Mechanisms of Ageing and Development 177 (2019) 150–156

Contents lists available at ScienceDirect

Mechanisms of Ageing and Development

journal homepage: www.elsevier.com/locate/mechagedev

Age-related evolutions of the dermis: Clinical signs, fibroblast and extracellular matrix dynamics

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ARTICLE INFO

Keywords:
Dermis
Ageing
Development
Fibroblasts
Papillary
Reticular
Extracellular matrix

ABSTRACT

Ageing is today a major societal concern that is intrinsically associated with the increase of life expectancy. Outside the context of severe degenerative diseases that affect the elderly populations, normal visible signs of ageing, notably skin sagging and wrinkles, influence the social and individual perception of peoples. Accordingly, there is a strong demand for researches on skin ageing. Deciphering the cellular and molecular processes of skin evolution through ageing is thus an active scientific domain, at the frontier of tissue developmental and ageing biology. The focus of the present article is to provide an overview of the current knowledge concerning the evolution of dermis characteristics at different life stages, from intra-uterine to post-natal life. The description will integrate stage-specific and age-related changes in dermis characteristics at the tissue, cell, and molecular levels.

1. Roots of the ageing concept

Referring to Greek mythology, the quest for immortality is embodied in the story of Eos, the immortal goddess of dawn. She falls madly in love with Tithon, a mortal human. Not supporting the idea of seeing him die, she claims for him eternity. Zeus agrees, but poor Eos realizes her mistake too late, as what she wanted for Tithon was not eternity but eternal youth. She will therefore be condemned to see him eternally grow old. This myth of ancient Greece refers directly to the current perception of ageing: accept the temporary nature of life, while differing as long as possible the appearance of the signs of ageing. Today, in industrialized countries, this quest seems strongly motivated by the fear of social exclusion. Indeed, a study conducted on a cohort of 1713 American women, over 50 years old and mostly of Caucasian type, highlights a great psychological suffering based both on the image that these women have of themselves but also on the degrading image that the rest of society sends back to them. More than 50% of these women reported the perception of physical changes that occur during ageing, notably sagging skin and wrinkles. Their cognitive adaptations to the physical experience of ageing and the psychological experience of body image altered in parallel (Hofmeier et al., 2017). This point is extremely important because it shows how much women correlate the initiation of their ageing-related psychological malaise with the appearance of visible signs revealing their age. Indeed, if we ignore the pigment spots, wrinkles and sagging are the 2 main clinical disorders that signify skin ageing. Even though atlases are now available for scoring the severity of these clinical disorders (Bazin and Doublet, 2007; Bazin and Flament, 2010; Bazin et al., 2012), we still have insufficient information on the biological processes involved in the appearance and perpetuation of skin wrinkles and sagging.

2. The wrinkle

The histological description of the wrinkle made by Contet-Audonneau et al. shows that the epidermis and the superficial dermis are modified below the wrinkle (Contet-Audonneau et al., 1999). At the epidermal level, a decrease in the quality of keratinocyte differentiation is observed. Expression levels of filaggrin, transglutaminase I, and desmoplakins are reduced, and the epidermis thickness is decreased. The desquamation process is also altered. The *stratum corneum* is often thickened, as the result of accumulation of corneocytes, thus forming a horny plug. The dermo-epidermal junction is atrophied, exhibiting a

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https://doi.org/10.1016/j.mad.2018.03.006
Received 26 February 2018; Accepted 12 March 2018
Available online 13 March 2018
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decrease in the expression of collagen IV and VII. Organization of the papillary dermis (superficial part of the dermis) is also modified. In this zone, there is a virtual disappearance of chondroitin sulphates, which are known to ensure water retention in skin, and alteration of oxytalan fibers, which are thin fibers of the elastic network, organized perpendicularly to the skin surface. Under the wrinkle, the oxytalan fibers are either sparser or have disappeared. In addition, a change in the orientation of collagen fibers has been reported in the margin of the wrinkle (Scott and Green, 2004). In this study performed on periorbital wrinkles, the authors described that on the wrinkle sides, collagen fibers run parallel to the fold, whereas at the bottom, they form an accumulation of fibers mostly perpendicular to the wrinkle. Finally, dermal and hypodermic atrophy is observed below the wrinkle (Aubinière, 1985; Elnekave, 1989), suggesting that tissue organization is altered over the entire skin. For in-depth review on wrinkle, see Humbert et al. (Humbert et al., 2012).

