Journal of Pathology
J Pathol 2013; **229:** 250–263
Published online in Wiley Online Library
(wileyonlinelibrary.com) **DOI:** 10.1002/path.4108

INVITED REVIEW

Hanging in the balance: endogenous anti-inflammatory mechanisms in tissue repair and fibrosis

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Abstract

Inflammation is the physiological response to tissue injury caused by pathogens or trauma. Nevertheless, inflammation should be resolved in a timely manner, resulting in elimination of the inflammatory cells and mediators from the injured tissue, to avoid its deleterious consequences. Uncontrolled inflammation can lead to inflammatory, autoimmune, and cancerous disorders that are the result of improper resolution. The healing of the injured tissue during the termination of inflammation must also be tightly controlled since excessive tissue repair can lead to fibrosis and scarring of the affected organ. In the last three decades, it has been revealed that the resolution of inflammation is tightly orchestrated by specific cells, protein, and lipid mediators that are produced at proper timing and distinct locations. The bioactivity of these anti-inflammatory, pro-resolving, and immunoregulatory agents results in clearance of the tissue from inflammatory leukocytes and their products, and the return of homeostatic tissue architecture and function. Here, we will survey the current endogenous mechanisms governing the resolution of inflammation and directing it towards injury healing and halting of acquired immune responses while preventing excessive tissue repair and fibrosis. We focus on the role played by apoptotic polymorphonuclear cells (PMNs), 15-lipoxygenase (LO)-derived lipid mediators, and TGFβ in this macrophage-governed decision-making process and suggest new modes of action for fibrosis prevention and return to homeostasis.

Keywords: resolution of inflammation; fibrosis; macrophages; TGFβ; lipid mediators

Received 29 August 2012; Revised 5 September 2012; Accepted 12 September 2012

No conflicts of interest were declared.

Introduction

Complete resolution of an acute inflammatory response and return to homeostasis are key processes in maintaining good health. Sustained, non-resolving inflammation can lead to various autoimmune, metabolic, and inflammatory disorders, such as rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, asthma, atherosclerosis, obesity, chronic obstructive pulmonary disease (COPD), and cancer [1,2]. The final stages of resolution of inflammation lead to tissue remodelling and repair, as well as immune regulation and shutting off of acquired immune responses at primary and secondary lymphoid tissues. Nevertheless, if tissue repair is not properly controlled, it might lead to fibrosis and tissue scarring that disrupt tissue structure and can have fatal outcomes. Fibrosis is a pathological condition that comes about due to chronic, non-resolving inflammation that allows simultaneous production and action of inflammatory, reparative, and angiogenic factors in an unbalanced fashion [3,4]. Under these conditions, excessive deposition of extracellular matrix (ECM) severely impairs tissue architecture and function. The progression of fibrosis typically leads to organ failure and death. The major cell type involved in ECM production and secretion is the myofibroblast, which produces large amounts of collagen I (Col I) and fibronectin [5]. Myofibroblasts differentiate from tissue fibroblasts and are characterized by the expression of Col I and α-smooth muscle actin (α-SMA). Other sources of myofibroblasts are still under scrutiny, but the contribution of bone marrow-derived fibrocytes, pericytes, and epithelial–mesenchymal transition has been reported (reviewed in refs 3 and 4). Macrophages are a significant balancing element in normal tissue repair and fibrosis since they are the major source of TGFβ, a key cytokine in the resolution of inflammation, immune regulation, wound healing, and fibrosis, as well as pro- and anti-inflammatory cytokines and lipid mediators [6]. TGFβ induces myofibroblast differentiation, activation, and survival in different organs and through various mechanisms [7–10], and is therefore an important convergence point in tissue fate.

