responses including trained immunity (Bei et al., 2015a; Enciu and Popescu, 2013; Franceschi et al., 2017b), regenerative processes in wound healing/transplantation (including stem cell maintenance and tissue repair) as well as modifying cellular gene expression via specific micro/nano vesicle secretions (Bei et al., 2015a; Cretoiu et al., 2016; Wang et al., 2015). For all these attributes it is conceivable that TCs may be involved in aging process and pathologies as well as in regenerative processes where they are essential as nursing stem cells in the regeneration of liver (Edelstein and Smythies, 2014).

As far as liver-gut axis is concerned, intestine and liver form a bi-directional connection via portal vein and bile duct. Therefore, liver receives environmental signals from gut microbiota, which transforms dietary molecules into signaling metabolites able to communicate with different organs and tissues in the host. Further, gut microbiota displays circadian fluctuation (Liang and FitzGerald, 2017), which is mainly driven by diurnal food intake, and leads to rhythmic abundance of microbial metabolites (Thaiss et al., 2014), thus inducing oscillatory effects in liver metabolism (Thaiss et al., 2016). The crucial role of gut microbiota in liver function was recently demonstrated in conventional and germ free (GF) mice models suggesting that xenobiotic metabolism (involving drug-processing genes) was the most downregulated pathway in absence of intestinal bacteria and in a sex-specific manner (Selwyn et al., 2015).

Liver-gut axis influences not only absorption and storage of nutrients and liver homeostasis signaling, but also may induce the activation of many types of immune cells (ICs) and liver cell receptors. Among those, toll-like receptors (TLRs), receptors for advanced glycation end products (RAGEs), NOD- and RID-I-like receptors (NLRs, RLRs) converging in NLR-inflammasomes, cGAS-STING signaling and NF-κB activation (Franceschi et al., 2018b). This potential activation is due to the passage of pathogen-(or danger) associated molecular patterns (PAMPs or DAMPS) or other types of self-misplaced molecules/alarmins in the portal blood. This physiological and crucial role of liver and ICs preserve the development of infections or liver injury. Thus, liver-gut axis represents an essential frontline to counteract infections and to repair or favor detoxification against harmless compounds or drugs. An important result has been obtained in animal model, where GF, antibiotic-treated, and conventional mice have been investigated for both KCs development/function and response to different types of stress including transplantation. Authors have demonstrated that gut bacteria drive KCs expansion via PAMP-mediated ICAM-1 induction on sinusoidal endothelium and influence preservation-reperfusion injury after orthotopic liver transplantation (Corbitt et al., 2013).

On the other side, the persistence in the portal blood of self-danger molecules, or non-self (bacteria, virus, toxic compound) and quasi-self (microbiota products) (Franceschi et al., 2018b) induces the increase of pro-inflammatory molecules at liver level, thus favoring eventually chronic inflammation and liver disease onset (Sheedfar et al., 2013). Therefore, all above mentioned receptors and eventually ICs activation may contribute to both the development of liver damage and its consequent progression to more advanced stages, including autoimmunity diseases, hepatitis/cirrhosis and hepatocarcinoma (Federico et al., 2017; Milosevic et al., 2019).

Importantly, intestinal permeability increases with aging (Malaguarnera et al., 2014; Santoro et al., 2018) and eventually with surgery events, including transplantation (De Vlaminck et al., 2013). Gut microbiota remodeling occurs with age and the increase of pathobionts species has been recognized in centenarians (Biagi et al., 2010; Santoro et al., 2018). The flow of bacterial products increases with intestinal permeability (e.g LPS, or danger molecules) which in turn may increase the inflammatory status and accelerate aging and inflammaging (Franceschi et al., 2017a, 2018b) including local effects at liver level. The role of the gallbladder-derived surfactant protein D which has prebiotic properties in gut microbiome as well as the documented function of liver-gut axis in bilirubin catabolism, have recently been reviewed highlighting possible effects on health status and liver diseases (Adolph et al., 2018; Hamoud et al., 2018).

Importantly, semi-super centenarians (> 100 and < 110 years of age) show a gut core microbiome shrinkage in comparison with centenarians and younger subjects. Nevertheless, an increase of subdominant species, such as *Akkermansia*, *Bifidobacterium*, *Christensenellaceae*, has also been revealed. Thus, extreme healthy aging is accompanied by a re-shaping of gut microbiota species with the increase of beta-biodiversity of longevity-adaptation and possible health-promoting subdominant species (Biagi et al., 2016; Santoro et al., 2018). Importantly, centenarians do not show alterations of liver function or hepatic enzymes (Cevenini et al., 2014; Catera et al., 2016). These data may suggest that liver-gut axis is an essential player for longevity achievement and it can be explained with the peculiar environment and life style of centenarians, as recently reviewed by our team (Franceschi et al., 2018c).

