Epithelial stem cell exhaustion in the pathogenesis of idiopathic pulmonary fibrosis

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Abstract. New paradigms have been recently proposed in the pathogenesis of idiopathic pulmonary fibrosis (IPF), evidencing that in IPF the cumulative action of an accelerated parenchymal senescence determined by either telomere dysfunction or genetic defects, together with the concurrent noxious activity of tobacco smoking, are able to severely compromise the regenerative potential of parenchymal epithelial stem cells, triggering a cascade of molecular signals and events (scarring, bronchiolar proliferation, abnormal remodelling) eventually leading to severe and irreversible functional impairment. New pathogenic schemes focus on the complex molecular mechanisms driving in a vicious circle the different signalling pathways (e.g. Wnt/β-catenin, TGF-beta, caveolin-1, etc.) potentially involved in epithelial-mesenchymal transition and irreversible lung remodelling. (Sarcoidosis Vasculitides Diffuse Lung Dis 2010; 27: 7-18)

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a severe multifactorial pulmonary syndrome functionally characterised by a progressive restrictive pattern with low diffusion capacity for carbon monoxide and low total capacity. IPF is the most common and severe form of idiopathic interstitial pneumonia, and its median survival is 3-4 years (1-3). Effective treatments are lacking for IPF, and this can be a consequence, at least in part, of the limited understanding of its pathogenesis, despite the overwhelming plethora of studies and theories proposed so far. In addition, although many clinical and pathological evidences have been provided favoring IPF as a clinical entity, a general consensus has not been definitely reached on its distinction from other idiopathic interstitial pneumonias, and conflicting opinions remain regarding the utility of distinguishing IPF from other diseases characterized by the usual interstitial pneumonia (UIP) pattern (4-7).

Evolving views in the pathogenesis of IPF

In recent years evolving opinions regarding the pathogenesis of IPF have raised stirring discussion, and different models have been proposed. The “inflammatory theory” of IPF/UIP has been challenged, and new hypotheses assuming that abnormal epithelial-mesenchymal interactions and aberrant wound healing are in fact the crucial events in its pathogenesis have been proposed (8-11). It is now clear and widely accepted that the central pathogenic mechanism in IPF is the progressive loss of alveolar-capil-
lary barrier integrity determined by increased injury and death of alveolar epithelial cells, followed by a deranged regeneration of parenchymal tissue. According to this notion, parenchymal fibrosis and tissue remodelling are triggered by the abnormal activation of reparative processes leading to fibroblast and myofibroblast recruitment and activation. A large number of human and experimental studies and models support this pathogenic scenario for IPF (12-22). Accordingly, patchy alveolar damage and regeneration can be observed in most UIP samples, focal pneumocyte-type-II hyperplasia and cytologic atypia are common, and causal relationship between type II alveolar epithelial cell injury and interstitial collagen accumulation can be experimentally demonstrated in pulmonary fibrosis (20). Nevertheless, a number of issues remain open including the causes of alveolar loss in IPF, as well as the mechanisms linking pneumocyte apoptosis with the striking subversion of pulmonary structure leading to progressive and irreversible scarring and remodelling.

**What causes alveolar loss and apoptosis of alveolar epithelial cells in IPF?**

*Accelerated senescence of epithelial precursors. The lesson from familial IPF.*

A major issue regards the specific cause (or causes) of the epithelial damage occurring in IPF. The search for an etiology of IPF has been so far frustrated, although a large number of hypothetic factors have been proposed (viral infections, toxic substances, gastro-esophageal reflux, etc.) (23). In other interstitial lung diseases (e.g. nonspecific interstitial pneumonia, organising pneumonia, or hypersensitivity pneumonitis), alveolar epithelial cell damage is considered among the major pathogenic mechanisms as it is in IPF, but the underlying mechanisms are known or partially known, and identification of the cause (e.g. chronic exposure to antigens, drugs, or autoimmunity-related damage) may represent a relevant step in the diagnostic work-up. In addition, in many cases of interstitial pneumonitis other than IPF the alveolar loss can be variably reversed by therapy, and complete restoration of normal parenchyma is possible in a proportion of cases, whereas the alveolar damage in IPF is progressive and irreversible.

