The role of lipid-based signalling in wound healing and senescence

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Abstract

Lipid-based signalling modulates several cellular processes and intercellular communication during wound healing and tissue regeneration. Bioactive lipids include but are not limited to the diverse group of eicosanoids, phospholipids, and extracellular vesicles and mediate the attraction of immune cells, initiation of inflammatory responses, and their resolution. In aged individuals, wound healing and tissue regeneration are greatly impaired, resulting in a delayed healing process and non-healing wounds. Senescent cells accumulate with age in vivo, preferably at sites implicated in age-associated pathologies and their elimination was shown to alleviate many age-associated diseases and disorders. In contrast to these findings, the transient presence of senescent cells in the process of wound healing exerts beneficial effects and limits fibrosis. Hence, clearance of senescent cells during wound healing was repeatedly shown to delay wound closure in vivo. Recent findings established a dysregulated synthesis of eicosanoids, phospholipids and extracellular vesicles as part of the senescent phenotype. This intriguing connection between cellular senescence, lipid-based signalling, and the process of wound healing and tissue regeneration prompts us to compile the current knowledge in this review and propose future directions for investigation.

1. Introduction

Over the course of the last decades, our knowledge of cellular senescence evolved from being considered as a mere cell culture phenomenon (Hayflick, 1965) to a promising target for clinical drug development (Kirkland and Tchkonia, 2020) after it was shown that senescent cells accumulate with age in vivo (Dimri et al., 1995; Herbig et al., 2006; Lewis et al., 2011; Ressler et al., 2006) and at etiological sites in multiple chronic diseases (Muñoz-Espín and Serrano, 2014). Their clearance extends the health and life span of mice and attenuates...
several age-associated diseases and disorders (Baker et al., 2016; Xu et al., 2018). Interestingly, in the context wound healing and tissue regeneration several studies have shown a positive effect of senescent cells (Demaria et al., 2014; Jun and Lau, 2010; Krizhanovsky et al., 2008; Ritschka et al., 2017; Wang et al., 2019b) and senescent cell clearance delayed wound healing (Baker et al., 2016; Demaria et al., 2014; Johmura et al., 2021), which is in stark contrast to the decline of the regenerative potential and the wound healing capacity during the human ageing process (Ding et al., 2021).

It is believed that senescent cells exert their influence on their surrounding microenvironment mainly by the increased secretion of a pro-inflammatory and pro-tumorigenic mixture of cytokines, chemokines, matrix metalloproteases (MMPs) and growth factors, collectively termed the senescence-associated phenotype (SASP) (Copp et al., 2010). Initially, the list of SASP components included solely proteins, but recent studies by us and others demonstrated that the secretion of several bioactive lipids (Narzt et al., 2020; Ni et al., 2016; Wiley et al., 2019), extracellular vesicles (EVs) and therein enclosed miRNAs (Borghesan et al., 2019; Terlecki-Zaniewicz et al., 2019, 2018; Weilner et al., 2016a, 2016b) is similarly induced in senescent cells and functionally modulates the surrounding tissue making them novel members of the SASP.

We here aim to compile the current knowledge on the vital role of senescence-associated lipids and EVs in wound healing and tissue regeneration. We selected diabetic non-healing wounds, idiopathic pulmonary fibrosis and ischemic reperfusion injury as clinically relevant examples of age-associated diseases to illustrate the connections between lipids and senescence. Finally, we highlight remaining obstacles in translating our current knowledge from bench to bedside and propose future directions for investigation.

2. Lipid-based signalling in wound healing

Tissue regeneration and repair requires the joint cooperation of many cell types and their products in order to reconstitute lesion sites. The different phases of wound healing represent hemostasis, inflammation, proliferation, and remodelling. Firstly, when an injury occurs, the platelets must aggregate to make the bleeding stop. In the inflammation phase, immune cells are recruited to the lesion site and proliferate. In the proliferation phase fibroblasts, keratinocytes and endothelial cells multiply and form the new tissue (granulation tissue). Lastly, during the remodelling stage, immune cells clear apoptotic cells, and collagen deposition begins. Prolonged phases or aggravated responses of the organism to the wound may lead to hypertrophic scarring, keloids, fibrosis or ulcers. For a detailed discussion of wound healing, the reader is referred to other reviews (Caídeo-Dorantes and Caídeo-Ayala, 2019; Ganapathy et al., 2012; Shaw and Martin, 2009; Sorg et al., 2019).

Table 1

| SYMBOL       | DESCRIPTION                        | Wound Healing Phase | EFFECT IN Woundhealing | REGULATION in Senescence/Ageing |
|--------------|-----------------------------------|---------------------|------------------------|---------------------------------|
| TXA2         | Thromboxane A2                    | hemostasis/         | platelet aggregation †| n.d.                            |
|              |                                   | inflammatory        |                        |                                 |
|              |                                   | proliferation       |                        |                                  |
|              |                                   | macrophage activation †|                        |                                  |
|              |                                   | inflammation †      |                        |                                  |
|              |                                   | endothelial cell migration †|                  |                                  |
| PGE2         | Prostaglandin E2                  | proliferation       |                        | † (Zdanov et al., 2007)         |
|              |                                   | angiogenesis †      |                        |                                  |
|              |                                   | fibroblast proliferation †|                   | † (Borghesan et al., 2019)      |
|              |                                   | keratinocyte proliferation †|                  | † (Weilner et al., 2016a)       |
|              |                                   | remodelling         |                        | † (Nakajima et al., 1997)       |
|              |                                   | collagen deposition ↓|                        | n.d.                            |
|              |                                   | macrophage polarization †|                   |                                  |
| PGD2         | Prostaglandin D2                  | proliferation       |                        | † (Nakajima et al., 1997)       |
|              |                                   | angiogenesis †      |                        |                                  |
|              |                                   | fibrinolysis †      |                        |                                  |
| LTB4         | Leukotriene B4                    | proliferation       |                        | † (Weilner et al., 2016a)       |
|              |                                   | hemostasis/         |                        |                                 |
|              |                                   | inflammatory        |                        |                                  |
| 12-HHT       | 12(S)-hydroxyheptadeca-5Z,8E,10E-trienoic acid | proliferation | keratinocyte migration †| n.d.                            |
|              |                                   | keratinocyte proliferation †|                  |                                  |
| LTC4/LTD4 (CysLT) | Leukotriene C4/ Leukotriene D4 | remodelling         |                        | † (Weilner et al., 2016a)       |
| EET          | Epoxyeicosatrienoic acid          | proliferation       | angio genesis †       | 14,15-EET ↓ (Yang et al., 2014) |
|              |                                   | keratinocyte migration †|                   | n.d.                            |
|              |                                   | inflammation ↓      |                        |                                  |
| RvE1         | Resolvins E1                      | proliferation       |                        |                                 |
|              |                                   | keratinocyte migration †|                   |                                  |
|              |                                   | inflammation ↓      |                        |                                  |
| RvD2         | Resolvins D2                      | proliferation       |                        |                                 |
|              |                                   | keratinocyte migration †|                   |                                  |
|              |                                   | fibroblast proliferation ↓|                  |                                  |
|              |                                   | fibroblast migration ↓|                        |                                  |
| LXA4         | Lipoxin A4                        | proliferation       |                        |                                  |
|              |                                   | fibroblast proliferation ↓|                  |                                  |
|              |                                   | fibroblast migration ↓|                        |                                  |
| Mar          | Maresins                         | remodelling         |                        | † (Arnardottir et al., 2014)    |
|              |                                   | macrophage polarization †|                   |                                  |
|              |                                   | inflammation ↓      |                        |                                  |
| LPA          | Lysophosphatidic acid             | proliferation       | keratinocyte migration †| † (Chen et al., 2020)          |
|              |                                   | EVs ↑ (Buratta et al., 2017) |
| S1P          | Sphingosine-1-phosphate           | hemostasis/         | keratinocyte migration †| † (Heffernan-Stroud et al., 2012; Kim et al., 2019) |
|              |                                   | inflammation ↑      |                        |                                  |
|              |                                   | angio genesis ↑     |                        |                                  |
|              |                                   | fibroblast proliferation ↑|                  |                                  |
|              |                                   | collagen deposition ↓|                        | n.d.                            |