During the resolution of inflammation, PMNs that took part in its onset undergo apoptosis and get cleared

by macrophages which as a result undergo reprogramming [11,12]. Macrophage reprogramming leads to the production of wound healing, immuno-regulatory and angiogenic cytokines and growth factors, such as TGFβ, IL-10, and VEGF [13–16]. It is also associated with liver X receptor (LXR)-mediated induction of arginase-1 expression [17–19] and 12/15-LO expression in murine macrophages (15-LO in human monocytes/macrophages) [17,20]. Arginase-1 diverts arginine metabolism in macrophages from inducible NO synthase (iNOS/NOS2)-mediated production of NO towards the production of ornithine (and consequently polyamines and proline/hydroxyproline), which promotes fibroblast growth and collagen synthesis [21] and is thus instrumental in both wound repair and fibrosis [22]. Of note, macrophage arginase-1 deletion increased type 2 cytokine production and exacerbated fibrosis in *Schistosoma mansoni* infection [23], thus suggesting different modes of action for arginase-1 in different settings. 12/15-LO produces various hydroxylated fatty acid derivatives with different resolution-promoting, wound-healing, and anti-fibrotic actions, which will be further discussed in the following sections.

Endogenous mediators in the balance between tissue repair and fibrosis

As indicated above, both tissue repair and fibrosis can be the outcome of endogenous anti-inflammatory events that are regulated by soluble and cellular moieties (Figure 1). The role played by apoptotic cell clearance, TGFβ, 15-LO, and its products in this context and the interactions between these modules during the resolution of inflammation and prevention of fibrosis will be discussed in detail in the following sections. However, in this section we would like to indicate select soluble anti-inflammatory mediators that possess either tissue-healing or pro-fibrotic properties to illustrate the dichotomy in tissue remodelling [1,3].

Gases

Another oxygenase (other than 15-LO) with well-established anti-inflammatory properties is heme oxygenase-1. This enzyme produces the anti-oxidant bilirubin and carbon monoxide (CO). CO's anti-inflammatory properties include up-regulation of IL-10 and IL-1R antagonist expression and abrogation of TNFα production induced by LPS [24–26], and seem to abrogate sepsis as well as Th1- and Th2-mediated autoimmunity [27]. CO is also responsible for some of the anti-inflammatory properties of IL-10, such as inhibition of TNFα production [28,29]. Of note, heme oxygenase-1 expression in hepatocytes and endothelial and corneal epithelial cells is up-regulated by the pro-resolving lipid mediator LXA_4 [30–32], and accounts for LXA4's anti-fibrotic, anti-inflammatory, and wound-healing properties. CO also exerts anti-fibrotic actions, such as abrogation of bleomycin-induced lung fibrosis and TGFβ-induced α-SMA expression [33–35]. Hydrogen sulphide (H_2S) is another recently discovered gaseous anti-inflammatory mediator. It is formed by the enzymatic breakdown of cysteine, performed by cystathionine-γ-lyase, and has significant anti-inflammatory actions, in particular on the vascular system during ischaemic events [36] and on the resolution of inflammation in the mucosal system [37]. Interestingly, H_2S was also found to inhibit cardiac hypertrophy and fibrosis induced by abdominal aortic coarctation, possibly through diminishing cardiac angiotensin II [38,39], and inhibits inflammation and fibrosis in the liver and lungs as well [40].

Cytoplasmic proteins

A well-appreciated inhibitor of inflammatory responses, especially when acting on neutrophils, is the cytoplasmic protein annexin A1. Studies by Perretti and co-workers [41,42] have revealed annexin A1 expression and release to be a major mode of action for glucocorticoids (GCs) during the resolution of inflammation. GCs also induce expression of the lipoxin (LX) A_4 receptor (ALXR/FPRL1) on monocytes/macrophages, and this receptor binds annexin A1 [43,44]. Macrophage activation by annexin A1 leads to improved uptake of apoptotic PMNs, while PMN apoptosis is also enhanced by annexin A1 [45,46]. Notably, annexin A1 was recently found to abrogate fibrosis following bleomycin instillation in the lung and following nerve injury in corpus cavernosum tissue [47].