3. Skin sagging

Two theories are proposed to explain the phenomenon of face skin sagging associated with ageing. One involves gravity as a causal factor, and the second associates volumetric changes with skin sagging. Historically, the more intuitive gravitational theory was firstly proposed, which explains a vertical descent of soft tissues, secondary to a progressive weakening of their ligamentary attachment (for anatomic description see Furnas, 1989). Weakening of the ligaments that anchor the dermis to the deep osteo-fibrous structures of the face is proposed to be due to the repeated muscle activity inherent in facial movements such as the smile, resulting in the descent of the soft tissue and the falling aspect of the face (Stuzin et al., 1992). The volumetric theory emerged in the early 2000s. It is based on the fact that the use of fillers (collagen fillers, hyaluronic acid…) in aesthetic surgery leads to satisfactory results in terms of reduction of apparent age. Accordingly, it has been proposed that the apparent age of the face depends on the coexistence of hypertrophic and atrophic skin zones. The resulting 'hills and valley' pattern appears as skin irregularities that visually identify aged faces (Donofrio, 2000). This volumetric theory is supported by the comparison of face photographs taken with a delta age between 10 and 50 years between the 2 shots. This long-term follow-up indicated that the border of the pigmented lid skin, the thicker cheek skin, the lid-cheek junction, moles, and other markers on the upper midface are remarkably stable in position over time. These findings suggest that vertical descent of skin and subcutaneous tissue is not necessarily a major component of ageing (Lambros, 2007). An anatomical study of the face fat masses also sustains the volumetric theory of sagging (Mertens et al., 2016). This study conducted on 40 dissected cadavers of different genders, ages, and body-mass indexes, showed that the mean weight of the deep fat compartments was 2-fold lower in the group with subjects aged > 75 years. Regarding the superficial fat compartments, a moderate non-significant decrease was observed. Accordingly, authors conclude that fat atrophy affects preferentially the deep midface compartments thought ageing, and that this loss of fat masses is at the origin of volume changes. Moreover, alterations of skin mechanical properties due to ageing would no longer allow it to adjust to these new contours. Indeed, a strong correlation between the modification of elastic parameters of the skin and sagging has been demonstrated in a clinical study conducted on 24 individuals spread over 3 age groups (30/40, 50/60, 70/80 years-old) (Trojahn et al., 2015). Skin extensibility, residual deformation, and immediate elasticity, increased with ageing, whereas elastic recovery decreased. In conclusion, the combination of the two processes: alteration of skin mechanical properties and decrease of fat masses, would therefore be responsible for the process of face sagging.

4. Prenatal development of the dermis

An important part of the mechanical properties of the skin depends on dermis composition, structure and organization. Precursor cells of the dermis have different embryonic origins, depending of body topology. In the head, dermal precursors emerge from neural crests (Le Lièvre and Le Douarin, 1975), while they derive from the medial and lateral halves of somites in the rest of the body (Ben-Yair et al., 2003). Interestingly, in the adult organism, cutaneous fibroblasts maintain embryonic patterns of *HOX* gene expression related to the anatomic anterior-posterior and proximal-distal axes (Rinn et al., 2006, 2008). During human development, the dermis passes through 3 successive organizational phases: the cellular dermis (5–8 weeks of gestational age), the cellular to fibrous transition (9–12 weeks of the gestational age), and the fibrous dermis (starting from than 13 weeks of estimated gestational age) (histological data described below were extracted from Smith et al., 1982; Smith and Holbrook, 1986).

During the 'cellular dermis' developmental step (5–8 weeks), dermis appears as an open cellular network that seemed to be devoid of fibrous extracellular matrix. Dermal cells exhibit a stellate morphology, are highly connected, contain an abundant quantity of glycogen, and are poorly filled with rough endoplasmic reticulum and Golgi complex. As described for cartilage and bone at the same step of development (Caplan et al., 1983), extracellular matrix is essentially composed of hyaluronic acid that retains high water content, and is poor in sulfated glycosaminoglycans. Thin collagen fibrils (type I and III) are the first to appear. Around 6–8 weeks, cell structure evolves to a higher ultrastructuration, with more abundant endoplasmic reticulum and Golgi apparatus. At this step, all dermal cells express the neuroepithelial stem cell marker 'nestin' and the component of intermediate filament of cytoskeleton 'vimentin' (Sellheyer and Krahl, 2010).