Recently, genetic studies have provided new precious information about the mechanisms that can lead to alveolar damage and their failure to regenerate. There is in fact accumulating evidence supporting that in both familial and sporadic IPF cases, abnormalities affecting the telomere length are common (24-28). Efficient telomere length control is central to the survival of stem cells (29), and a defective regeneration potential and senescence of parenchymal epithelium can occur in IPF when this mechanism is impaired (30, 31). Type-II pneumocytes in fact, behave as precursor cells and express telomerase after alveolar damage (32). Taking into account these accumulating evidences, the cause of abnormal alveolar re-epithelialization occurring in IPF should be ascribed to the precocious hexaustion of the renewal potential of epithelial stem cells. The concurrent action of environmental factors, such as the exposure to toxic substances, and especially tobacco smoking and pollution, can be necessary to the full development of the pathogenic process. Telomere stricture and endoplasmic reticulum stress are in fact relevant injurious effects of tobacco smoking on pulmonary parenchyma (33, 34). Accordingly, IPF is typically a disease of advanced age, and there is increased risk for IPF in male smokers and in people exposed to other toxic substances (35-38). All these data taken together suggest that IPF can be included within the category of diseases of lung “premature aging” with similarities with diseases characterised by telomere stricture and stem cell dysfunction (31, 39-42). This latter category of progeroid diseases, mostly represented by dyskeratosis congenita, are characterised by stem cell failure due to mutations affecting the telomerase complex, forming a spectrum of variants presenting with bone marrow failure, liver fibrosis, and also pulmonary fibrosis (40, 43, 44). Pulmonary disease is described in up to 20% of patients with dyskeratosis congenita (45). Nevertheless, in a proportion of familial and sporadic IPF cases short telomeres are present in leukocytes, without evidence of abnormalities affecting the telomerase complex. The mechanisms accounting for defective telomere maintenance are complex and only partly understood, but the concurrence of variability in the genetic background, including polymorphisms in telomere maintenance, and in environmental exposures are likely candidates to explain this heterogeneity (40, 46, 47). Promising new approaches for
deciphering this complexity include the identification and evaluation of signalling hubs and networks of human longevity and age-related diseases (48).

It is possible to argue that other genetic abnormalities characterize a proportion of familial IPF, mostly affecting the production of surfactant proteins (mainly surfactant protein C, surfactant protein A2, and the phospholipid transporter ABCA-3) (49-54). These abnormalities are able to impair the regenerative potential of pneumocyte precursors (type-II pneumocytes), to disrupt the cellular protein trafficking, and/or to cause endoplasmic reticulum stress and apoptosis, thus determining in alveolar precursors a functional defect comparable to the one induced by telomere shortening and accelerated senescence (51, 55). Similar pathogenic mechanisms can operate in Hermanski-Pudlak, another genetic pulmonary syndrome pathologically characterized by a UIP-like pattern, and where lysosomal defects can trigger alveolar apoptosis and pulmonary fibrosis (56-58).

In conclusion, in different forms of familial and sporadic pulmonary fibrosis a common pathogenic scheme can be proposed, where different underlying genetic defects and/or predisposing conditions affecting the “stemness” of epithelial precursors, acting in concert with relevant concurrent environmental toxic exposures, can be able to induce breakdown of epithelial regeneration leading to chronic and irreversible alveolar loss. Obviously, these “intrinsic” defects can not be reversed as in other interstitial pneumonias. Further studies are needed to better define the reasons why this breakdown is commonly triggered at susceptible locations (peripheral lower lung sections as commonly observed in IPF).

Mechanisms of fibroblast and myofibroblasts recruitment and activation

If we accept this general scheme, a further issue is represented by mechanisms triggering the progressive and irreversible parenchymal fibrosis occurring in IPF. In all injured tissues, the damage of an epithelial layer is followed by a concurrent stimulation of epithelial and mesenchymal precursors, aimed to repair the wound. This repair process follows a series of stereotypical events, tightly regulated by molecular signalling finely tuning cell proliferation and differentiation of both the epithelial and mesenchymal components. When this renewal occurs in a pathologic environment, e.g. at sites where epithelial stem cells are exhausted and/or impaired in their functions as occurring in IPF, excess of molecular pro-fibrotic signals are generated by damaged basement membrane and activated type-II pneumocytes, leading to over-production of reparative signals (growth factors, cytokines, chemokines), and abnormal recruitment of fibroblasts and myofibroblasts. Scarring and remodeling in this pathogenic scenario can be consequences of the establishment of a vicious circle of injury and abnormal repair, leading to perturbation of the ordered cross-talk between epithelial and mesenchymal cells (59-60). Interestingly, the molecular pathways aberrantly activated in IPF seem to be the same involved in epithelial-mesenchymal communications occurring in lung development and differentiation (21-60).