Cytokines/growth factors

IL-10 is a major anti-inflammatory and regulatory cytokine with pleiotropic actions in various immune responses and pathologies [1,48,49]. Importantly, it is produced by macrophages during the initial phase of resolution of inflammation and in response to apoptotic cells, but its secretion seems to decrease during latter resolution and prior to macrophage departure of the healing tissue towards lymphoid organs [20,50–52]. In agreement with its suppressive nature and its anti-inflammatory and regulatory properties, most studies have shown an anti-fibrotic role for IL-10 (reviewed in ref 3). Nevertheless, some studies indicate that its impact on fibrosis might vary significantly and depends on the experimental model used [53–55].

Other soluble mediators are better known for their anti-fibrotic effect, but also exert anti-inflammatory actions in select settings. For example, bone morphogenic protein (BMP) 7 is a TGFβ family member that regulates the proliferation and differentiation of both mesenchymal and epithelial cells [56–58]. Recent studies indicate that BMP7 prevents fibrosis by promoting epithelial wound repair and regeneration in the

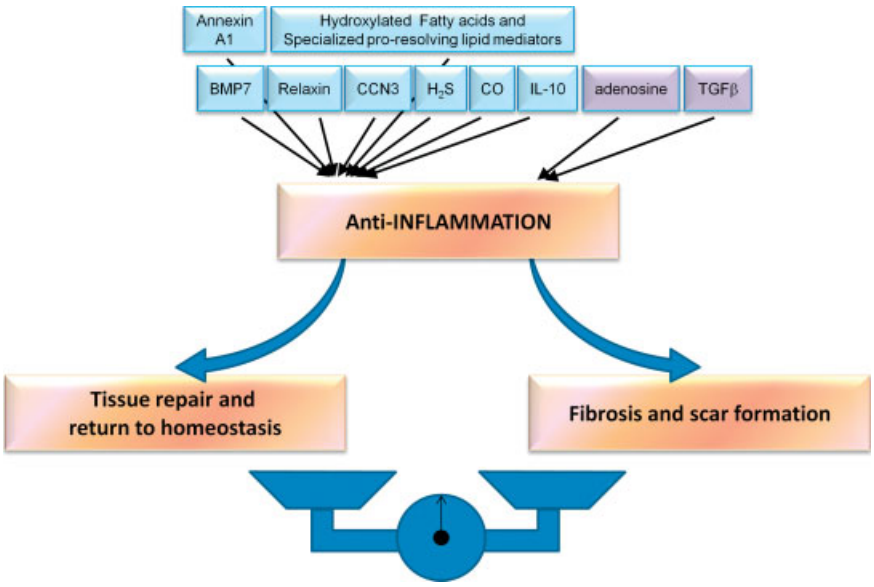

Figure 1. Endogenous mediators in the balance of tissue structure and function. Select soluble mediators released during the resolution of inflammation that exert anti-inflammatory properties and tip the scale of wound healing towards tissue repair and homeostasis (light blue boxes), or alternatively towards fibrosis and scar formation (purple boxes).

kidney and liver [56,57] and fibrogenesis in mesengial cells [59] with inhibitory Smad family members as the target molecule to curtail TGFβ signalling. Of interest, BMP7 also exerts inhibitory/reversing actions in the chronic phase of trinitrobenzene sulphonic acid (TNBS)-induced colitis [60] and prevents neutrophil infiltration in ischaemic kidneys [61].

Another recently appreciated inhibitor of fibrosis is the CCN (CYR61/CTGF/NOV) family member CCN3/NOV. CCN family members are matricellular proteins that regulate ECM production and deposition. TGFβ down-regulates CCN3 expression in mesengial cells, while the expression of its pro-fibrotic family member CCN2/CTGF is up-regulated [62]. In turn, CCN3 antagonizes CCN2-induced Col I expression in a Smad-independent manner. Thus, CCN3 acts downstream of TGFβ; the trigger to its expression is unknown [62]. In animal models, CCN3 was found to inhibit diabetic renal fibrosis [63] and experimental glomerulonephritis [64]. In inflammatory settings, CCN3 inhibited endothelial VCAM-1 expression and monocyte adhesion [65], reduced pain through MMP2 and MMP9 repression, and reduced CCL2 expression [66]. CCN3 also promoted skin wound healing through angiogenesis and promotion of fibroblast proliferation [67].