During the 'cellular to fibrous transition' (9–12 weeks of the gestational age), establishment of a large subcutaneous plexus of blood vessel and nerves that will demarcate the dermis from the subcutaneous area occurs. In parallel, fibrous collagen accumulate, leading to an increase of individualized collagen fibrils (25–40 nm) and a greater numbers of fibrils associated into bundles. Organization of the extracellular matrix starts to diverge between the upper and the deeper regions of the dermis, which initiates the development of the papillary and reticular dermis (week 12 of gestation) (Smith and Holbrook, 1982).

During the 'fibrous dermis' stage (13 weeks of gestation and later), accumulation of the fibrous part of the matrix continues and leads to a histological organization becoming equivalent to a miniature version of post-natal dermis. Formation of the *rete subpapillae plexus* that will separate the papillary and reticular dermis occurs at week 14 of gestation. In addition, characteristics of the fibroblasts present within these dermal areas start to be distinct. In mice, Driskell et al. have investigated the phylogeny of two fibroblast lineages during the intrauterine life, and have shown that dermal fibroblasts segregate into the papillary (Fp) and reticular (Fr) fibroblast sub-types at the stage 16.5 days of development, then ensuring distinct roles in the constitution of more mature skin architecture. The embryonic Fp sub-population is at the origin of the upper dermal region, the *arrector pili* muscle, and the dermal papilla that regulates hair growth. The embryonic Fr sub-population contributes to formation of the lower dermis and hypodermis (Driskell et al., 2013). This kind of investigations, based on genetically modified animals, is evidently impossible to conduct in human. Nevertheless, a study of Sellheyer and Krahl on the kinetics of nestin expression during human fetal development has shown that fibroblasts present in the reticular area lose expression of this biomarker before fibroblasts present in the papillary area, suggesting likewise an early phenotypic separation of these two cell subpopulations (Sellheyer and Krahl, 2010).

5. Prenatal setup of the dermal extracellular matrix scaffold

Regarding the fibrous part of the dermis extracellular matrix, the ratio between the collagen I and III will progressively be inverted

during prenatal development. While this ratio is in favor of collagen III (ratio: 0.6/1) during the first weeks of the 2nd trimester of pregnancy, it will reach 2.7/1 in favor of collagen I during the 3rd trimester (Epstein, 1974; Sykes et al., 1976; Sykes et al., 1977). In parallel, a decrease in the hydroxylation rate of collagen I and III is observed, due to a decrease in the activity of lysyl oxidase, which activity decreases by 5 between the 4th and 7th month of pregnancy (Anttinen et al., 1973). This change leads to a marked increase of collagen fibril diameter, which can reach 25–60 nm in the papillary dermis, and 45–60 nm in the reticular dermis, at the end of pregnancy (Smith et al., 1982). The monitoring of establishment of the dermal elastic network has been a source of controversy. Its observation using electron microscopy would be only possible from the 6th month of pregnancy, and exclusively in the reticular zone. At earlier developmental stages, this network may be still immature and devoid of mechanical function (Smith et al., 1982). Concerning proteoglycans, hyaluronic acid is progressively replaced by chondroitin sulphates such as versican, which strongly co-localizes with elastic fibers (Zimmermann et al., 1994), by dermatan sulphates such as decorin, which strongly co-localizes with collagen fibers (Brown and Vogel, 1989), and to a lesser extent by biglycans (Carrino et al., 2000). Chondroitin sulphates concentrate preferentially in the papillary region (Coolen et al., 2010). During the fetal life, analysis of the carbohydrate portion of these molecules revealed predominant forms of glycosaminoglycans. Concerning versican, 3 chains represent the vast majority of isolatable forms: ΔDi6S (2-acetamido-2-deoxy-3-*O*-(β-D-*gluco*-4-enepyranosyluronic acid)-6-*O*-sulfo d-galactose) representing 54–62% of versicans, ΔDi4S (2-acetamido-2-deoxy-3-*O*-(β-D-*gluco*-4-enepyranosyluronic acid)-4-*O*-sulpho-D-galactose) representing 21–24%, and finally ΔDiOS (2-acetamido-2-deoxy-3-*O*-(β-D-*gluco*-4-enepyranosyluronic acid)-D-galactose), representing 14–18% depending on individuals. Concerning decorin, 83–85% correspond to the form ΔDi4S (2-acetamido-2-deoxy-3-*O*-(β-D-*gluco*-4-enepyranosyluronic acid)-4-*O*-sulpho-D-galactose), the rest corresponding to 8 other chain types (Carrino et al., 2011).