n.d. = not determined.
and that not only proteins but bioactive lipids are secreted by senescent cells (Narzt et al., 2020; Ni et al., 2016; Wiley et al., 2019), suggesting a potential connection between senescent cells and wound healing via lipid mediators.

Wound healing is a process involving a plethora of different cell types such as immune cells, fibroblasts, endothelial and epithelial cells. Together, they have a repertoire of proteins and lipids which can act in an autocrine and paracrine way to orchestrate the different phases of wound healing. The distinct roles of these bioactive lipids combined with their intertwined synthesis pathways suggests a complex and time-dependent regulation that, if altered, results in impaired wound healing as observed in aged individuals. In the following, we will describe the lipid classes involved in wound healing, discuss how these lipid mediators are regulated in ageing and senescence (Table 1), and then describe their role during different phases of wound healing (Fig. 1).

2.1. Lipid classes involved in wound healing

For detailed information about the synthesis and signalling pathways of lipid mediators during wound healing, we recommend other recent reviews (Than et al., 2017; Yasukawa et al., 2020).

2.1.1. Phospholipids and other important membrane lipids

Bioactive phospholipids, such as lysophospholipids, ceramides and sphingomyelin, are not solely constituents of cell membranes but are also known to play an important role in intra- and intercellular communication (Casares et al., 2019; Horn and Jaiswal, 2019). They are either released by the cells as free molecules or as part of EVs, either as constituents of their membrane or as cargo. Compared to their donor cells the lipid composition of EVs was enriched in lysophospholipids (lysophosphatidylcholine (LPC), lysophosphatic acid (LPA), lysophosphatidylethanolamine (LPE)) (Buratta et al., 2017), ceramids (Trajkovic et al., 2008) and sphingomyelin, among others (Laulagnier et al., 2004). Even EVs originating from the same cells differ in their lipid composition and at least three different subpopulations of EVs could be identified in mesenchymal stem cells (MSCs) (Lai et al., 2016; Lai and Lim, 2019). If the lipid composition of the EVs influences their uptake or exerts different biological functions still remains to be investigated. However, there are several cellular responses where vesicle bound (Kabarowski, 2001; Perrin-Cocon et al., 2006) or free (Lauber et al., 2003) lysophospholipids play a role. In addition, recent reports show that the cargo of EVs also encompasses not only nucleic acids and proteins (Raposo and Stoorvogel, 2013), but also bioactive lipids, such as eicosanoids (Lacy et al., 2019).

2.1.2. Eicosanoids

Lysophospholipids and free fatty acids, such as poly-unsaturated fatty acids (PUFAs), are generated by phospholipases hydrolysing membrane lipids. PUFAs, namely arachidonic acid (AA), docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), function as precursors of eicosanoids, a class of well-established mediators of intercellular communication (Henderson and Brown, 2000). The lipoxygenase pathway (5-LO, 12-LO, 15-LO) produces leukotrienes, whereas the primarily anti-inflammatory prostaglandins are derived from the cyclooxygenases (COX) pathway (COX-1/PTGS1, COX-2/PTGS2). Cytochrome P450 epoxyeicosatrienoic acids (EETs). An interesting subgroup of eicosanoids are specialized pro-resolving mediators (SPMs), which are synthesized through the metabolism of PUFA by LO and CYP (Serhan, 2014). Since their discovery in 1984 (Serhan et al., 1984), the now extensive list of SPMs includes lipoxins (LX), resolvins (Rv), maresins (MaR), and protectins. The D-series resolvins (RvD) are derived from DHA, the E-series from EPA (RvE) (Serhan and Levy, 2018).

2.2. Senescence-associated changes in lipid-based signalling

Several of the described lipid classes undergo profound changes during cellular senescence. In senescent cells, one of the most prominent members of the phospholipases, cytosolic phospholipase A2 (cPLA2), was shown to be activated (Wiley et al., 2019). This is in line with recent findings from us, showing increased enzymatic PLA2 activity in several senescent cell types which could be attributed to cPLA2 (our unpublished data). Tumor necrosis factor alpha (TNF-α), interleukin 1b (IL-1b), signal transducer and activator of transcription 3 (STAT-3), nuclear factor kappa-light-chain-enhancer (NF-κB), CCAAT/enhancer-binding protein beta (CEBPB) and activator protein 1 (AP-1) are all transcriptional regulators of cPLA2 (Bickford et al., 2015; Dronadula et al., 2005; Lee et al., 2010, 2013). Moreover, cPLA2 is also regulated via phosphorylation by mitogen-activated protein (MAP) kinases (ERK1/2, p38) or by increases in intracellular calcium (Leslie, 2015), thereby creating a possible link to pathways involved in cellular senescence. In addition, COX-2 (Zdanov et al., 2007) and 5-LO (Catalano et al., 2005) are overexpressed in replicative and stress-induced premature senescence. In line with these findings, leukotrienes and prostaglandins, the biosynthesis products of 5-LO and COX-2, are increasingly released from senescent cells, independent of the senescence inducer, and function analogous to the protein SASP (Wiley et al., 2019; Zdanov et al., 2007). Interestingly, the inducible transgenic expression of COX-2 in a mouse model led to a premature ageing phenotype (Kim et al., 2016). Together, these reports indicate that key enzymes of the eicosanoid pathways are differently regulated in cellular senescence and likely influence wound healing, because several classes of eicosanoids play an important role during the different phases of this process (see 2.3).