Tissue regeneration cycles are significant events in the maintenance of the female reproductive system and hence avoidance of excess production of ECM components is essential to fertility. Relaxin is a peptide hormone from the insulin family that inhibits uterine contraction and induces growth and softening of the cervix [68]. Relaxin has been shown to be responsible for ECM remodelling in various sites, during pregnancy, through the induction of collagen proteolysis [68]. Relaxin deficiency leads to fibrotic foci formation in old mice, both male and female, suggesting that it plays a role outside the reproductive system as well [69]. In inflammation-associated fibrosis, relaxin was found to inhibit Col I deposition and α-SMA expression in fibroblasts through various mechanisms, including MMP expression and contraction inhibition [70–72]. Relaxin was also found to exert vasorelaxing actions and to inhibit vascular inflammation [73–77]. Importantly, relaxin inhibits inflammatory cytokine production in macrophages and during acute pancreatitis [76,78], possibly through its binding to the GC receptor. Thus, relaxin might act concomitantly to promote resolution of inflammation and inhibit/reverse fibrosis.

Nucleosides

As indicated in Figure 1, some endogenous anti-inflammatory mediators also promote fibrosis due to overt activation of the tissue remodelling and repairing system. The role of TGFβ in this context will be elaborated on in the next section. Another intriguing example is the nucleoside adenosine produced from ATP by ectonucleotidases. Adenosine exerts inflammatory, wound-healing, pro-resolving, and pro-fibrotic actions [1,79–81], and therefore its metabolism also plays a role in these processes [82,83]. This perplexing array of responses could be explained by the fact that adenosine is released by both necrotic cells during trauma and inflammation and macrophages that engulf apoptotic cells during resolution [79,84]. In addition, adenosine has four receptors (A1, A2A, A2B, and A3) and exerts opposing actions when binding to different receptors. Interestingly, the adenosine A2A receptor was found to be involved in regulating the anti-inflammatory and pro-resolving properties of macrophages, such as down-regulation of NO-induced

chemokine secretion and PMN infiltration to inflamed sites [84], and was critical for the survival of animals that were subjected to sub-lethal inflammation [85]. Moreover, this receptor was found to abrogate fibrosis during crescentic glomerulonephritis [86]. However, the same receptor was also involved in arginase-1 and TIMP-1 up-regulation in macrophages [81,87,88] and promoted fibrosis and scar formation in other experimental models [89]. The adenosine A3 receptor has been linked to the anti-inflammatory and anti-apoptotic actions of GCs in monocytes/macrophages [90,91].

In sum, the sampled evidence presented here indicates an active and complicated network of endogenous soluble mediators that act in concert and in perfect timing to ensure proper resolution of inflammation, tissue repair, and avoidance of excessive ECM deposition and scarring of the healing inflammatory wound. This complexity was underscored by Perretti and co-workers [92], who found LXA_4 to induce the release of annexin A1 from PMNs and consequently block their infiltration to inflamed sites. Moreover, Souza *et al* found IL-10 to be essential for the protective actions of LXA_4 and annexin A1 in germ-free mice undergoing intestinal ischaemia/reperfusion [93]. Clearly, changing the timing of release or the dosage of the above-indicated soluble mediators can severely hamper this balance and result in deleterious outcomes.