3. Does human liver age?

During last years, our team has been intensely involved in an Italian national project to collect and analyze samples from differently aged liver donors (13–90 years) pointing to the answer of the provocative query: does human liver age?

The first evidence was a relative low grade of aging signs in liver of aged donors at histological and cytological level, also including the three major proteolytic activities of proteasome that appeared preserved comparing young and old livers (Bellavista et al., 2014). These data complement those previously published both on liver volume, which is reduced by 20%–40% in the elderly with sex differences, and on parenchyma, where hepatocytes in elderly subjects contain denser body compartments, such as secondary lysosomes and lipofuscin, than do hepatocytes in younger subjects (Schmucker and Sachs, 2002; Schmucker, 2005; Tajiri and Shimizu, 2013).

Further, we investigated the gold standard marker of cell senescence, i.e. telomere length shortage, which was significant in liver of oldest donors and confirmed the presence of aging process (Capri et al., 2017). Nevertheless, other authors showed that cells responsible for telomere attrition were not hepatocytes and cholangiocytes, but sinusoidal and stellate cells (Verma et al., 2012). This cell-related effect drives the hypothesis that hepatocytes have peculiar characteristics and are largely preserved by aging process (Dlouha et al., 2014).

When we investigated the epigenetic age-related modifications in terms of liver microRNAs (miRs) and gene expression, we discovered

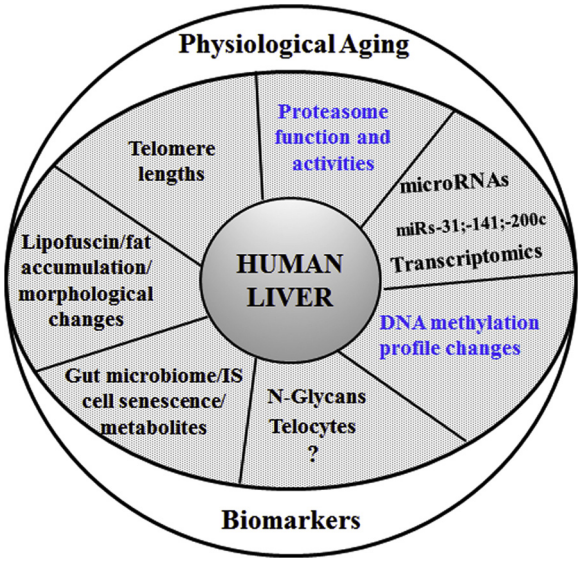

Fig. 2. Biomarkers for the evaluation of physiological aging of liver.
The most recent biomarkers are reported in black when significantly associated to the aging of liver, in blue when not fully associated (or not completely investigated). In the case of N-glycans serum profile, data suggest that they are very promising. Telocytes are still to be investigated in deep (see text).

that at 60–70 years of chronological age, three miRs start to increase their expression level, *i.e.* miR-31-5p; miR-141-3p; miR-200c-3p (Capri et al., 2017), and we proposed such an increase as marker of aging in human liver. Notably the mRNA target of both miR-31-5p and miR-200c-3p, i.e. GLT1 (or SLC1A2 or EAAT2), the solute carrier family 1 (glial high-affinity glutamate transporter) member 2, resulted decreased in the Zones 2–3 obtained from oldest donors, thus highlighting that the three metabolic zones can differently be affected by aging process.

Since a role of GLT1 is related to glutamine synthesis, our results suggest a major effect of genes involved in glutamine pathway along with aging of human liver. These results are in accordance with those obtained in animal models (mice and rats), where an age-related transcriptional remodeling in liver linked to the glutamine pathway (Shenvi et al., 2012) and metabolites of the polyamine biosynthesis (Kwekel et al., 2010; Maes et al., 2008) were shown.