6. Dermis in the newborn

Birth gives rise to a major environmental change, which notably leads to the end of the situation of aquatic life, the newborn being exposes to the atmosphere. The major immediate vital physiological changes associated with birth include the lung function and changes in cardiac flow. Concerning skin, the production of *vernix caseosa* helps in the transition from the aqueous *in utero* environment to the dry extra uterine environment (Hoath, 2004), but cutaneous reactions can occur. Erythema toxicum neonatorum is a benign, self-limited, transient and evanescent eruption that occurs in approximately 48%–72% of full-term infants (Roques et al., 2017). Millia is characterized by 1- to 2-mm pearly white or yellow papules caused by retention of keratin within the dermis that occur in up to 50% of newborns (Paller et al., 2006). From a histological point of view, the overall organization of the skin becomes globally similar to that of an adult (Smith et al., 1982). In contrast, the skin of newborns transiently presents its own functional characteristics, which are in some aspects intermediate between fetal and adult cutaneous physiology. Even if the *stratum corneum* maturation is still incomplete at the stage of birth, the permeability barrier becomes functional (Visscher et al., 2015; Fluhr et al., 2012). A notable functional characteristic associated with this transition phase concerns skin wound healing capacity. Indeed, it has been observed that, in newborns, wound healing generates only very slight scars in comparison with what happens to few weeks older infants. These descriptions were made during the post-operative long-term follow-up of plastic surgery, in the context of lip cleft reconstruction. Thus, 6 years after surgery, scars are almost invisible on children operated in the first 10 days after birth, contrary to what is observed in children with reconstruction performed later (Borsky et al., 2012; Krejčí et al., 2015). Specific cellular properties including phenotypic parameters, secretome, contractility, that are still not fully characterized, may explain the capacity of the skin from very young infants for scarless wound-healing.

7. Fetal and newborn dermis and wound-healing

The regenerative potential of fetus skin is known to be highly efficient. Indeed, cutaneous wound healing *in utero* does not generate any scar, which led to the terminology 'fetal scarless wound healing' (Rowlatt, 1979; Lorenz et al., 1993). A cellular feature of the fetal dermis is that the myofibroblastic phenotype is much less present than in children and adults (Parekh and Hebda, 2017). Fetal dermal fibroblasts exhibit a reduced contractile capacity (Moulin et al., 2001) but a high secretory activity of type I and III collagens. In case of skin wounding (*in utero* surgery), neosynthesized type III collagen by fetal fibroblasts is deposited in a reticular network that is indistinguishable from that of uninjured skin, whereas later in life, the predominant secretion of type I collagen during wound-healing leads to regenerating tissue with more strength and rigidity that correlate with the apparition of the scars (Beanes et al., 2002). In addition, the expression of the different isoforms of the growth factor TGF-β family, which play a major role in healing, is also different. In particular, expression of TGF-β3 is more abundant during fetal scarless wound-healing than during skin scarring at later stages of life (for review, see Larson et al., 2010). With regard to the very narrow time window corresponding to birth and the few following days, only few studies are found, analyzing skin adaptation to live in a non-aqueous environment, and its scarring properties. Interestingly, Krejčí et al. (2015) have reported that the cellular phenotypes present in the dermis of human neonates (less than 10 days after birth) differ from those collected from the skin of older infants (from 3 months to 9 years old). A marked difference concerned the expression levels of fibronectin and tenascin, two proteins involved in healing processes, which were both increased in infants older than 3 months, compared to neonates (Krejčí et al., 2015). Another study has shown that, even if neonate fibroblasts differ from adult fibroblasts, they show properties not equivalent to a fetal status. In particular, neonate dermal fibroblasts secrete more collagen V and less collagen III, compared to the fetal stage (Gosiewska et al., 2001). These authors have also reported that synthesis of decorin, which is involved in the regulation of collagen fiber organization (diameter and stability), is controlled in a different manner in neonate and fetal fibroblasts. In particular, neonate fibroblasts respond to TGF-β1 by increasing the synthesis of decorin, while this factor has an opposite effect on fetal fibroblasts, repressing decorin expression. Consequently, different decorin levels in the neonate and fetal dermal matrix environment contribute a parameter distinguishing the two life stages, with a direct impact on collagen fiber characteristics (Danielson et al., 1997; Reed and Iozzo, 2002). These results suggest specific mechanical properties of the scar in the newborn.