The hydrolysis of phospholipids by cPLA2 also generates lysophospholipids, which are increased in senescent cells (Buratta et al., 2017; Narzt et al., 2020) and exert many biological functions associated with cellular senescence. They were shown to induce senescence in cholangiocytes (Shimizu et al., 2015). Indeed, in Hutchinson Gilford progeria syndrome cells and in vivo, scientist identified a decline in the LPA-receptor as a major contributor of the premature ageing phenotype (Chen et al., 2020). Lysophospholipids function as “find me” signals (Peter et al., 2007), but also impair phagocytosis resulting in a “look, don’t touch” mechanism (Narzt et al., 2020), which possibly contributes to inefficient clearance of senescent cells. In addition, the formation and release of EVs is influenced by lysophospholipids (Hirsova et al., 2016) and ceramides (Bianco et al., 2009; Nurminen et al., 2002; Tepper et al., 2006; Trajkovic et al., 2008). The induction of these phospholipid species in senescent cells likely plays a role in the induction of EV secretion observed in senescent cells (Terlecki-Zaniewicz et al., 2019, 2018). EVs released by senescent fibroblasts differed in their mRNA content (Terlecki-Zaniewicz et al., 2018) and, when taken up by keratinocytes, impaired the epidermal differentiation while enhancing wound closure in a scratch assay (Terlecki-Zaniewicz et al., 2019).

EV secretion is also induced by neutral sphingomyelinase (N-SMase) (Hitomi et al., 2020; Menck et al., 2017; Trajkovic et al., 2008) which is associated with cellular senescence (Trayssac et al., 2018) and elevated in ageing tissues (Jensen et al., 2005). N-SMase is one of the two isoforms of sphingomyelinases that generate ceramides through the salvage pathway out of sphingomyelin. Consequently, ceramides are increased in replicative (Khayrullin et al., 2019; Venable and Yin, 2009) and senescence induced senescent cells (Hirsova et al., 2016).

In addition, the lipid composition of EVs changes upon induction of senescence (Buratta et al., 2017; Sagini et al., 2018), indicating that EVs derived from senescent cells might influence their microenvironment not only by their cargo (proteins, nucleic acids), but also by the altered lipid composition in their outer membrane (Wallis et al., 2020). Interestingly, phosphatidic acid, phosphatidylethanolamine, phosphatidylserine and ceramides were reduced in EVs derived from senescent fibroblast compared to their non-senescent counter-parts, whereas...
Fig. 1. The different stages of wound healing. The four phases including hemostasis, inflammation, proliferation, remodelling and the influence of eicosanoids (blue), SPM (yellow) and phospholipids (green) are shown. No claim for being complete. Images contain modified material from Servier Medical Art by Servier (licensed under a Creative Commons Attribution 3.0 Unported License [CC BY 3.0]).
sphingomyelin (SM) and LPA were increased (Buratta et al., 2017). Since EVs where found at the site of wounds (Huang et al., 2015) and the lipid composition of the vesicle membrane changes after induction of senescence, the EV membrane lipid composition may not only be regarded as the “bottle that harbour the message” but rather the “bottle that is the message”.

Other lipid classes like triacylglycerol (TAG) change during senescence (Millner and Atilla-gokcumen, 2020) as well, but were so far not reported to modulate wound healing.

### 2.3. The role of lipids in the different phases of wound healing

Several lipid mediators, which are associated with cellular senescence, participate in different stages of wound healing.

#### 2.3.1. Hemostasis and inflammation

Upon injury, the first and foremost reaction of the organism is the aggregation of platelets to stop the bleeding, followed by the activation of tissue resident macrophages and dendritic cells (Leslie, 2010). Through their pattern recognition receptor, these cells bind damage-associated molecular patterns (DAMPs). DAMPs are related to cell injury and damage, include lipids and are, in contrast to pathogen-associated molecular patterns (PAMPs), indistinguishable from host molecules (Ni et al., 2016). Thereupon the blood vessels dilate and increase the blood flow. Prostaglandins, among others, cause cell injury and damage, include lipids and are, in contrast to pro-inflammatory cytokines and prostaglandin E2 (PGE2) (Daniel et al., 2018; Li, 2012; Flacher et al., 2012; Srikrishnan et al., 2014). TXA2 receptor deficient mice experience prolongation of bleeding (Thomas et al., 1998), similar to humans, where a TXA2 antagonist significantly increased the bleeding time (Lau et al., 1991). Moreover, the effect of TXA2 on wound healing is not limited to platelet aggregation but also extends to the inflammatory phase. In one study, TXA2 activated macrophages ameliorated the synthesis of pro-inflammatory cytokines and prostaglandin E2 (PGE2) (Daniel et al., 1999). Prostacyclin (PGI2) is primarily produced by endothelial cells and is a vasodilator that ensures blood flow to the peripheral tissues (Jackson et al., 1993). The leukotrienes C4 (LTC4), D4 (LTD4) and E4 (LTE4), also known as cysteine leukotrienes (cysLTs), as well as leukotriene B4 (LTB4) are synthesized from LTA4, a 5-LO product of AA. They play a vital role as potent chemoattractant during the inflammatory phase of wound healing by recruiting leukocytes (Guimaraes et al., 2018; Lammermann et al., 2013), sensitizing neutrophils (Theron et al., 2009) and activating phagocytosis (Okamoto et al., 2010). Leukotrienes are implicated in several inflammatory pathologies including chronic inflammatory skin diseases (Honda and Kabashima, 2019). Indeed, 5-LO inhibition or knockout resulted in enhanced wound healing (Broglio et al., 2014; Guimaraes et al., 2018).

In addition, initiation of an inflammatory cascade and an increased wound healing capacity was also observed after co-incubation with keratinocyte EVs (Huang et al., 2015). Whether these effects are a direct result of EV uptake and subsequent post transcriptional regulation, or if the mere presence of EVs exerted this effect was not tested yet. It is feasible to assume the latter case, since EVs per se may be constituted with a significant regenerative potential due to their lipid envelope und lipid composition.

#### 2.3.2. Proliferation

After hemostasis the blood clot needs to be removed (fibrinolysis) to ensure the formation of granulation tissue. During the proliferation stage, endothelial cells divide and migrate to form intact blood vessels (angiogenesis), while activated proliferating fibroblasts secrete extracellular matrix (ECM) and epithelial cells migrate into the wound bed promoting re-epithelization through proliferation and differentiation processes.

Several processes during the proliferation phase are orchestrated by different classes of eicosanoids. Prostaglandins stimulate proliferation and migration of fibroblasts as well as angiogenesis and fibrinolysis during the early stage of the proliferation phase. PGII2 manages fibrinolysis, stimulates fibroblast migration (Hatane et al., 1998) and promotes angiogenesis in endothelial cells (He et al., 2008; Pola et al., 2004). PGE2 mainly produced by immigrating macrophages and stromal cell induces angiogenesis and fibroblast proliferation (Sakai et al., 2001). It has been shown that TXA2 is synthesized by microvascular endothelia cells and promotes angiogenesis (Daniel et al., 1999; Nie et al., 2000). On the other hand, prostaglandin D2 (PGD2) contributes to limit fibroblast migration to avoid fibrosis or keloids (Kohyama et al., 2002).