On the other side, when we investigated the epigenetic age-related modifications in terms of DNA methylation profile (performed on about 450,000 CpGs genome wide), we found that a large remodeling of DNA methylation patterns occurs (Bacalini et al., 2018). Remarkably, these age-associated changes are in part specific for the liver, i.e. do not occur in other tissues, and tended to level off after the age of 60 years, i.e. when the miR changes start to be affected by age. These apparently conflicting data suggest the relevance and the complementary of the selection of specific- markers/molecules to identify aging process at different levels in the same organ and likely organism. In fact, these results may be explained not only by the contribution of different cells inside the parenchyma, but also by different layers of molecular networks regulating aging process (Castellani et al., 2016) with different timing. In this regard, genome wide DNA methylation profile and the transcriptomic analysis raised up a number of differently methylated genes in 75+ liver donors involving both Wnt/β catenin pathway, such as ZIC1, NEFM, FOXD3, MIR155HG, CELS3, HEYL, and epithelial to-mesenchymal transition (EMT), such as PRDM14 (Bacalini et al., 2018). Importantly, the combination of two levels of information (DNA methylation and expression) highlighted three genes sharing differential methylation and expression, i.e. ZIC1, TSPYL5, and FZD2 with age (Bacalini et al., 2018). ZIC1, belonging to Wnt signaling, was found involved in liver regeneration process in a murine model (Jochheim-Richter et al., 2006) and the protein encoded by FZD2, Frizzled2, is a Wnt receptor (Song et al., 2015). It is relevant to note that miR-141-3p and miR-200 family are also important regulators of Wnt/β signaling components (Song et al., 2015), thus making more robust the involvement of this pathway along with the aging process of human liver. Wnt/β catenin pathway is also crucial for contributing and maintaining the metabolic zonation (Kietzmann, 2017; Kusminski and Scherer, 2018); in fact, genes belonging to β catenin pathway can be modulated by hypoxia signaling system and hypoxia-inducible transcription factors (HIFs).

A wider role of Wnt signaling in aging mechanisms has been proposed being downregulated in cellular senescence (Ye et al., 2007). In particular, age-dependent variations of Wnt pathway expression have been revealed in bone turn over (Lerner and Ohlsson, 2015), tissue homeostasis and fibrosis (Hofmann et al., 2014), while EMT pathway has been found to be associated with liver fibrosis (Lee et al., 2014). Furthermore, transcriptome liver analyses indicate that genes involved in DNA repair system are upregulated in long-lived animal models and humans (MacRae et al., 2015), thus likely involved in counteracting aging process. Accordingly, data obtained from liver donors in terms of transcriptomic and methylome suggest that this organ has peculiar characteristics, permitting a slower aging process than other organs when disease-inflammation signs are absent or minimized, as usually occurs in liver donors. Importantly, not only the liver-specific DNA methylation signature, but also the Horvath's epigenetic clock (Horvath, 2013), a well-established biomarker of aging, shows a decrease in the epigenetic aging rate after 60 years in liver from healthy donors (Bacalini et al., 2018). In this regard, Fig. 2 summarizes the most interesting and promising markers that could be determinant for the identification of biological age of liver, thus potentially important in the transplant context.

Overall, the peculiar and slow-moving aging process characterizing liver strongly depend on environment conditions and life styles of its recipient, being an organ at the forefront with external exposure of food, drugs/alcohol, toxic compounds, among others.

4. Accelerated liver aging: environment, life style effects and liver diseases

The presence of resident ICs and the huge profile of detoxifying enzymes make the liver able to respond immediately to internal and external danger antigens/molecules and concomitantly, may contribute to severe acute effects leading eventually to liver failure. Acute hepatotoxicity events, such as ingestion of toxic substance/poisons, overdoses of drugs or hepatotropic virus infections are out of scope of the current review, as well as genetic and autoimmune diseases affecting liver functions. Similarly, primary sclerosing cholangitis and cholangiocarcinoma for their peculiar pathogenesis will be not addressed; nevertheless, a recent review in this topic is suggested (Dyson et al., 2018).

Frequently, the development of chronic hepatitis is due to different etiological/environment noxious agents or life style habits. Fig. 3 shows a scheme on the contribution of liver-gut axis and chronic inflammation to the main liver diseases up to the end-stage organ within an envisioned time clock. In fact, it is well known that many of them can be considered as different stages (steatosis, fibrosis, cirrhosis) eventually resulting in primary hepatocarcinoma (HCC) and in end –stage organ (Sheedfar et al., 2013).

The first sign of liver degeneration is the triglyceride over accumulation, leading to small/large-droplet fatty liver and progressively to steatosis (primary non–alcoholic fatty liver disease or NAFLD) often featuring aging process of liver (Gong et al., 2017). When large vacuoles coalesce and produce irreversible lesions the IS activation, such as STING stimulation (Yu et al., 2018), favors non-alcoholic steato-hepatitis (NASH) onset. Excluding secondary effects (e.g. drug or hormone effects), the type of diet and life styles, such as overfeeding with