8. Dermis maturation from birth to adulthood

Following the pivotal event of birth, the skin will continue to evolve both in terms of tissue organization and at a molecular level. In addition to the role of intrinsic physiological mechanisms, this evolution can be impacted by exposition to exogenous stress factors, such as UV irradiation, pollution, and tobacco. Notably, it is well established that repeated exposures to UV rays can promote disorders affecting the collagen network and elastic fibers (elastosis), which skin alterations are termed as photo-ageing (Kawabata et al., 2014). This paragraph will be focused on the intrinsic factors responsible for dermis ageing, from birth to the age of fifty. Ultrastructural and morphometric analyzes converge to position at this age the appearance of clear chrono-aging-related signatures (Quaglino et al., 1996; Marcos-Garcés et al., 2014), which will be described in the following paragraph. In a histological study conducted on a cohort of 45 individuals aged between a few

months and 95 years, Marcos-Garcés et al. (2014) have described a significant increase in the thickness of the abdominal dermis until the age of about 50 years (Marcos-Garcés et al., 2014). Thickness of the reticular dermis increases by about 2 folds, with an average thickness in the first months of life around of 1.6 mm, reaching about 3.2 mm at 50 years. In parallel, thickness of the papillary dermis increases, but to a lesser extent (about 20 µm gain). Concerning the macroscopic organization of collagen bundles, the dermis papillary and reticular areas also evolve differently. While mean thickness of collagen bundle decreases from 1.0 µm to 0.8 µm in the papillary area, this parameter increases from 5 µm to 10 µm in the reticular area.

During the first 10 years of childhood, dermis markedly evolves at a cellular level. In the interfollicular dermis areas, fibroblast density decreases from 4000 cells/mm^2 to around 2000 cells/mm^2 (Gunin et al., 2011), which then remains globally constant during the whole life. Dermal fibroblasts are mostly in a quiescent post-mitotic state during post-natal life (Coolen et al., 2010; Gunin et al., 2011). In addition, it has been reported that the potential of skin-derived progenitor cells (SKP) present in the hair follicle dermal papilla markedly decreases after the age of 12 years (Gago et al., 2009). The involvement of this stem cell reservoir has in particular been shown for healing, at least in mouse (Biernaskie et al., 2009). In young adults, the phenotypic separation between papillary (Fp) and reticular (Fr) fibroblasts is clear, with distinct transcriptional signatures, in particular suggesting different extracellular matrix component synthesis (Nauroy et al., 2017). At a functional level, Fp and Fr fibroblasts from adult human skin exhibit different growth and contractile capacities, and do not have equivalent capacities for promoting epidermal reconstruction (Mine et al., 2008). Notably, Fr exhibit a more efficient capacity for collagen lattice contraction that Fp, although Fp promote a better epidermis organization and differentiation by keratinocytes, in a reconstructed skin model. Taken together, these observations suggest that the Fp and Fr subpopulations exert distinct functions in the maintenance of adult skin homeostasis. Fp may contribute to epidermis maintenance, although Fr may have more important functions in skin the mechanical properties.

9. Extracellular matrix in adult dermis

Dermal extracellular matrix ensures an essential role in skin cohesion. In adult skin, it comprises the collagen network as a major constituent that corresponds to 70–80% of the skin dry weight, the elastic fiber network, proteoglycans, glycosaminoglycans (GAGs), and water. This later component is functionally important, as its interactions with GAGs such as hyaluronic acid allow generating a large osmotic swelling pressure conferring skin stiffness and resistance to the deformation (Juhlin, 1997). Concerning the collagen network, adult dermis contains in majority fibrillary collagens, including type I (80% of all collagens), type III (15%), and type V collagen (5%). Types I and III collagens constitute the principal skeleton that drives dermis matrix organization. In addition, minority collagen types influence the characteristics of this network, which can differ according to specific intra-tissue localizations. These subtle modulations of dermis matrix architecture are notably ensured by the family of 'fibril-associated collagens with interrupted triple helices' (FACIT) that comprises type XII, type XIV, and type XVI collagens. Preferential localization of type XII and type XVI collagens is the papillary area, whereas type XIV collagen is mainly located within the reticular area (Garrone et al., 1997; Ruggiero et al., 2005). FACIT collagens along the surface of fibrils have been show to affect fiber suprastructures and tissue biomechanics in the tendon (Ansorge et al., 2009; Zhang et al., 2003). It is proposed that these proteins are capable to bridge collagen I and III fibrils with proteoglycans such as decorin and perlecan, which are known to regulate fibrillogenesis (Reed and Iozzo, 2002). Within the complex structure that is extracellular matrix, different 'regulators' including tenascin X, perlecan, decorin, and lumican, can influence the rate of assembly, size and structure of collagen fibril (review by Kadler et al., 2008; Schönherr and Hausser, 2000). The distribution within the dermis of these matrix structure regulators is heterogeneous. For example, perlecan is mainly localized in proximity with the *basal lamina* (Oh et al., 2011), although decorin is present within the whole dermis with a higher abundance in the papillary dermis (Schönherr et al., 1993). In addition to the 'regulators' of fibrils expansion and size, 'nucleators' initiate collagen incorporation into the fibrils. Collagens V and XI, which are respectively present in the papillary and reticular dermis (Nauroy et al., 2017), are considered as nucleators, due to their prime location at the fibril core (Kadler et al., 2008). Finally, in addition to their role in the regulation of the collagen network assembly, FACIT collagens can participate to interactions between the collagen and elastic fiber networks. Collagen XVI, which is predominantly located within the superficial region of the papillary dermis, colocalizes with fibrillin-1, a major component of the elastic network microfibrils (Kassner et al., 2003).