Following fibroblast proliferation, the synthesis and deposition of collagen is crucial to substitute the damaged connective tissue. This process is initiated by the activation of fibroblasts. Later, their differentiation into alpha smooth muscle actin (α-SMA) positive myofibroblasts is induced by transforming growth factor β (TGFβ) signalling. Hereby, PGE2 acts as an antagonist of TGFβ signalling to limit fibrosis (Warsinske et al., 2015), whereas the leukotrienes LTB4 and LTC4 were associated with the aberrant activation of fibroblasts and fibrosis (Liang et al., 2020; Oyoshi et al., 2012).

At the end of the proliferation phase, wound closure is mediated by proliferation and differentiation of keratinocytes during re-epithelialization. The stimulation of keratinocytes is orchestrated by a variety of prostaglandins. PGE2 induces keratinocyte proliferation and differentiation (Evans et al., 1993; Konger et al., 1998; Pentland and Needleman, 1986). Moreover, 12-HHT enhances epidermal keratinocyte migration and proliferation, thereby accelerating cutaneous wound healing in vivo (Liu et al., 2014a).

These processes are also regulated by resolvins and lipoxins which are both subgroups of SPMs that belong to the eicosanoids. SPMs are important mediators of re-epithelialization and wound closure, which was enhanced by RvE1 in a cutaneous wound setting (Menon et al., 2017) and in the intestine (Quiros et al., 2020). In addition, human keratinocyte migration was increased in an in vitro scratch-assay in a receptor-dependent manner after incubation with RvD2 and the enhancement of re-epithelialization was abrogated in mice deficient for the RvD2 receptor (Hellmann et al., 2018). Moreover, in a similar experiment, RvD2 inhibited TGFβ induced fibroblast proliferation and migration (Herrera et al., 2015), thereby suggesting RvD2 as modulating factor of fibrosis. Thus, the D-series resolvins inhibit fibroblast proliferation and migration but enhanced keratinocyte migration. Lipoxins are derived from AA through the sequential action of 5-LO and 15-LO or 12-LOX and the anti-fibrotic and anti-scarring LXA4 enhanced fibroblast proliferation and migration in vivo (Herrera et al., 2015).

In addition to eicosanoids, the diverse class of phospholipids also plays a role during the proliferation phase. LPA is a derivate of phospholipids and can act as signalling molecule (van Corven et al., 1989). It appears to have a positive effect on epithelial migration and enhanced wound healing in the cornea (Xu et al., 2007) and the mouth (Thorlakson et al., 2017). Sphinogosine-1-phosphate (SIP) is a lysolipid, which is mainly produced by spingosine-1-kinase (SPH1K). Higher activity of SPH1K and increased levels of SIP have been positively correlated with proliferation (Zhang et al., 1991). Recently, this enzyme was found to be present in significantly higher amounts in the wounds of mice. Knock-out experiments and pharmacological stimulation showed that SPH1K positively regulates inflammatory cell recruitment and angiogenesis while attenuating scarring in mice (Aoki et al., 2019). It was further hypothesized that the SIP receptor-2 (SIP2) may play a key role in the beneficial properties of SPH1K and SIP in wound healing. Indeed, knockout of SIP2 in mice reduced proliferation of hepatic
myofibroblasts, which mirrored the weakened activation of remodelling in response to liver injury in the knockout animals (Serriere-Lanneau et al., 2007). Thus, S1P plays a role in cutaneous wound healing and tissue regeneration.

Moreover, phospholipids influence the synthesis of eicosanoids, adding another layer of complexity to the regulation of these processes. The sphingolipid ceramide-1-phosphate (C1P) binds directly to cPLA2 and thereby coordinates the synthesis of eicosanoids. In mice, replacement of endogenous cPLA2 with cPLA2 lacking the interaction site for C1P resulted in an enhanced wound maturation, while the wound closure rate remained unaffected (Macknight et al., 2019). In addition, collagen remodelling was enhanced, tensile strength was increased, and the eicosanoid profile altered, showing decreased levels of pro-inflammatory prostaglandins (PGE2, TXB2) and an increase of hydroxyeicosatetraenoic acids (HETEs). Specifically, 5-HETE enhanced dermal fibroblast migration and collagen deposition. This suggests a role for C1P in promoting the inflammatory stage, and an inhibitory effect on proliferation and remodelling phases of wound repair. This indicates a connection between phospholipids and eicosanoids synthesis in the proliferation and remodelling phase.

Furthermore, EVs may also play an important role in the proliferation phase. When ASCs-derived EVs are taken up by fibroblasts, they stimulate their migration, proliferation and collagen synthesis in a dose-dependent manner, which leads to an increased collagen deposition and therefore enhanced wound healing in vivo (Hu et al., 2016). EVs secreted from myofibroblasts stimulate mesenchymal cell growth as well as angiogenesis (Moulin et al., 2010) and exercise-derived EVs promote endothelial function (Wilhelm et al., 2016). Sereval reports suggest that EVs from endothelial cells (Mzentsev et al., 2005) or other in vivo sources (Ramakrishnan et al., 2016) impair angiogenesis. Thus, it remains to be elucidated if EVs have a positive or negative effect on angiogenesis in the context of wound healing.

2.3.3. Remodelling

The differentiation of fibroblast to myofibroblast and the synthesis of ECM represent processes of the proliferation stage that continue to the remodelling phase (Hinz, 2016). While the deposition of ECM by activated myofibroblasts ceases, the newly synthesized ECM undergoes remodelling to prevent fibrotic scarring. Simultaneously, the inflammatory process is resolved with macrophages switching from the pro-inflammatory M1 polarization, which is associated with phagocytic activity and the production of pro-inflammatory mediators, to the anti-inflammatory M2 phenotype. Macrophages in M2 polarization secrete anti-inflammatory cytokines and phagocytose apoptotic neutrophils, a process called effecyositis.

Again, in this phase, important processes are regulated by prostaglandins. PGE2 disturbs collagen synthesis by regulating the balance between MMPs and their inhibitors (inhibitors of metalloproteinases, TIMPs), counter-acting pro-fibrotic TGFβ signalling, and thereby reducing the risk of hypertrophic scar formation (Zhao et al., 2016). The M1 to M2 phenotype switch is promoted by PGE2 (Luan et al., 2015; Zhang et al., 2018), PGD2 and its metabolite 15d-PGJ2, which activate their migration, proliferation and collagen synthesis in a dose-dependent manner, which leads to an increased collagen deposition and therefore enhanced wound healing in vivo. EVs secreted from myofibroblasts stimulate mesenchymal cell growth as well as angiogenesis (Moulin et al., 2010) and exercise-derived EVs promote endothelial function (Wilhelm et al., 2016). Sereval reports suggest that EVs from endothelial cells (Mzentsev et al., 2005) or other in vivo sources (Ramakrishnan et al., 2016) impair angiogenesis. Thus, it remains to be elucidated if EVs have a positive or negative effect on angiogenesis in the context of wound healing.