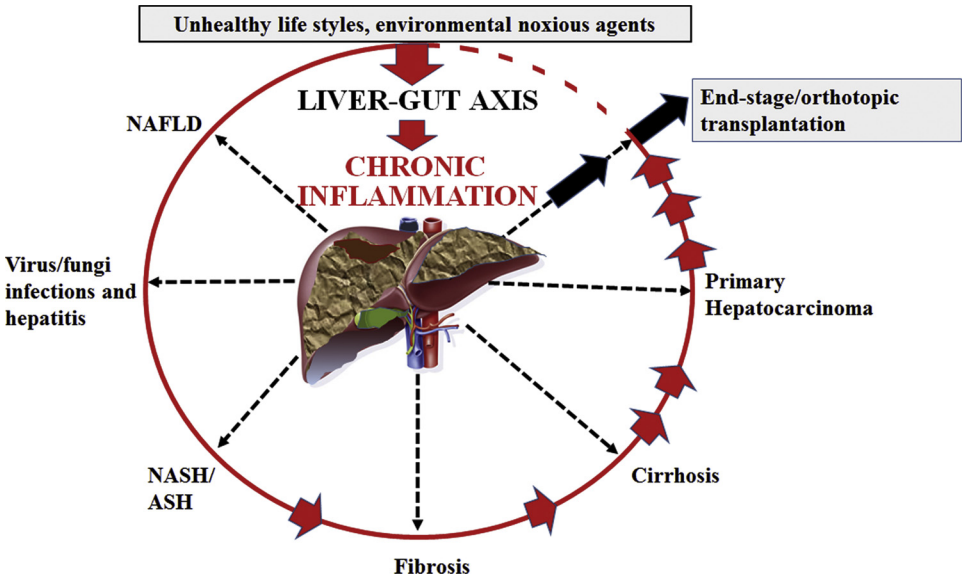

Fig. 3. Liver-gut axis and chronic inflammation contribution to liver diseases.
Non-alcoholic fatty liver disease (NAFLD), non-alcoholic steato-hepatitis (NASH), alcoholic steato-hepatitis (ASH), Virus/Fungi-derived Hepatitis, Fibrosis, Cirrhosis, and Hepatocarcinoma until the end-stage organ as a molecular continuum (red arrows) in a time-clock framework.

saturated fatty acids or high fat diet (HFD), abuse of alcohol and sedentary life, favor steatosis onset and liver diseases. In particular, NASH is commonly associated with obesity, type 2 diabetes, insulin resistance, hypertriglyceridemia and metabolic syndrome, while alcoholic steato-hepatitis (ASH) is associated with alcohol abuse and problems of addictions. Both NASH and ASH patients can develop fibrosis, cirrhosis and tumorigenesis if left untreated, even if the tumor development rate and the number of proteins involved in progression to tumor is known to be different in ASH and NASH (Nguyen et al., 2018). A possible contribution of TC decrease (Fu et al., 2015) and of HSCs on fibrosis development (Tsuchida and Friedman, 2017) has recently been proposed.

Overall, chronic inflammation is the basic mechanism that sustains the progressive liver dysfunction and leads to an accelerate aging of the organ. Interestingly, this condition may be considered similar to the aging process at systemic level, known as inflammaging (Franceschi et al., 2000, 2007), where a chronic low-grade inflammatory status is a risk factor for the development of age-related diseases. In this perspective, interleukin-6 (IL-6), one of the most pointed out inflammaging markers (Calder et al., 2017), is mainly produced by KCs, while hepatocytes express, not only gp130 (expressed on all cells of the body), but also IL-6R, which is only expressed in few cell types (Schmidt-Arras and Rose-John, 2016). Therefore, only IL-6R expressing cells can directly respond to IL-6 and the signaling mediates both acute phase response and regeneration/proliferation responses, making IL-6 a sensitive marker of hepatocyte activation and inflammatory response. Importantly, the reaction to liver injury is mediated by ICs, in particular by macrophage/KCs, and is modified by aging process able to influence fibrosis development in old livers, as recently shown in mice model (Collins et al., 2013). These data strongly encourage a parallelism, based on inflammaging, between liver aging and organismal aging process, where chronic inflammation sustains and contributes to disease onset.

Moreover, common molecular mechanisms may be observed in both liver diseases and aging process. Table 1 shows some recent articles focused on molecular features of liver diseases shared with inflammaging, thus highlighting the molecular continuum between aging/inflammaging and liver diseases according with our previous conceptualization (Franceschi et al., 2018a).

In this perspective, the prevalence of liver diseases, such as NASH, ASH, HCC increases with aging, even if an apparent paradox is described, i.e. the decrease of HCC incidence in 75+ old subjects (Sheedfar et al., 2013), suggesting a possible effect of age-related epigenetic changes likely making more robust the organ *versus* HCC development at oldest ages. However, caution should be taken about this hypothesis because of a large variability of HCC incidence based on geography/ethnicity (White et al., 2017).