As observed for the collagen network, the organization of the elastic fiber network differs according to specific dermis sublocalizations. In the papillary area, thin elastic fibers (elaunin fibers) are perpendicular to the epidermis, and merge with the microfibrillar cascade (oxytalan fibers) that intercales into the dermal-epidermal junction. In contrast, in the reticular area, elastic fibers are thick and parallel to the epidermis. Oxytalan fibers are essentially composed of fibrillin that take rod conformation in the presence of Ca^{2+}. Structural integrity of oxytalan fibers depends on interactions with proteins of the 'microfibril-associated glycoprotein' (MAGP) family, and their integration within the collagen matrix involves intractions with proteoglycans such as decorin and biglycan. At the interface between oxytalan and elaunin fibers, the 'elastin microfibrillar interface protein' (emilin) family is proposed to regulate the accumulation of tropoelastin around elastic microfibrils (review by Kielty et al., 2002). As for the collagen network, organization of the elastic network may be influenced by 'regulators' such as emilins. Finally, a parameter that distinguishes superficial and deep dermis is the fibrillin-elastin ratio. Elastin is almost absent from oxytalan fibers of the superficial part of the papillary dermis. The two proteins are present in equal quantities in elaunin fibers of the papillary dermis and superficial reticular dermis. In the deep reticular dermis, fibers are essentially composed of elastin (Naylor et al., 2011).

10. Dermis ageing at the tissue and cell levels

From the age of 50, the quality of the dermis gradually deteriorates. Thickness decreases, in parallel with progressive attenuation and loss of dermal-epidermal junction undulations (Mizukoshi et al., 2015). Age-related alteration of the papillary area was documented by medical echography. Indeed this imaging method revealed the existence of a sub-epithelial non echogenic band (SENEB) whose thickness increases with ageing (de Rigal et al., 1989). This modification of the echogenic properties of the tissue may sign alterations of the matrix organization and composition, with decrease in perlecan and hyaluronic acid (Oh et al., 2011) and collagen fibrils' density (Ahmed et al., 2017). In parallel, reticular dermis is also affected. For example, reticular dermis thickness is around 3.2 mm in abdominal skin of 50 years-old peoples, and is decreased to around 1.3 mm in centenarians (Marcos-Garcös et al., 2014). Concurrently with dermis atrophy, the thickness of collagen bundles decreases and the space between bundles increases, which leads to a reduction of tissue density both in the papillary and reticular areas (Marcos-Garcés et al., 2014). Consequently, dermis atrophy is associated with dermatoporosis in 30% of elderly peoples, which clinical signs are extreme skin weakening, lacerations, and dissecting hematomas in the most severe cases (Kaya and Saurat, 2007). At the cell level, a change in the quality of fibroblast anchoring in the extracellular matrix is observed *in situ*. The open space surrounding the cells increases whereas the number of contacts between cells and collagen fibers decreases (Varani et al., 2006), with a possible deleterious impact on traction forces and dermis cohesion. Comparison of the