In IPF, an overwhelming number of data have been produced concerning abnormal features of fibroblasts and myofibroblasts compared to normal. The numerical increase of fibroblast and myofibroblasts in IPF has been ascribed to a variety of concurrent mechanisms such as increased local proliferation and/or resistance to apoptotic signals, recruitment of fibrocytes from the circulation, and also epithelial mesenchymal transition (EMT) (10, 61, 62). Many studies have revealed molecular abnormalities characterising IPF fibroblasts/myofibroblasts, focussing on the paradoxical imbalance in cell death between IPF pneumocytes, characterised by increased apoptosis, and IPF fibroblasts/myofibroblasts, characterized by decreased apoptosis. This imbalance has been attributed to abnormal expression of a variety of molecules, but the precise role of these abnormalities is far from clear. Epigenetic suppression of Thy-1/CD90, a GPI-anchored protein involved in the regulation of fibroblast proliferation and migration, characterises IPF myofibroblasts, and this decrease has been considered as part of their pro-fibrotic phenotype (63, 64). Decreased production of caveolin-1, a critical regulator of lung fibrosis, has been evidenced in IPF, and this abnormality has been proposed as relevant in its pathogenesis (65, 66). Interestingly, caveolin-1 participates in a complex molecular network including TGFβ and telomerase, thus linking molecular signalling and genetic predisposition in the pathogenesis of lung fibrosis (67-68). Caveolin-1 is a key player in promoting fibroblast senescence (69-70), and its down-modulation in IPF could contribute to their increased survival
and activation. Nevertheless, perturbation of caveolin-1 functions can not be considered as specific, since abnormal levels of this molecule are not restricted to IPF (71, 72). It is not easy to substantiate whether all these features are intrinsically related to specific abnormalities of IPF myofibroblasts, or merely result from abnormal stimulation of “normal” fibroblasts by “abnormal” environmental signalling.

In IPF/UIP the fibrotic reaction is distinctive, since discrete collections of myofibroblasts, generally known as fibroblast foci (FF), are scattered at the borders between normal and dense scar tissue. FF are considered a key element for defining the UIP pattern, since they give the appearance of temporal heterogeneity and represent the leading edge of ongoing lung injury and abnormal repair. FF occur in the majority of UIP samples, and their frequency has been related to disease severity and prognosis (73). The FF in UIP are similar to those observed in organizing pneumonia (the so-called Masson’s body), but have different location (interstitial/intramural versus intra-alveolar), and biological features such as the absence of blood vessels and inflammatory cells (74).

A number of studies have been focused on the molecular characterization of myofibroblasts forming the FF in UIP samples, and abnormalities and differences have been in fact described (e.g. increased proportion of myofibroblasts expressing the proliferation marker Ki67+, elevated expression of TIMP-2, a member of tissue inhibitor of metalloproteinases), justifying the increased proliferation and/or decreased apoptotic clearance of these cells (75).

Abnormal nuclear accumulation of β-catenin has been demonstrated in FF of UIP, at variance with samples of organizing pneumonia (76). This finding can be considered as evidence of activation of the Wnt-pathway in IPF (see below in more detail), and suggests that transactivation of anti-apoptic and/or pro-proliferative β-catenin target genes is implicated in the abnormal persistence of FF (76, 77). As above described, myofibroblasts in IPF can accumulate with several mechanisms, including local recruitment and differentiation from fibroblasts, migration of fibrocytes from the periphery (78), and EMT (79). The transition between fibroblasts and alpha-smooth-muscle (α-SMA) expressing myofibroblasts is regulated by a complex array of molecular signals, including TGF-β1, tumour necrosis factor alpha, and also telomerase activity (80). Activation of the Wnt- and/or TGFβ pathways can synergistically contribute to mechanisms triggering EMT, and can also induce an abnormal survival phenotype in myofibroblasts, increasing their resistance to apoptosis and invasive behaviour (62, 81, 82).