3. The dual role of senescent cells in wound healing

Although lipid profiles during cellular senescence and wound healing partially match (Table 1), a direct causal connection was not established yet. However, an increasing body of evidence suggests that cellular senescence and the SASP contribute to age-related changes in wound healing.

Acute senescence which is endogenously induced during wound healing was shown to exert essential functions during this process (Demaria et al., 2014) and to limit fibrosis (Jan and Latu, 2010; Krizhanovsky et al., 2008). Consequently, the clearance of senescent cells in genetic mouse models or with senolytics during wound healing prolonged wound closure (Baker et al., 2016; Demaria et al., 2014; Johnura et al., 2021).

With persistent damage, pathology and ageing, the immune system fails to efficiently clear senescent cells (McElhaney and Effros, 2009). Consequently, tissues are burdened by the accumulation of dysfunctional chronically senescent cells and by the constant exposure to the SASP (van Deursen, 2014), which ultimately contributes to several age-associated disorders (Muñoz-Espín and Serrano, 2014). Both, ageing and age-related diseases like non-healing wounds, lung fibrosis and ischemic reperfusion injury, are characterized by low-grade chronic inflammation. This phenomenon that gave rise to the term “inflammAgeing” (Franceschi and Campisi, 2014).

Tissue regeneration in general, and wound healing more specifically, become less efficient with age (Guo and Dipietro, 2010). With age, platelet aggregation is increased after an injury (Grigorova-Boros et al., 1988) and vascular permeability was found to decrease in aged mice, delaying the infiltration of macrophages and lymphocytes (Ashcroft et al., 1997). Even though more macrophages are finally present in ageing, they are less phagocytic (Swift et al., 2001), produce less growth hormones (Swift et al., 1999) and show a generally impaired immune response (Chelvarajan, 2006). In the proliferating phase, keratinocytes and fibroblasts displayed a reduced proliferation potential (Ashcroft et al., 1997; Bruce and Deamond, 1991; Gosain and DiPietro, 2004) and human fibroblasts show an impaired migration, integrin function and altered MMP and TIMP synthesis (Reed et al., 2001). MMPs are generally elevated while TIMPs’ expression is decreased (Gosain and DiPietro, 2004). Since wound healing is also strongly dependent on vascularization, senescence of endothelial cells might directly reduce the potential of re-vascularization (Yokoi et al., 2006) as these cells show clearly reduced angiogenic potential (Dellago et al., 2013) as well as a pro-inflammatory secretory phenotype (Hampel et al., 2006). Platt and Rühl demonstrated that young mice can turnover and remodel the collagen much faster and more efficiently than aged animals due to elevated collagenase activity (Platt and Rühl, 1972). In aged individuals, wounds display delayed closure (Sussman, 1973; Whiton and Everall, 1973) and decreased tensile strength (Gosain and DiPietro, 2004).

While these age-associated impairments of wound healing might represent a consequence of senescent cell accumulation, a direct relationship has not been established so far. However, cellular senescence is associated with an altered eicosanoid synthesis (Wiley et al., 2019; Zdanov et al., 2007), a decrease in SPM (Arnardottir et al., 2014), a transformed phospholipid profile (Narzt et al., 2020) and increased release of EVs (Terlecki-Zaniewicz et al., 2019, 2018), which might together explain some of the reported alterations in wound healing. Similarly, the presence of senescence-associated bioactive lipids and their influence on wound healing might contribute to the pathology of specific diseases.
4. Lipids and senescence in diabetic non-healing wounds

Diabetic ulcers represent a prime example of non-healing wounds. Diabetes mellitus is a pathological disorder of the sugar metabolism. The blood sugar level of those affected is permanently elevated and over time, this damages the blood vessels and various organs (Baltzis et al., 2014). Interestingly, senescent cells were implicated in the development and progression of diabetes type I (Thompson et al., 2019) and type II (Aguiyo-Mazzucato et al., 2019; Palmer et al., 2019) and both types of diabetes were attenuated by senolytics.

The low-grade inflammation associated with diabetes, a common hallmark of cellular senescence, may depend on 5-LO and its products, mainly pro-inflammatory leukotrienes. These are increased in senescence (Catalano et al., 2005; Wiley et al., 2019) and cause impaired wound healing. In vitro, a 5-LO inhibitor led to decreased ROS formation accompanied by accelerated wound healing (Brogliato et al., 2014). In line with this, the resolving M2 phenotype of macrophages were increased and the wound healing was accelerated in diabetic 5-LO−/− knockout mice (Ramaulo et al., 2018). Diabetes may depend a systemic circulation of the leukotriene LTB4 (Figueiras et al., 2015). Indeed, the increased production of LTB4 has been found to cause excess neutrophil chemotaxis and insufficient bacteria clearance in the wounds of diabetic mice (Brandt et al., 2018). Inhibition of leukotriene receptors, using receptor antagonists, improved wound healing similar to 5-LO deficiency (Guimaries et al., 2018). Therefore, selective antagonism of these receptors might be beneficial for patients with an unresolved cutaneous wound such as a diabetic ulcer.

While leukotrienes are increased, prostaglandins such as PGE2 are reduced in cutaneous wounds of the chronic diabetic ob/ob mouse model (Kämpfe et al., 2005), which is not in line other reports for senescent cells, where COX-2 and PGE2 levels are elevated (Zdanow et al., 2007). However, the prostaglandin synthesis might be differently regulated in acute and chronic senescent cells. PGE2 promotes M2 polarization of macrophages (Juan et al., 2015), which is important process during wound healing (Kotwal and Chion, 2017). Indeed, the topical application of PGE2 led to accelerated wound closure by promoting the switch from M1 to M2 macrophages (Zhang et al., 2018). Furthermore, DHA, a precursor of eicosanoids, was found to promote diabetic wound healing in rats, at least in part by restoring impaired plasticity of macrophage progenitor cells (Jia et al., 2020).

PGD2 and 15dPGJ2 act as ligands for PPARγ (Kliever et al., 1995) and PPARγ signalling is essential for the remodelling phase during normal wound healing (see above, 2.3 Remodelling). In mice, myeloid cell specific genetic deletion of PPARγ resulted in impaired wound healing, whereas topical treatment of PPARγ agonists on the cutaneous wounds of db/db diabetic mice led to lowered inflammation and enhanced wound healing, indicating a beneficial effect of PGE2 and 15d-PGJ2 in the regeneration of diabetic wounds by stimulating PPARγ (Bouhlel et al., 2007; Mirza et al., 2015). Interestingly, PPARγ accelerated senescence in fibroblasts (Gan et al., 2008), but how PPARγ, PGE2 and 15d-PGJ2 levels change during senescence remains unclear.