The different contribution of risk factors such as age, life style habits/environment are not yet clearly assessed in liver diseases onset (Kanwal et al., 2011; Tajiri and Shimizu, 2013). In a recent paper, serum alanine aminotransferase (ALT) and gamma-glutamyltransferase (GGT) have been measured in 6269 apparently healthy individuals. Life styles, including alcohol consumption, smoking habits, coffee consumption, BMI, gender, age and their interactions were able to differently modulate the two serum enzymes and making all these parameters potential health risk factors for liver diseases onset (Danielsson et al., 2014). However, damage accumulations and different levels of inflammatory stimuli (Brenner et al., 2013) may sustain and accelerate liver disease progression within the continuum of molecular processes similarly to the effects of inflammaging on age-related diseases (Franceschi et al., 2018a, 2018b).

In this perspective, chronic hepatic inflammation mirrors inflammaging as persistent inflammatory stimuli and possible accumulation of damages contribute both to the different severity of diseases, and to accelerate aging through a systemic propagation and eventually until organ-end stage (Franceschi et al., 2017a, 2018a, 2018b; Reccia et al., 2017).

Accordingly, cellular senescence may contribute to liver diseases (Aravinthan and Alexander, 2016; Ogrodnik et al., 2017; Tajiri and Shimizu, 2013; Wei and Ji, 2018) involving different types of cells, such as KCs (Lebeaupin et al., 2015; Wan et al., 2014), mast cells (Grizzi et al., 2013) and HSCs (Saito et al., 2017). In this regard, polyploidy is generally indicated as senescence status leading both to the progressive loss of cell pluripotency and to a markedly decreased capacity of replication. In particular, polyploidy characterizes hepatocyte senescence even if this condition appears to be reversible, as shown in mouse model and appears to be regulated by miR-122 (Celton-Morizur and Desdouets, 2010; Wang et al., 2017). Interestingly, in animal models hepatocyte senescence seems to be the driving force leading to NAFLD onset (Ogrodnik et al., 2017). But individuals escaping unhealthy environment/life styles may undergo a decelerated/physiological aging including liver, and become eventually good candidate for donation at old chronological ages. Paradigmatic are the cases of 26 octogenarian livers being transplanted between 1998 and 2006, 15 patients out of 26 still alive in the 2017 (after ten years from transplantation) and 2 of those organs being centenarians (Salizzoni et al., 2017), thus suggesting

Table 1
Liver diseases share molecular, cellular and organelles- features with inflammaging process (based on recent papers/reviews).

LIVER DISEASES	Molecular mechanisms shared with Inflammaging	References
NAFLD	Cellular senescence, lipid droplets accumulations; insulin resistance; GH-IGF-1 axis.	(Aravinthan and Alexander, 2016; Gong et al., 2017; Ogrodnik et al., 2017)
ASH	ER stress and NLRP3 inflammasome activation; IL-1beta signaling; TLR4 –via MyD88-independence activation; increase of gut permeability resulting in an increased release of LPS and inflammatory response.	(Greuter et al., 2017; Ji, 2014; Masouminia et al., 2016)
NASH	ER stress, Autophagy dysregulation; insulin resistance and lipotoxicity; TLR4 –via MyD88-dependence activation; fatty acids lead to organelle dysfunction and oxidative stress inciting proapoptotic cascades; mitochondrial respiratory chain complexes alterations¸ NLRP3 inflammasome activation and hepatic apoptosis.	(Engin, 2017; Greuter et al., 2017; Lebeaupin et al., 2015; Masouminia et al., 2016; Mendoza et al., 2015)
ASH/NASH	TLRs activation; presence of DAMPs, ROS increase lead to inflammasome activation; dysregulation of different microRNAs.	(Greuter et al., 2017)
Fibrosis/Cirrhosis	ICs activation including KCs and NKT, ROS increase, excess of extracellular matrix components.	(Albillos et al., 2014; Pellicoro et al., 2014; Rashid et al., 2017; Rutkowski, 2018)
Hepatocarcinoma	ER stress (hepatotropic virus/fungi), autophagy impairment, chronic immune system activation and chronic necroinflammation which favors DAMPs increase production and hepatocytes death; p62 involvement in preneoplastic lesions.	(Umemura et al., 2016; Yu et al., 2017)

Abbreviations: DAMPs: danger-associated molecular patterns, ER: endoplasmatic reticulum, ICs: Immune cells, KCs: Kupffer cells, NLRP3: NLR family pyrin domain containing 3; NKT: Natural killer T cells, ROS: reactive oxygen species.

a great potential of liver function maintenance in younger recipients.