Interestingly, β-catenin stabilisation (e.g by gene mutation) can lead to abnormal Wnt activation and eventual development of aggressive myofibroblastic lesions (83, 84). Although β-catenin mutations are not demonstrable in IPF, abnormal Wnt activation can be responsible of the expansion of mesenchymal stem cells and the invasive behaviour of myofibroblasts in involved areas (76, 60, 85).

Functional abnormalities of IPF fibroblasts can be in turn involved in the abnormal regeneration of pneumocytes and the progressive alveolar loss observed in this disease, as elegantly shown in a recent study demonstrating that the basal HGF secretion by IPF fibroblasts is decreased by 50% when compared with control fibroblasts (86).

Abnormal activation of the Wnt-pathway in IPF

It is possible to speculate that the abnormal genetic background occurring in IPF can affect differently the diverse tissue components forming the pulmonary parenchyma, because the precursor cells are different, use different molecular mechanisms, and likely heterogeneously respond to the renewal impairment. Following this hypothesis, we proposed that a severe perturbation of the molecular signals interconnecting pneumocytes, mesenchymal cells and proximal lung epithelial precursors can drive a divergent effect on the proximal versus distal pulmonary components leading to the abnormal remodelling of the pulmonary structure (21). A key element in this pathogenic model is represented by the abnormal activation of the canonical Wnt-signalling pathway (76). The Wnt-signaling pathway plays diverse key roles in development and morphogenesis, in stem cell renewal and differentiation, and in tissue maintenance (87, 88). Beta-catenin signalling in fact determines a vast array of fundamental functions including cell proliferation, migration, apoptosis, and also epithelial mesenchymal transition (EMT) (62, 89, 90). EMT is a physiological mechanism involved in embryogenesis, but it is also relevant in patholog-
ical conditions such as metastatic spread and fibrosis (79). Several human and experimental studies have confirmed that the Wnt-pathway is abnormally activated in IPF, and this notion is included in recent pathogenic models for IPF (60, 76, 91-95). In line with the relevance of Wnt-signalling in IPF, a number of molecules that are abnormally expressed in human or experimental pulmonary fibrosis are among the downstream target genes of beta-catenin. These include the metallo-proteinase matrilysin/MMP7, cyclin-D1, tenasin, osteopontin, and different factors regulating epithelial cell survival, cell migration, and EMT (c-Myc, laminin-5 gamma-2 chain, WISP1, snail, twist, slug)(82, 96-101) (figure 1). Alveolar type II pneumocytes after injury show in fact many features of precursor cells with increased levels of telomerase, and also activation of EMT, as revealed by the expression of the transcription factors snail, slug, and twist, as well as decreased levels of E-cadherin (figure 1) (21, 32, 102). Telomerase

Fig. 1. Evidences of epithelial mesenchymal transition in IPF. A fibroblast focus located in lung parenchyma is shown in a, where α-SMA expressing myofibroblasts (red) co-express the EMT-related transcription factor twist (brown). Reactive type-II pneumocytes express nuclear slug (b), and decreased E-cadherin (c) in affected alveoli.

Abnormal remodeling in IPF. An enlarged bronchiole, with some features of microscopic honeycombing is shown in d, where laminin-5 γ2 expression is evident in activated type II pneumocytes in neighboring damaged alveoli, and also in a basal cell cluster overlying fibroblast foci (FF) (d, e). Abnormal nuclear and cytoplasmic expression of beta-catenin is observed in both alveolar and bronchiolar epithelial cells (f), together with increased expression of matrilysin/MMP7 in basal cells (arrow - g). Bronchiolar hyperplasia and abnormal colonization are evidenced by the basal-cell marker CK5 (h). Increased expression of cyclin-D1 (a Wnt-pathway target gene product) is evident in hyperplastic bronchiolar structures and affected alveolar epithelial cells (i)
seems to be crucial for maintaining the stem cell properties of type II pneumocytes in smokers, since telomere shortening can be increased by oxidative stress, and lung alveolar integrity is compromised in telomerase-null mice (103, 104).