TGFβ – a multifaceted cytokine in the resolution of inflammation, tissue repair, and immune regulation

TGFβ is a pleiotropic peptide released by many cell types and involved in the regulation of tissue growth and homeostasis in many processes including embryonic and haematopoietic development, inflammation and its resolution, tissue remodelling and repair, immune tolerance, and cancer ([94] and refs cited therein). TGFβ is expressed by all immune cells in the adult, and all of its family members (TGFβ-1, -2, and -3) undergo proteolytic cleavage to become active. The activity of TGFβ in the tissue is highly regulated by its pre-pro-peptide [latency-associated protein (LAP)] and other tissue proteins and proteases that control its bioavailability [95]. TGFβ induces intracellular signalling through two serine/threonine kinase receptors and a family of transducers termed Smads [96,97]. Importantly, TGF inhibitory activity has also been attributed to Smad proteins, with Smad7 playing a major role [97]. The role of TGFβ1 as a mediator and initiator in wound healing and fibrotic responses has been heavily studied [98], with its production mostly attributed to circulating monocytes and tissue macrophages and its actions mostly affecting fibroblasts/myofibroblasts [6]. During the resolution of inflammation, however, macrophages are both the producers of TGFβ1 and the responders to its signalling. TGFβ was found to be released by apoptotic T cells [99] as well as by macrophages that engulf apoptotic PMNs (efferocytosis) [15,100], and this effect is further enhanced by pro-resolving and efferocytosis-promoting mediators, such as thrombospondin, LXA_4, surfactant protein A, and annexin A1 [16,101–103]. TGFβ, in turn, promotes efferocytosis and immune silencing/reprogramming of macrophages, resulting in reduced inflammatory cytokine production [15,17,100,101,104]. TGFβ also enhances CCR5 expression on apoptotic PMNs to assist in the clearance of its ligands during peritonitis [105]. Of note, TGFβ also induced PPARγ expression in macrophages [17], thereby possibly promoting the apoptotic cell-induced anti-inflammatory and anti-fibrotic effect [106–110].

Fibrosis has also been reported to be associated with type 2 inflammation, regulated primarily by the cytokines IL-4 and IL-13 [3], which induce several tissue repair-associated genes, such as procollagens I, III, and VI, arginase-1, and MMPs [3], and are counteracted by type 1 responses [111,112]. There is evidence that Th2 cytokines cooperate with TGFβ to promote fibrosis, although they might induce TGFβ-independent fibrosis as well [113]. IL-13 promotes the production of latent TGFβ in macrophages [114,115] as well as the expression of LAP- and ECM-degrading enzymes [116–118].

TGFβ also plays a central role in lymphocyte development, immune regulation/suppression, and tolerance [119,120]. It induces the differentiation of regulatory T cells (Tregs) that is hallmarked by expression of the transcription factor forkhead box 3 (FOXP3). TGF is essential for the induction and maintenance of FOXP3 in inducible Tregs (iTregs) that are induced in the periphery and cooperates with another macrophage-produced immunoregulatory cytokine, IL-10, in promoting their suppressive activity [121–123]. Importantly, PDGF production by Tregs was recently found to promote lung fibrosis [124], and Tregs were also found to support Th17-mediated fibrosis [125].

Recently, a distinct subpopulation of peritoneal macrophages, termed $CD11b^{low}$/Mres, was identified during late resolution of inflammation [20]. These cells secrete higher levels of TGFβ than their neighbouring $CD11b^{high}$ macrophages; express high levels of 12/15-LO; and migrate to lymphoid organs. These properties make them prime candidates for connecting acute and acquired immune responses, and hence for promoting immune regulation and tolerance in lymphoid tissues. Curiously, TGFβ is also released from macrophages undergoing reprogramming following the engulfment of cellular debris during muscle injury and repair, and promotes muscle regeneration and return to normal function [126,127]. Macrophage reprogramming also takes place during the prevention of insulin resistance and recovery from spinal cord injury [128,129], suggesting additional roles for the M2–Mres axis in other macrophage-responsive pathologies.