5. Liver transplant and marginal donors. The quest of biological age markers

The high request of organs moves toward an increased use of marginal donors, including organs from old or very old donors usually transplanted into younger recipients (Durand et al., 2018; Lué et al., 2016). Within the context of orthotopic liver transplants, many clinical data suggest that livers from aged donors do have function and duration comparable to those achievable with livers from younger donors (Bertuzzo et al., 2017; Cescon et al., 2003, 2008; Thorsen et al., 2015). This clinical evidence clearly emerged during last decade along with the improvement of organ maintenance techniques, such as the use of perfusion machines able to perform different modes of dynamic organ preservation including hypothermic and normothermic conditions (Boteon et al., 2018; Czigany et al., 2018). A recent review, based on datasets from US, shows that long-term survival, comparing young and old liver donors, has considerably been improved over the study period (from 1990 up to 2014) (Gao et al., 2018). Accordingly, the use of liver obtained from very old donors (≥80 years) has successfully been applied in Italy since many years and in different hospital transplant units, reaching also the exceptional cases of centenarian living livers (Salizzoni et al., 2017). This achievement reinforces the safety of evaluating all donor ages for potential utilization in a liver transplant, and evidences the uniqueness of the liver as an organ, which has life extension potentialities. In fact, important scores are evaluated for liver donors and recipient allocation, such as the Model for End-Stage Liver Disease (MELD) score and donor risk index (DIR), aiming at the improvement of graft duration (Bertuzzo et al., 2017; Flores and Asrani, 2017).

Recently, some conflicting results on graft duration and outcomes after transplantation of liver from old donors emerged (Dasari et al., 2017; Dayoub et al., 2018), but many variables can explain the different results, such as the organ preservation protocols, the expertise of each surgery unit, the type of organ allocation procedure, the immune-suppression therapy, and donor-recipient age-mismatches effects. The latter is a topic rather neglected despite its great biological potential and clinical interest (Lau et al., 2019).

In this regard, our team has shown that age-related miR-31-5p, 141-3p, 200c-3p expression, significantly increases in liver when a relatively young organ is transplanted into a relatively older recipient. Noteworthy, we were not able to document the reverse effect in the number of cases available, as shown in Fig. 4 (Capri et al., 2017). Indeed, when a liver from an old donor is transplanted into a younger recipient, the expression of the three above-mentioned miRs did not change. These data suggest that aging phenotype can be “transmitted/propagated” more easily than young phenotype via recipient (micro)-environment at least in the complex setting of liver transplantation. Different results have been obtained in hematopoietic stem cell transplantation, where DNA methylation age of donor seems to be unaffected by recipients’ age (Søraas et al., 2019). Nevertheless, data are still scanty in this field and particularly in the case of very old donors (> 80 years) that in exceptional cases may become centenarian livers into the younger recipient (Fig. 4) (Salizzoni et al., 2017), thus highlighting the positive interaction with the younger recipients and the need of grasping the effect of donor/recipient-age interaction. This interaction was previously demonstrated in heterochronic parabiosis experiments in mice model, both in the brain (Villeda et al., 2011) and in the liver (Conboy et al., 2005) and similarly, transplant conditions may resemble heterochronic parabiosis experiments.

Undeniably, biological and chronological age can differ substantially and chronological age is becoming an inadequate parameter to summarize and label health and clinical status of individuals or organs (Capri et al., 2018). Biological age of the recipients, measured by glycoage test, i.e. evaluating the ratio of two serum N-glycan isoforms (Vanhooren et al., 2007), is older than healthy-never transplanted-age-matched controls and “rejuvenate” after transplantation independently of donor age (Capri et al., 2017). This condition may be influenced by renewed liver function that recovers the normal profile of N-glycans in the serum proteins. Noteworthy data suggest the applicability of N-glycan serum profile to investigate liver function and diseases (de Oliveira et al., 2018; Kamiyama et al., 2013).

In addition, the role of liver-gut axis in the organ transplant is a field of extreme interest, not yet fully investigated. Surgery events may affect gut permeability (De Vlaminck et al., 2013), thus a strong role of liver-gut axis in graft successful can be predicted. In fact, intestine epithelium is a central coordinator of mucosal immunity and immune response could be modulated based on gut-microbiome biodiversity (Allaire et al., 2018), thus new protocols of immune tolerance could ultimately be developed. Further, KCs play a central role to up-take damaged molecules originated from engraftment and enhance the response to allogenic or self-immune cells (Li et al., 2017). As described above, danger molecules and DAMPs/PRRs activations are at the core of aging process and age-related diseases (Franceschi et al., 2017a). Similarly, liver aging, liver disease onset until end-stage organ and transplant rejection mechanisms may be considered as an accelerated process of tissue/organ damage mediated by DAMPs/PRRs activations.