Interestingly, there is a substantial connectivity between Wnt and other signalling pathways orchestrating the physiological tissue renewal and repair, including bone morphogenetic protein (BMP) and transforming growth factor beta (TGF-β), and deregulation of this network may trigger a vicious circle amplifying abnormal tissue remodelling in IPF (105, 106). Gremlin, an inhibitor of BMP, is hyper-expressed in IPF, and induces lung fibrosis in the mouse lung via decreased BMP- and increased TGF-β signalling. (107, 108). The TGF-β pathway is able to trigger EMT and fibrosis, and its pathogenic role in IPF has been suggested in many studies, as also the involvement of its downstream effectors SNAI and transgelin (81, 109-112). The possible role of WNT5A and non-canonical Wnt-signalling has been also hypothesized (113).

In different systems, the classical role of the Notch signalling, acting in concert with Wnt, is the maintenance of self-renewal potential of epithelial stem cells by regulating cell differentiation (114-117). Notch is crucial for myofibroblast differentiation and alveogenesis, and Notch- and Wnt-signalling can cooperate in triggering pulmonary fibrosis (118-119).

The abnormal expression of c-FLIP, an inducible endogenous inhibitor of Fas-mediated apoptosis, in the lung tissues of patients with IPF/UIP compared with non-diseased control subjects also suggests a role for the NF-kB pathway (120).

Taking all these data into account, a general pathogenic model can be traced for IPF where aberrant activation of the WNT-signalling and the other involved pathways are chronically and aberrantly triggered by signals derived from senescent alveolar epithelial cell precursors, attempting in vain to repair injured epithelium (figure 2).

**Lung remodelling, bronchiolar proliferation and honeycombing**

In IPF the UIP pattern is characterized by heterogeneously distributed alterations of the pulmonary parenchyma, usually described with the generic term “remodelling”. A number of abnormalities are encompassed under this term, including dense fibrosis, structural distortion, and abnormal proliferative lesions affecting the small airways, (hyperplasia, metaplasia, bronchiolization and honeycombing) (76, 96, 121). How can be reconciled these morphological appearances with the pathogenic model above described? We proposed a scheme where the aberrant activation of Wnt/β-catenin signalling, and other involved pathways, is able to trigger a divergent epithelial regeneration at bronchiolo-alveolar junctions, with loss of alveolar epithelium on one side, and abnormal proliferation of bronchiolar epithelium on the other, concurrent with mesenchymal proliferation and scarring (76). In fact, we can expect that epithelial precursors (type II pneumocytes in the alveoli and basal cells in bronchioles) provide distinct responses to abnormal molecular proliferative and apoptotic signals, since these precursors utilise distinct molecular strategies and mechanisms for their survival and differentiation. In our view, the variegated appearance, from early lesions to extensive fibrosis and remodelling characterizing IPF/UIP lesions, is produced by the progressive interference on physiological tissue repair mechanisms due to abnormal β-catenin activation, starting from foci of ongoing injury and repair processes, as following a gradient of Wnt-signal concentration. Deregulated expression of Wnt target genes could exert divergent effects on different airway components (namely bronchiolar and alveolar), eventually leading to alveolar loss on one hand, and bronchiolar proliferation on the other. In lung development Wnt-signalling can differentially stimulate the expansion of distal and proximal lung components, and Inhibition of Wnt/β-catenin signalling by tissue-specific deletion of β-catenin results in disruption of distal airway development and expansion of proximal airways (122). In this model, senescent alveolar cells in IPF could be particularly vulnerable to pro-apoptotic signaling (as evidenced by increased expression of p53, p21\textsuperscript{wt}, and also transactivating isoforms of p63 (121, 123-126). On the other hand, bronchiolar basal cells could be more protected from apoptosis by the constitutive expression of truncated dominant-negative AN-p63 isoforms exerting potent anti-apoptotic signals (128-130). The β-catenin/TCF complex is the master switch that controls proliferation versus differentiation, and c-myc
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Fig. 2. General scheme describing the different steps of IPF pathogenesis as proposed in this review.

is one of its most relevant mediator (131-133). Accordingly, in different systems and cell types, the activation of the Wnt-pathway is able to either trigger or inhibit survival and death by modulating the availability of cyclin-D1 and c-myc, two proteins that play roles in both cellular proliferation and apoptosis (132, 133). The specific role of c-Myc, in amplifying divergence between distal and proximal lung tissue components warrants further investigation, since at sites where abnormal levels of β-catenin, and hence c-myc, are expressed, migrating bronchiolar cells could behave as super-competitors (131, 133-135).