Altogether, the pleiotropic and sometimes opposing actions of TGFβ in tissue repair and return to homeostasis, as well as in fibrosis and scar formation, indicate that it is greatly affecting the delicate equilibrium of these processes and that excessive concentrations, prolonged exposure, or absence of limiting signals from various sources can account for the well-established role of this cytokine in fibrotic disorders.

Engulfment of apoptotic leukocytes – a balanced endogenous anti-inflammatory and resolution-promoting trigger

Unlike dominant soluble anti-inflammatory mediators, such as TGFβ and adenosine, apoptotic leukocytes seem to induce a more balanced pro-resolving and wound-healing response that does not result in fibrosis. Rather, deficiencies in apoptotic cell clearance can result in autoimmune disorders that stem from the immunogenic exposure of nuclear self-antigens and 'converted' pro-inflammatory proteins, such as high mobility group protein B1 (HMGB1 [130,131]), but can also be attributed to hampered immune silencing/reprogramming of macrophages that results in excessive pro-inflammatory NO, cytokine, and chemokine production by macrophages and diminished anti-inflammatory mediators [11,132,133]. The recognition, engulfment, and responsiveness to apoptotic cells are fundamental properties of resident and inflammatory macrophages and are cardinal events in processes such as tissue morphogenesis and homeostasis, embryonic development, haematopoiesis, immunity, and the resolution of inflammation [134–136]. The recognition and uptake of apoptotic cells by macrophages through 'eat me' signals (and the absence of 'do not eat me' signals) expressed on their surface and their cognate receptors have been extensively studied and reviewed [137]. However, apoptotic cells also transduce signals to the engulfing macrophages that result in significant molecular and functional adjustments that address physiological needs consequent to the identified cell death. During the resolution of inflammation, the recognition and engulfment of apoptotic cells by macrophages evokes distinct signalling events [132,138] that block the release of pro-inflammatory mediators from macrophages. This release is activated by bacterial moieties, and its silent, non-phlogistic blockage [52,100,139] is accompanied by the production of TGFβ and IL-10 [13,15–17,51,140], cytokines that can promote resolution and wound repair. The engulfment of apoptotic leukocytes by macrophages also leads to inhibition of inducible NO synthase (iNOS) expression and stimulates the expression of arginase-1 in the RAW 264 macrophage cell line [17,106], thereby preventing reactive NO production. In addition, the production of angiogenic growth factors [14] by macrophages is consequent to the uptake of apoptotic cells. Elucidation of the signalling pathways activated directly and indirectly by apoptotic cells revealed significant roles for nuclear transcriptional regulators, such as peroxisome proliferator-activated receptor (PPAR)-γ [17] and -δ [141], as well as LXR [18], in promoting anti-inflammatory properties.

All types of apoptotic cells express phosphatidylserine (PS) on the outer leaflet of their cytoplasmic membrane, and this is apparently the major signalling module used by these cells to communicate their mortal status with phagocytic cells [135] and to induce suppressive efferocytosis-promoting signalling in macrophages through PPARγ and 15-LO expression [108]. This efficient anti-inflammatory mechanism is mimicked by parasites that induce TGFβ production through PS expression on their surface [142]. Other opsonizing molecules, such as iC3B and milk fat globule-EGF factor 8 protein (MFG-E8), have been shown to promote the immune silencing of macrophages by apoptotic leukocytes [143–145]. Importantly, apoptotic leukocytes also release soluble anti-inflammatory mediators, such as sphingosine-1 phosphate and lactoferrin [146–148], which exert macrophage reprogramming and apoptosis resistance properties as well as blocking of neutrophil infiltration, while other such mediators are chemoattractants of macrophages termed 'find me' signals [137]. Recent reports have identified new inhibitory molecules expressed on the surface of apoptotic PMNs that limit efferocytosis and regulate the immune-silencing of macrophages (Figure 2 [149,150]). Intriguingly, these molecules act in different manners. D6 is a membrane-embedded GPCR with well-established pro-resolving properties [151] that has been found to enhance the ending of macrophage phagocytic activity (efferocytic satiation) and to promote their reprogramming to an anti-inflammatory phenotype [149], possibly through the binding and presentation of efferocytosis-enhancing chemokines [152–154]. Proteinase-3, on the other hand, is a neutrophil granule protein with pro-inflammatory and autoimmune actions [155] that binds calreticulin on apoptotic PMNs and macrophages to disrupt its homotypic interactions when mediating efferocytosis and reprogramming/immune-silencing [150,156].