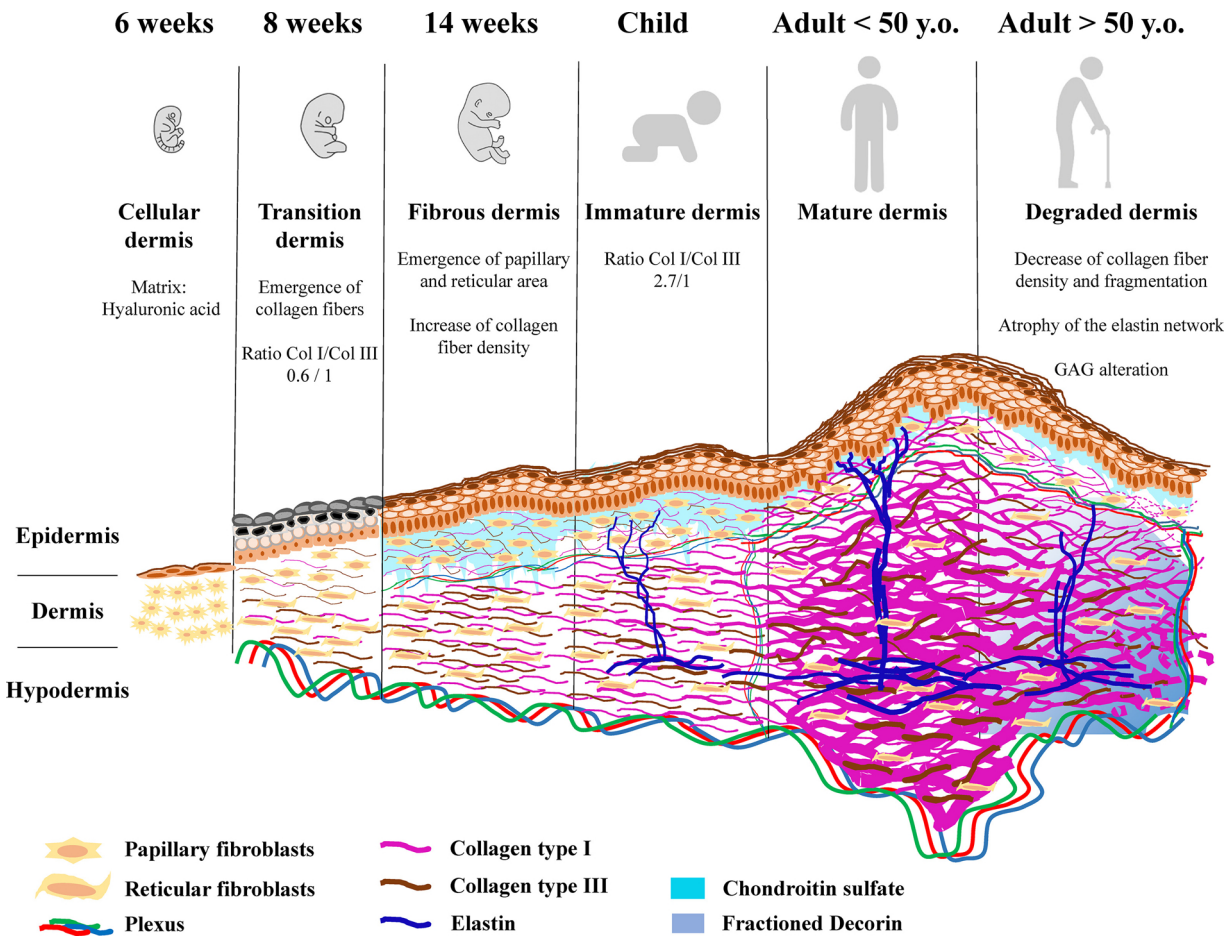

Fig. 1. Schematic representation of dermis evolution during human development and ageing.

contractile capacity of Fp fibroblasts isolated from skin biopsies of young and old adult individuals in a lattice contraction *in vitro* assay indicated an increased contractility in cells from old skin (Mine et al., 2008), suggesting possible compensatory mechanisms. In addition, considering unfractionated dermal fibroblasts, it has been shown that these cells evolve with age in their secretory profile. Among 998 identified secreted proteins, 77 exhibited an age-dependent secretion pattern, and were named 'skin aging-associated secreted proteins' (SAASPs) (Waldera Lupa et al., 2015). Interestingly, some of the SAASPs are also found in a signature identified by Coppé et al. in the context of induced senescence (Coppé et al., 2008), including proteins involved in matrix degradation and proinflammatory processes. Others SAASPs, including proteins involved in metabolic regulations and adherens junction interactions, are not found in the senescence-associated signature. At the level of fibroblast subpopulations, different phenotypic and functional specificities of Fp and Fr cells have been described at the fetal stage (Driskell et al., 2013) and in adult skin (Mine et al., 2008; Janson et al., 2012; Nauroy et al., 2017). With regard to adult skin ageing, changes affecting Fp and Fr cell characteristics have been reported, including modifications in their secretion profiles of cytokines, matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) (Mine et al., 2008). However, full understanding of their evolution during ageing would require further investigations, notably molecular analyses at the global genomic and epigenomic levels. The role of epigenetic regulatory mechanisms in the biology of the epidermis is considered with an increasing interest (Botchkarev, 2017). In the dermis, exploring epigenetic mechanisms may be of great importance to further understand ageing. This aspect is illustrated by a recent study showing that age-related down-modulation of the lysyl oxidase gene *LOXL1* (involved in the maintenance and the renewal of elastic fibers) is mediated by an increased methylation degree in its promoter region (Moulin et al., 2017).