Besides lipoxigenases and cyclooxygenases, the third class of enzymes involved in eicosanoid synthesis are epoxygenases. The expression of two epoxygenases CYP2C65 and CYP2J6 was significantly decreased in the newly formed connective tissue (granulation tissue) of diabetic ob/ob mice and was associated with impaired wound healing and capsular formation. Conversely, treatment with their downstream metabolites improved the wound healing process. By injection of 11,12-EET, the inflammatory response was decreased, collagen production enhanced and wound healing improved (Zhao et al., 2017). Interestingly, 14,15-EET had an inhibitory effect on endothelial senescence (Yang et al., 2014).

Furthermore, the formation of granulation tissue was improved by S1P signalling. When streptozotocin-induced diabetic rats were treated with a plasmid that contained SPHK1, more granulation tissue and capillaries formed (Yu et al., 2014) and S1P subcutaneous injection in diabetic mice and rats significantly enhanced the neo-vascularization process and thereby wound healing (Kawanabe et al., 2007). Interestingly, reduced transcriptional activity of SPHK1 and lower levels of S1P are linked to accelerated senescence (Heffernan-Stroud et al., 2012; Kim et al., 2019). However, the status of S1P in ageing remains yet to be determined.

Besides eicosanoids and phospholipids, EVs were also studied in the context of diabetic wound healing. In a diabetic rat model, EVs from endothelial progenitor cells exhibited a beneficial effect on the proliferation stage. They reduced scar formation, improved neo-vascularization and accelerated wound healing (Li et al., 2016). If this could be attributed to EV-derived lipids or their cargo still needs to be investigated.

5. The role of senescence and lipids in idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis (IPF) is a fatal chronic disease characterized by a steady decline in lung function due to a fibrotic scarring of the lung tissue. The exact cause is not yet known (Raghu et al., 2011), but cellular senescence is suggested to play an important role (Lehmann et al., 2017; Pan et al., 2017; Schafer et al., 2017). Pulmonary fibrosis is mimicked by bleomycin exposure in a mouse model. Upon treatment the mice show a high expression of enzymes involved in leukotriene und prostaglandin biosynthesis, elevated levels of hydroxyproline in the lung (profibrotic), as well as cysteiny1 leukotrienes and PGE2 in broncho-alveolar lavage fluid (BALF). However, when the mice were treated with ABT-263 (Navitoclax) or with Ganciclovir, which in this model eliminates the p16-positive cells, all pathological conditions were attenuated (Wiley et al., 2019). Similar to that, the removal of senescent cells in various genetic (Wiley et al., 2019) or pharmacological animal models (Lehmann et al., 2017; Pan et al., 2017; Schafer et al., 2017) alleviated the development of pulmonary fibrosis.

The detrimental effects of senescent cells in the context of pulmonary fibrosis are thought to be a consequence of paracrine signalling events. Conditioned media from senescent lung fibroblasts induced α-SMA and collagen alpha-2(I) chain (COL1A2) expression in non-senescent fibroblasts and prior treatment of the senescent fibroblasts with a COX-2 and 5-LO inhibitor rescued this effect, indicating a role for prostaglandins and leukotrienes in the activation of fibroblasts and collagen synthesis, respectively (Wiley et al., 2019). α-SMA-induced myofibroblast differentiation is an essential transition necessary for proper wound healing (Demaria et al., 2014), but also a crucial step in the initiation of pulmonary fibrosis (Schafer et al., 2017). No changes were observed in the expression of α-SMA between 5-LO−/− and wildtype mice (Brogliato et al., 2014), indicating a potential role of prostaglandins in the aberrant activation of fibroblasts during pulmonary fibrosis. In IPF, human fibroblasts express the leukotriene biosynthesis mediator 5-LO but not COX-2, which is responsible in part for prostaglandin metabolism (Wiley et al., 2019). When human IPF lungs were stimulated by a variety of different agonists, COX-2 and PGE2 did not increase (Wilborn et al., 1995). In fact, PGE2 levels are decreased in patients with IPF (Petrkova et al., 2003; Wilborn et al., 1995) and inhibition of prostaglandin synthesis via either genetic deletion or inhibition of COX-2 aggravated the development of pulmonary fibrosis in mice (Hodges et al., 2004). PGE2 protected against lung fibrosis when it was administered before bleomycin challenge, but had no therapeutic effect when applied thereafter (Dackor et al., 2011). Conversely, the inhibition of PGE2 degradation by 15-hydroxyprostaglandin dehydrogenase (15-PGDH) resulted in a reduced fibrotic response and improved lung function following bleomycin treatment (Smith et al., 2020). Diminished COX-2 and PGE2 may contribute to the apoptosis paradox: Alveolar epithelial cells become apoptotic, whereas fibroblasts develop a resistance against apoptosis in the lungs (Maher et al., 2010). The positive role of PGE2 in pulmonary fibrosis was corroborated by a recent study where PGE2...
supplementation induced de-differentiation of myofibroblasts via cAMP/PKA and resulted in a transcriptional profile reminiscent of lung fibroblasts undergoing resolution after bleomycin-induced lung fibrosis (Fortier et al., 2021).

In contrast to prostaglandins, profibrotic leukotriene synthesis is constitutively active in IPF (Wilborn et al., 1996). Based on treatment with antagonists, it is more likely that the cysteinyl LTC4 and LTD4 contribute to the profibrotic effect rather than the non-cysteinyl LTB4 (Wiley et al., 2019). Bleomycin treatment of 5-LO−/− mice led to abrogated leukotriene synthesis, attenuation of fibrosis and elevation of PGE2 levels (Peters-Golden et al., 2002). In vitro, the leukotriene biosynthesis of senescent cells was biphasic, whereas prostanoid synthesis was monophasic. This was mirrored by observations in vivo after bleomycin treatment (Wiley et al., 2019). Thus, an imbalanced prostaglandin and leukotriene synthesis and their timely release may contribute to IPF. Further research will be necessary to determine whether the secretion or degradation time of prostaglandins and leukotrienes, or an impaired receptor interaction is the underlying cause.

As for lysolipids, LPA plays a key role as it was increased post injury in BALF of bleomycin-treated mice and in IPF. Conversely, fibrosis and mortality following bleomycin treatment were reduced in mice deficient for the receptor of LPA (Tager et al., 2008), indicating an essential role in bleomycin induced lung injury and fibrosis.

6. The contribution of senescent cells and lipids to the pathology of ischemic reperfusion injury

In ischemia-reperfusion injury (IRI) cells are deprived of oxygen and essential metabolites during the ischemic phase, causing cell death and scarring of tissue. When ischemia is halted by reperfusion of the injured tissue, additional tissue damage occurs through an increase of reactive oxygen species (ROS) which in turn induces DNA damage, lipid peroxidation, and cell death. IRI causes a complex immune response called sterile inflammation which extends the tissue damage further beyond the area affected by ischemia. The involved mechanisms and lipid mediators are similar to traditional wound healing despite the absence of pathogenic insults.