Furthermore, it is relevant to outline the potential role of TCs, not yet grasped in transplant context. Three-dimensional TC network is an

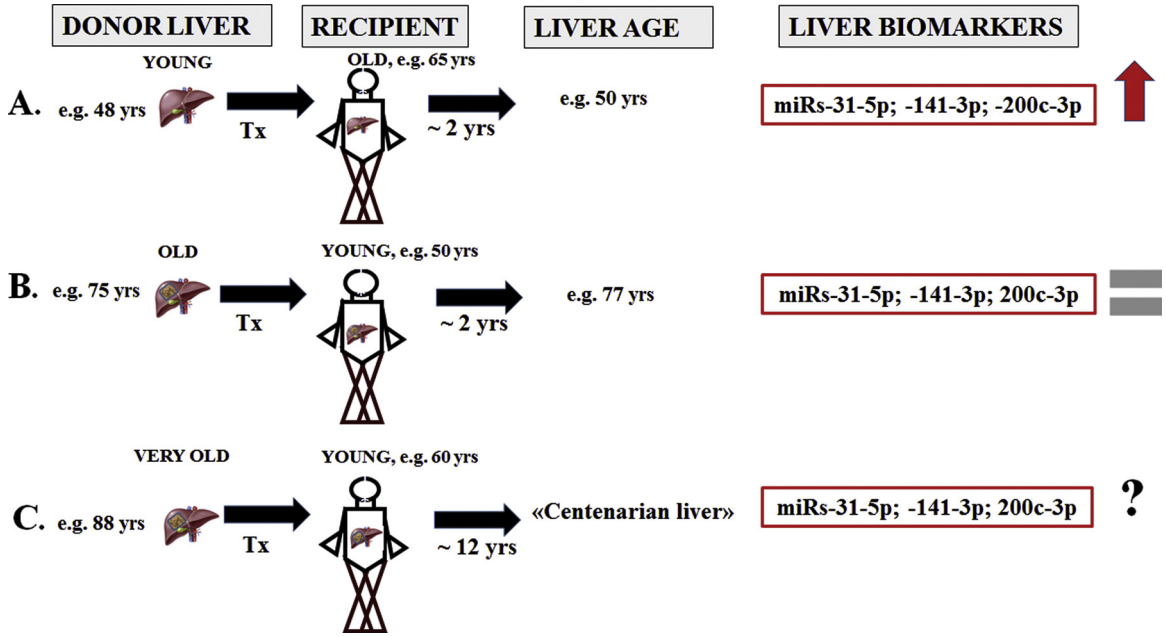

Fig. 4. Effect of donor-recipient age-mismatches on miR-expression.
MiRs-31-5p;-141-3p; -200c-3p expression increases in age-mismatch A; does not change in age-mismatch B. No data are currently available for age-mismatch C. Examples of donor-recipient ages are provided.

evolutionarily conserved system that in invertebrate (e.g. leeches) plays an important role in repair, regenerative processes and graft (Pulze et al., 2017). Thus, these results seem to withstand the possible role of TCs also in human liver graft, but data are required in this field.

Overall, combination of biomarkers, beyond liver-specific functional parameters, should be adopted to improve, when possible, the proper allocation of organs *vs* recipients as follows: i. epigenetics changes, such as histone modifications, DNA methylation profiles, tissue and circulating miRs; ii. N-glycan profiles; iii. Serum metabolites; iv. Gut microbiome species and their products. Other biomarkers are mentioned in Fig. 2. Combination of them could be extremely relevant to identify the biological ages of both liver donor and recipient at two different levels: the former at organ level (donor) and the latter at systemic level (recipient). It is expected that younger recipients may positively influence the transplant success, even if many other variables are involved besides the interactions of biological ages between organ and recipient, such as immune suppression efficacy, interactions of ICs from donor livers and recipients up to the chimera stabilization.

Certainly, the individual response is the other side of the coin involving the individual-specific (personalized) immunological and cellular responses, such as repair process efficacy, remodeling and adaptation largely modulated by personal "immunobiography" (Franceschi et al., 2017b), which could predict the final attainment of the therapy/transplant.

6. Conclusion

In accordance with the new Geroscience, inflammation (or inflammaging) is one out of seven highly connected mechanistic pillars involved in age-related pathology development. In the case of liver, chronic inflammation sustains the progression of different pathological levels and aging process may in turn favor their progression. In absence of inflammatory status, liver seems to have a physiological aging largely slowed-down in comparison with other organs, probably for its intrinsic feature of regeneration capacity. Similarly, chronic renal disease is sustained by the same inflammatory stimuli affecting both the organ and the systemic level (Kooman et al., 2017).