The prototypic anti-inflammatory Th2 cytokines IL-4, IL-13, and IL-10, as well as immune responses to parasites, were found to promote many of the outcomes of efferocytosis in macrophages. These cytokines are well-appreciated antagonists of the M1 response and macrophage pro-inflammatory properties [3,115,157,158], while IL-4 and IL-13 can also promote fibrosis through TGFβ production [159]. IL-13 was also found to promote vascular endothelial growth factor production during lung injury [160,161]. Importantly, IL-4 and IL-13 also activate PPARγ [161] and PPARδ [162] to promote monocyte/macrophage alternative activation. LXR was recently found to synergize with IL-4 in the induction of arginase-1 expression and promotion of an M2 phenotype in regressive atherosclerotic lesions [19]. Thus, efferocytosis

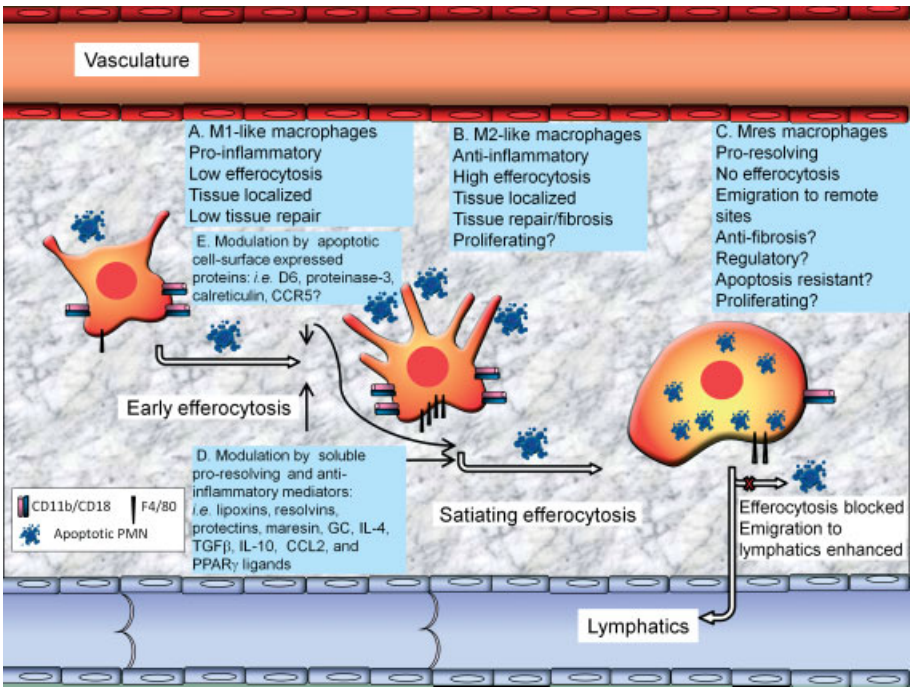

Figure 2. Macrophage reprogramming and immune-silencing by apoptotic PMNs in tissue repair and fibrosis. Early responses to pathogens or trauma are executed by type 1-like macrophages prior to encounter with apoptotic PMNs (A). Upon tethering and engulfment of cell corpses (early efferocytosis), the macrophage switches to a type 2-like phenotype that counters inflammation while being intensely involved in efferocytosis, tissue repair, and return to homeostasis. Importantly, type 2 macrophages can also promote fibrosis and scar formation and exert a proliferative potential (B). As the engulfment of apoptotic PMNs by the macrophage continues and reaches a threshold level determined by the resolving milieu (satiating efferocytosis), the macrophage undergoes another switch to the Mres phenotype (C). These macrophages reduce the expression of pro-fibrotic arginase-1 and MMP-9 (a protease involved in the release and activation of TGFβ) and display reduced phagocytosis of extracellular particles including apoptotic cells. Consequently, Mres exit the resolving tissue and reach lymphoid organs and other target tissues. At these remote sites, Mres presumably produce 12/15-LO-derived pro-resolving lipid mediators and deliver homeostatic signals to antigen-presenting cells and lymphocytes. Mres are probably more resistant to apoptosis and more amenable to proliferate and thereby enhance their immunoregulatory impact. Moreover, Mres that stay in the resolving tissue might express higher levels of anti-inflammatory, anti-fibrotic, and anti-oxidant proteins to limit tissue damage and fibrosis. 12/15-LO-derived lipid mediators and intermediates in their production probably also contribute to the anti-inflammatory and anti-fibrotic properties of Mres in the resolving tissue. Early and satiating efferocytosis can be modulated by soluble pro-resolving and anti-inflammatory mediators, such as lipoxins, resolvins, protectins, maresin, GCs, IL-4, TGFβ, IL-10, CCL2, and PPARγ ligands, or by apoptotic cell surface-expressed D6, proteinase 3, and calreticulin (D, E). As a result, the reprogramming and departure of Mres to the lymphatics may be adjusted to impact the termination of acquired immune responses.