11. Dermis ageing at the matrix level

As type I and type III collagens are major constituents of the dermis matrix, their quantities, neosynthesis and degradation by MMPs, have been analyzed in different studies, which do not necessarily converge. Studies performed on fibroblast cultures suggest a reduced capacity for pro-collagen I synthesis in cells from aged donors (Takeda et al., 1992; Varani et al., 2006), and deregulation of the MMP/TIMP balance (Mine et al., 2008), which is consistent with descriptions of photo-damaged dermis areas (Fisher et al., 2002). In contrast, other authors describe a stable level of collagen I and III synthesis by fibroblasts, whatever donor's age (Brinckmann et al., 1994), and a stable quantity of these collagens in the tissue (El-Domyati et al., 2002). It is however well established that ultrastructural, morphometric, and mechanical changes, affect the dermis collagen network during ageing (Quaglino et al., 1996; Ahmed et al., 2017). Some of these alterations may be explained by an accumulation of advanced glycation end-products, especially carboxy methyl lysine, which is proposed to induce conformational modifications of collagens (Jeanmaire et al., 2001; Ahmed et al., 2017). In addition, quantitative and qualitative changes affecting regulators of fibrillogenesis may be also responsible for alterations of the collagen network. Indeed, proteoglycans, including versican and decorin, are affected in terms of expression levels, protein splicing, and post-translational modifications during ageing (Carrino et al., 2000). In particular, an increase of a truncated form of decorin in the dermis together with a decrease of versican, are reported (Carrino et al., 2000). Finally, concerning the elastic network, a progressive atrophy of

oxytalan fibers is observed within the papillary area, whereas a thickening of elaunin and elastic fibers occurs deeper in the dermis (Montagna and Carlisle, 1979; Naylor et al., 2011). Due to their exceptionally long half-life, elastin molecules can accumulate damages that can alter their structure and affect the functionality of the elastic network, such as glucose-mediated cross-linking (Konova et al., 2004) and time dependent modification of aspartic acid residues (Ritz-Timme et al., 2003).

12. Conclusion and perspectives

In the present review article, we describe current knowledge on dermis characteristics at different stages of life, from intra-uterine to post-natal life, as well as alterations that occur during chrono-ageing. Stage-specific and age-related changes in dermis characteristics are analyzed at the tissue, cell, and molecular levels, with a focus on the dermal matrix scaffold, as schematized in the presented Fig. 1. However, it has been proposed that the ageing process can integrate as much as nine concomitant hallmarks, which are genomics instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication (López-Otín et al., 2013). Taking this wide diversity of possible biological mechanisms into consideration, there is still a long way to go before discovering all the keys of tissue ageing. Even within a single tissue, this complexity is increased by the existence of heterogeneities associated with specific anatomical sites, as reported for skin fibroblasts (Chang et al., 2002). Notably, opening a particularly innovative research field, the pioneering work of Rinn et al. had pointed the role of epigenetic molecular species such as non-coding RNAs in the regulation of these locoregional tissue specificities (Rinn et al., 2007).

During the earliest stages of embryogenesis, the dermis is mostly composed of cells. Then, the matrix becomes the most abundant component, and the dermis develops into two anatomical areas, the superficial papillary dermis and the deeper reticular dermis, which segmentation occurs between week 8 and week 14 of development. The subpopulations of fibroblasts present in these two territories have distinct phenotypes, and the matrix organization is also different. In the papillary zone, the collagen and elastic networks are composed of the thin fibers, whereas in the reticular zone, fibers are of a larger diameter and are much more compact (notion of bundle for the collagen fibers). Then, after full maturation, the quality of the adult dermis is progressively altered through ageing. An atrophy of the elastic network, a decrease in the diameter and fragmentation of collagen fibers, and modifications affecting proteoglycans such as decorin (GAGs) are notably observed.

Competing interests

VH and BAB are L'Oréal employees. NOF is a CEA employee and acts as L'Oréal scientific consultant, free of charge.

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