The possibility to counteract liver disease development largely depends on life styles and/or environments that each individual has and/or inhabits, respectively. Caloric restricted or balanced diet (Harrison and Day, 2007), reduced/abolished alcohol consumption and gut microbiome biodiversity have positive effects on liver function (Ma et al., 2017) and may decelerate liver aging process. Importantly, the personal "immunobiography" of each individual including social-economic status, may mitigate or accelerate liver disease onset (Fig. 5) likely through the modulation of inflammaging. A complex predictive model could be pursued based on specific variables (such as age, infections, antibody profiles against virus/bacteria, BMI, gender, life style habits, allergy, gut microbiome biodiversity, use of drugs, education, income, etc.) in longitudinal cohorts.

When liver is at the end stage, liver transplantation is today the elective cure, even if a relevant progress of regenerative medicine to avoid transplant is expected. This emerging field offers innovative methods of cell therapy and tissue/organ engineering as a novel approach to liver disease treatment (Rashidi et al., 2018). Liver regeneration is spontaneously activated after injury and can be further stimulated by cell therapy with hepatocytes, hematopoietic stem cells, human liver stem cells (Bruno et al., 2016), mesenchymal stem cells and recently with amniotic epithelial cells (Serra et al., 2018). However, many studies aimed at improving the outcomes of cell therapy of liver diseases are still underway (Kholodenko and Yarygin, 2017). Importantly, treatment of chronic hepatitis C virus (HCV) infection has been revolutionized with the development of direct-acting antiviral agents and highly positive results have been obtained so far, thus predicting to escape liver transplantation for HCV in the close future (Vermehren et al., 2018).

Overall, many unsolved questions emerge in the liver transplant context. In particular, burning questions are the following: i) The potentiality of the younger recipient on "rejuvenating" a liver obtained from an old donor, a phenomenon that we did not observe (Capri et al., 2017), but cannot be excluded in a larger sample (including different times of follow-up) and by means of other biomarkers. ii) The complexity of the interaction between the biological ages of donors and recipients, where a systemic rejuvenation effect of a young liver on the older recipient should be further pursued with adequate tools. iii) The quest of new biomarkers able to identify the biological age of the organ

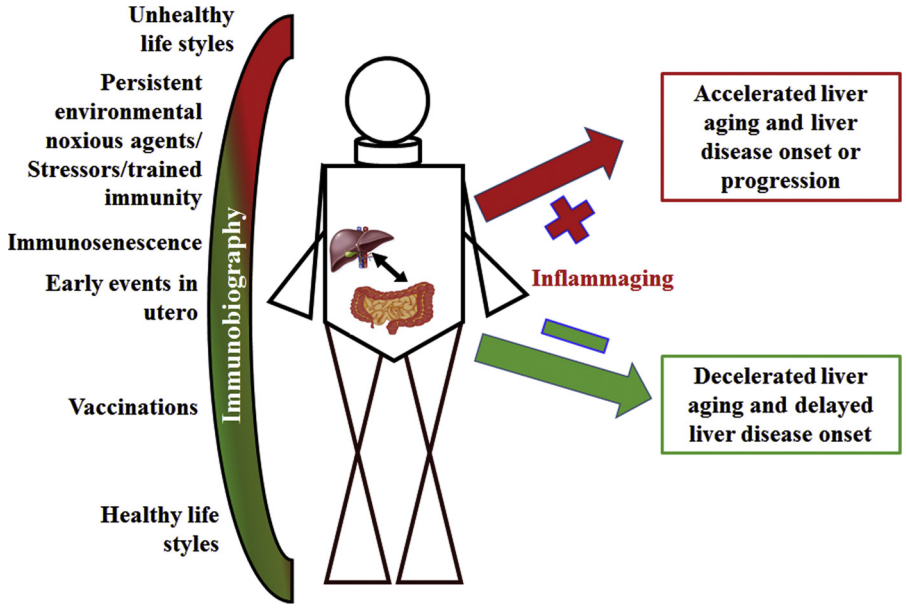

Fig. 5. Immunobiography, inflammaging impact on liver diseases onset and progression.
Immunobiography may mitigate or favor the onset/progression of liver diseases modulating inflammaging level.

and the biological age of recipient at systemic level.

In the future the use of bio-engineered organs is expected, but not in a short time and not with cost accessible to everyone. In the meantime, the idea that biological age-mismatch between donor and recipient could modulate the duration of the graft at least until the complete engraftment and eventually could favor the weaning of immunosuppressive therapy or operational tolerance seems extremely exciting. Further studies on biological ages of donors/recipients and their modelling in time series analyses could be essential for the prediction of engraftment successful and years-prolonged function.

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