The epithelial cells overlying fibroblast foci of UIP have been described as “cuboidal” epithelial cells of undetermined nature. These epithelial cells, that likely represent target cells in the injury-repair sequence occurring in IPF, have been recognized as either alveolar or bronchiolar in different studies. At immunophenotypic analysis the majority of FF are covered by bronchiolar epithelium (21, 96, 121), and honeycomb cysts have frequently myofibroblast collections resembling FF in their wall (figure 1). In most cases honeycomb cysts at histology appear as dilated bronchiolar structures, frequently filled by mucus and muciphages (136), and show features of hyperplasia and bronchiolization (so-called “microscopic” honeycombing). This latter type of honeycomb cyst are in most instances peripheral, and appear early in the evolution of the disease. Bronchio-
lar lesions in affected areas are frequent, and encompass basal cell hyperplasia, bronchiolization, squamous metaplasia and atypia (21, 121). In a large proportion of cases of IPF/UIP, the bronchiolar changes are prominent, and sometimes can mimic an epithelial neoplasm. Interestingly, the molecular abnormalities occurring in bronchiolar proliferative lesions are all centered on basal cells, mostly exhibiting activation of the wnt-β-catenin pathway, as evidenced by the expression of nuclear β-catenin, cyclin-D1 and MMP-7/matriplysin (76). This observation is relevant since basal cells are stem cells involved in the renewal of airway epithelium (129), and in physiological conditions they do not express significant levels of these molecules (76). In a recent study, we demonstrated that bronchiolar basal cells overlying fibroblast foci aberrantly express molecules involved in cell motility and invasiveness, including laminin-5-γ2-chain (LAM5γ2), the calcium binding protein fascin, and phosphorylated heat-shock-protein-27 (HSP27) (96). We hypothesized that this phenotype is likely related to the alveolar colonization observed in IPF (bronchiolization), and can significantly contribute to lung structure distortion and remodelling. HSP27 in fact can mediate resistance against cell death induced by stress and differentiation, preventing apoptosis by blocking interactions of Daxx with Ask-1 and Fas (137). The trimeric protein laminin-5 (α3, β3, γ2-chain) is an integral part of the basal lamina of stratified epithelia where it plays a crucial role in the organization of the basal stem-cell niche by providing epithelial-mesenchymal connections by interacting with integrin α6β4 (138). These interactions are critical for regulating cell migration, an event required in different processes, such as wound healing, embryogenesis and metastatic dissemination (139,140). The γ2 chain of laminin-5 (LAM5γ2) is induced by β-catenin, and acts as a soluble cell motility factor in a variety of conditions after its cleaving by metalloproteinases (141-142). The enhanced expression of LAM5γ2 is considered one of the best marker of invasiveness in different carcinomas (142,143). Within the FF the LAM5γ2 positive cells appear as linear clusters of cytokeratin-5 expressing basal cells, wedged between luminal epithelial cells and myofibroblasts, forming peculiar negative-positive-negative three-layered lesions (that we named “sandwich” fibroblast-foci, figure 1)(96). According to this study, the “sandwich-foci” appear as specific for IPF/UIP, since similar lesions are extremely rare in other interstitial lung diseases. Myofibroblasts are able to produce reactive oxygen species (ROS), and can then contribute to the induction of cell death in alveolar epithelium (144). In basal stem cells of sandwich foci, on the other hand, the coincidental expression of survival signals (provided by ΔN-p63 and Wnt-activation) and the genotoxic action of ROS locally produced by myofibroblasts might be involved in carcinoma development in IPF (145-147).

**Conclusions**

These evolving concepts open new options to better understand the pathogenesis of IPF, and also new perspectives for alternative treatment options, including drugs specifically addressing cell senescence. The possible action of drugs inhibiting and/or regulating the Wnt-pathway could positively interfere with EMT, but also with the complex mechanisms involved in the divergent behaviour of different epithelial components as described in this paper (148, 149). The central role of telomere-shortening in epithelial stem cells exhaustion is emphasised, and future efforts should be focused on their pharmacological protection and/or specific replacement (150-154).

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