Similar to wound healing, the production of PGE2 and the leukotrienes LTC4 and LTBE4 induced by ischemia is central in the early inflammatory phase by recruiting immune cells to the site of tissue damage, which in the case of IRI further transmits the damage to previously unaffected tissue during the reperfusion phase. Leukotrienes play a prominent role in the pathogenesis of cardiac IRI during which they are synthesized by activated polymorphonuclear leukocytes (PMNL) and endothelial cells (Rossi et al., 2009). LTC4 and LTBE4 are associated with neutrophil transmigration into tissues during IRI (Noiri et al., 2006; Takase et al., 1996) and inhibition of their synthesis resulted in a reduced infarct size (Hoshida et al., 1989). In cerebral ischemia, PGE2 mediates excitotoxic injury and neuroinflammation via its receptors EP1, EP2 and EP3 (Li et al., 2021) and is associated with kidney damage in renal IRI (Wang et al., 2019a).

After the initial pro-inflammatory phase, the production of eicosanoids switches to pro-resolving factors that were shown to exert protective effects in several models of IRI. In renal IRI, PGI2 and PGE1 are vasodilative and protect from hypoxia-mediated renal tissue damage (Wang et al., 2019a). Cardiac IRI was aggravated in mice lacking the receptor for PGI2 indicating a protective effect of endogenous PGI2, which was independent of its effects on neutrophils and platelets (Xiao et al., 2001) and is in line with experiments showing a protective effect of its analogues during cardiac IRI (Johnson et al., 1990; Simpson et al., 1987). 12(S)- and 15(S)-HETE ameliorated cerebral IRI by inhibiting NF-κB, INOS, and COX-2 through PPARγ activation (Sun et al., 2015). CYP450 eicosanoids, such as 11,12-EET and 14,15-EET rescued declined wound healing induced by ischemia (Sommer et al., 2019) and 14, 15-EET analogues decreased infarct size and promoted recovery after IRI by reducing contractile dysfunction (Campbell et al., 2017). 20-HETE on the other hand was shown to be beneficial or deleterious in renal IRI dependent on the model being uni-or bilateral (Roman et al., 2011), whereas in other studies it was shown to exert detrimental effects by promoting vascular inflammation, tubular injury and loss of renal function (Hoff et al., 2011). Inhibition of 20-HETE was shown to enhance blood brain barrier function, preserve tight junction integrity in cerebral IRI (Liu et al., 2014b) and decrease cerebrovascular inflammation by reducing ROS and NF-κB activation (Toth et al., 2013).

Specialized pro-resolving lipid mediators, such as LX4, RvD1, RvD2, RvD1, MaR1 and ProtectinD1, have similar roles in IRI by limiting PMN infiltration, tissue damage, pro-inflammatory mediators, ROS production, fibrosis and by promoting efferoicytosis and M2 polarization of macrophages (Chiang et al., 1999; Duffield et al., 2006; Kim and Conte, 2020; Xian et al., 2016). Remote lung injury following hind limb IRI was associated with a age dependent decline in the SPM:LT (RvD1:LTB4) ratio, defective efferoicytosis and unresolved inflammation (Rymut et al., 2020). Treatment with RvD1 mitigated IRI-induced lung injury, promoted efferoicytosis and decreased the cleavage of Mer proto-oncogene tyrosine kinase (MerTK), which is a known stimulator of SPM synthesis (Cai et al., 2016). Macrophages treated with conditioned media derived from senescent cells displayed increased MerTK cleavage, impaired efferoicytosis and a decreased SPM:LT ratio, which was not the case in macrophages derived from MerTK cleavage-resistant (MerTK−/−) mice. Aged MerTK−/− mice exhibited less infiltration of neutrophils and PMNs and displayed improved efferoicytosis compared to wildtype mice. Thus, paracrine effects of senescent cells impaired SPM-induced resolution through enhanced degradation of MerTK in IRI-induced lung injury.

cPLA2 is one of the key mediators of IRI-induced tissue damage by activating the production mainly of AA-derived eicosanoids, which are driving the inflammatory phase before a switch to pro-resolving species limits further damage. Thus, cPLA2 deficiency or inhibition was found to protect from cerebral, cardiac and pulmonary IRI (Bellido-Reyes et al., 2006; Liu et al., 2017; Saito et al., 2012; Zhang et al., 2012). Inhibition of monoacylglycerol lipase (MAGL), which degrades the endocannabinoid 2-arachidonoylglycerol (2-AG) and produces AA, attenuated pulmonary IRI and reduced AA and its downstream metabolites PGI2, TXB2 and LTBE4 again demonstrating a detrimental effect of AA-derived eicosanoids during IRI (Xiong et al., 2018).

Ceramides are upregulated in IRI and are implicated in cell death and tissue damage. However, during ischemic preconditioning ceramides exert protective effects that can be attributed to the formation of their metabolite SP1 (He and Schuchman, 2018), which seems to have great potential for limiting tissue damage through regulating cell survival, vascular integrity and inflammatory cascades after cardiac, renal and cerebral IRI (Raza et al., 2020).

The progression from acute kidney injury following renal IRI to chronic kidney disease accelerates with age and is associated with increased cellular senescence (Schmitt and Cantley, 2008; Sørensen-Zender et al., 2014). Similarly, aged mice suffered from increased mortality, elevation of creatinine levels and interstitial fibrosis which was associated with increased levels of senescent cells (Clements et al., 2013). Prevention of cellular senescence in renal tubular cells through inhibition of p53 with pifithrin-α resulted in decreased renal fibrosis (Yang et al., 2010) and prevented acute renal failure (Hochegger et al., 2007) following renal IRI. Knockout of INK4a, which encodes for the cell cycle inhibitors tumor suppressor ARF (p19ARF) and cyclin-dependent kinase inhibitor 2A (p16INK4a), resulted in decreased tubular cell apoptosis, increased cell proliferation and lower creatinine levels after renal IRI and enhanced tissue regeneration through attenuating capillary loss (Lee et al., 2012). Conversely, knockout of cyclin-dependent kinase inhibitor 1A variant 1 (p21), another cell cycle inhibitor and marker for cellular senescence resulted in an increased mortality after renal IRI indicating a positive effect of senescence in this context (Megyesi et al., 2001). Impairment of autophagy in autophagy protein 5 (ATG5) knockout mice reduced the formation of senescent...
cells and caused less tubular damage and inflammation after renal IRI and promoted the recovery by reducing interstitial fibrosis and enhancing renal function (Baisantry et al., 2016). After inducing renal IRI, clearance of senescent cells, either in the p16-3MR mouse model or by administering senolytic drugs, attenuated kidney fibrosis but had little effect on tubular damage (Jin et al., 2019; Li et al., 2021a). Similarly, after cardiac IRI, the removal of senescent cells improved cardiac function and vascularization, decreased scar size by attenuating biological processes associated with inflammation and fibrosis and increased the survival rate (Dookun et al., 2020; Walaszczuk et al., 2019). In addition, the process of organ transplantation involves IRI, and cellular senescence either present in the donor organ or induced in the host during the procedure is associated with impaired functionality of the transplant and increased mortality (McGlynn et al., 2009; Melk et al., 2008; Naesens, 2011; Siegenthaler et al., 2014; Tullius et al., 2010). Clearance of senescent cells or inhibition of senescence conversely improves transplant function and transplantation outcome (Braun et al., 2012; Iske et al., 2020).

7. Lipids and longevity

The lipidome undergoes fundamental changes during the ageing process, especially during wound healing (Gruber et al., 2021), and thus may represent an important link to extreme longevity. In fact, longer-lived animals have undergone an increased selective pressure in lipid composition genes (Jobson et al., 2010). Extreme longevity manifests itself in elevated levels of ceramides, involved in cellular-stress response, and a fatty acid profile that is resistant to lipid peroxidation (Borchman et al., 2017; Jové et al., 2017, 2013; Mitchell et al., 2007; Munro and Blier, 2012). Moreover, lipid-related interventions prolonged the longevity of several model organism (Johnson and Stolzing, 2019), especially lowering the amount of sphingolipids (Huang et al., 2014). At the NIA multicentre study, several life extending substances were identified, of which one was a non-selective COX-inhibitor, N-acetylalaclyclic acid, and one was an 5-LO-inhibitor, Nordihydroguaiaretic acid (Strong et al., 2008). Lipid-related non genetic and genetic interventions extend the lifespan of several model organisms. Therefore, the lipid metabolism is a direct and strong regulator of ageing (Johnson and Stolzing, 2019).

8. Conclusions and future perspectives

The beneficial role of senescent cells in wound healing is currently a widely accepted dogma and is based on the essential role of senescent cell derived PDGF-AA for the induction of myofibroblast differentiation (Demaria et al., 2014) and the limiting effect of senescent cells on fibrotic responses following tissue repair (Jun and Lau, 2010; Krizhanovsky et al., 2008). Yet, these studies leave many questions unanswered and do not address the paradox of the beneficial role of senescent cells and the impaired wound healing capacity of aged individuals (Ashcroft et al., 2002; Kim et al., 2015), where senescent cells are chronically present (Lewis et al., 2011; Ressler et al., 2006).

The clearance of chronically present senescent cells in aged mice prior to wounding using genetic models (Demaria et al., 2014) could provide a direct link between cellular senescence and impaired wound healing in wounds of aged individuals. Establishing such a relationship would warrant additional experiments to investigate the differences of chronic and acute senescence in wound healing. Several studies demonstrated that cellular senescence is a dynamic process with temporal alterations in the secretion of SASP factors (Hernandez-Segura et al., 2017; Ito et al., 2017), which could explain the dual role of senescent cells in wound healing. Interestingly, it was recently shown that the secretion of eicosanoids is also orchestrated in a time-dependent manner following induction of senescence (Wiley et al., 2019). An elegant way to decipher the impact of early and late senescent cells could be achieved by exogenous addition of these cells in a wound healing model deprived of endogenous senescent cells.

However, we currently cannot rule out the possibility that the prolonged presence of senescent cells in the aged tissue causes impaired wound healing rather than a change in the senescent phenotype. Thus, the chronic presence of senescent cells could deplete the regenerative potential by exhausting stem cell populations (Yosef et al., 2016), altering the microstructure of the skin (Blair et al., 2020) or creating a chronically inflamed microenvironment by recruiting pro-inflammatory immune cells (Chambers et al., 2021) and inducing M1 polarization in macrophages (Lujambio et al., 2013). The identification of molecules, and mechanisms of how these cells differentially affect the process of wound healing and the herein involved cell types, will be key for developing future clinical applications to combat chronic non-healing wounds.

One promising target clinical application are leukotrienes, which are increased in non-pathogenic conditions, such as IRI or bleomycin-induced lung injury, and dysregulated in non-healing wounds, where they delay wound healing through excessive inflammation. SPMs and selected prostaglandins on the other hand accelerate wound healing, as indicated by the promotion of resolution, without causing defects in the initial inflammation. Thus, the dysregulation of the eicosanoid metabolism in senescent cells could explain at least to some extend the mechanisms behind impaired wound healing in aged individuals. As it is relatively easy to administer topical treatments targeting the eicosanoid and SPM synthesis and signalling pathways in skin wounds, it represents a promising strategy for patients with acute injury or surgery-induced injury as well as chronic wounds with aberrant inflammation or impaired vascularization.

Another strategy to improve vascularization might be exogenous supplementation with EETs or inhibition of their degradation by soluble epoxide hydrolase (sHE) (Spector, 2009). The systemic administration of 11,12-EET, 14,15-EET and sHE inhibitor led to increased vascularization (Sander et al., 2013). Additionally, the treatment with sHE inhibitor or a combination of sHE inhibitor and EETs increased the vascularization of a transplanted skin graft (Supp et al., 2016). These studies suggest that administration of EET or sHE inhibitors may improve neovascularization and wound healing through their anti-inflammatory effect. In fact, endothelial-derived EETs play an essential role in promoting tissue growth in vivo, including liver regeneration, kidney compensatory growth, lung compensatory growth, wound healing, corneal neovascularization, and retinal vascularization (Panigrahy et al., 2013).

Another promising candidate might be MSC-derived EVs. Several reports suggest that they play a role during the proliferation phase of wound healing having a stimulating effect on proliferation and migration of fibroblast, epithelial and endothelial cells and also regulating collagen deposition (Samaeekia et al., 2018; Shabbir et al., 2015; Zhang et al., 2016, 2015) (reviewed in (Cabral et al., 2018; Than et al., 2017)). In fact, EVs from MSC enhance tissue regeneration, specifically by switching the macrophage polarization to M2 or by being generally anti-inflammatory (Deng et al., 2019; Heo et al., 2019; Willis et al., 2018).

As outlined in this review, lipids are important effectors in cellular senescence and wound healing, making them likely candidates to confer the beneficial and detrimental influence of senescent cells on wound healing and tissue regeneration. Yet, there are no comprehensive data available about the alterations of the lipidome during cellular senescence which encompasses all bioactive lipid species and includes time-dependent changes in the complete range of cell types involved in wound healing and tissue regeneration. Moreover, recent advances in mass spectrometry-based methods now facilitate the analysis of enzymatic and non-enzymatic modifications of lipids at a global scale, summarized under the term “eplitidrome” (Gruber et al., 2021). A recent study by us demonstrated a complex alteration of the eplitidrome in senescent dermal fibroblasts, which differed depending on the senescence-inducer (Narzt et al., 2020) indicating a complex regulation
of the lipid metabolism during senescence, as it was observed in other studies (Wiley et al., 2019). These intriguing results warrant further studies, specifically to unravel the involved enzymes and mechanisms behind observed changes.

Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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