induces phenotypic and molecular switches and activates signalling pathways in macrophages that resemble M2 polarization. Moreover, M2 polarization promotes efferocytosis through the induction of different molecular modules, whereas M1 macrophages exert reduced uptake of apoptotic cells. Along these lines, recent studies also found that efferocytosis is a self-promoting process and that M2 pathways play key roles in mediating this feature of macrophage function [163]. Significantly, the engulfment of apoptotic cells *per se* limits excessive tissue repair and fibrosis [164], possibly through the enhancement of MFG-E8-mediated phagocytosis of Col I [165]. Thus, it might have implications for fibrotic outcomes of tissue biology, such as tumour development and metastasis [166,167].

Macrophages are paradoxically involved in both the generation of fibrosis and its resolution [6], as well as efferocytosis and M2 polarization that generate a positive feedback loop during resolution of inflammation [20,163]. It is much less clear what the events and mediators that stop M2 differentiation and tissue repair/remodelling short of excessive, fibrotic outcomes are. Such events and mediators are inevitably required to complete the resolution of inflammation and restore homeostasis rather than end every infection with a debilitating scar.

15-Lipoxygenase and its products – endogenous healing mediators that escape fibrosis

A major enzymatic pathway that mediates key events in the resolution of inflammation involves the expression and activation of 12/15-LO in mice and 15-LO-1 in humans. The expression and activation of 12/15-LO-1 in murine macrophages are apparently the major course of action by which it exerts beneficial properties in various macrophage-governed inflammatory and autoimmune disorders as well as wound healing and fibrosis, including periodontitis and skin inflammation [168], experimental autoimmune encephalitis (EAE [169]), arthritis [170], lupus-like syndrome [171],

atherosclerosis [172], corneal wound healing [173], and skin fibrosis [174]. 15-LO expression and activity are up-regulated by IL-4 and IL-13 in murine and human monocytes, macrophages, and peripheral blood mononuclear cells [161,175–178]. This up-regulation leads to the production of 15-LO products from octadecadienoic, eicosatetraenoic, and docosahexaenoic acids (ODE, ETA, and DHA, respectively), such as 13-hydroxyoctadecadienoic acid (13-HODE), 15-hydroxyeicosatetraenoic acid (15-HETE), LXA_4 and B_4, 17*S*-hydroxy-DHA, and protectin D (PD) 1 (10*R*,17*S*-dihydroxy-DHA). Macrophage expression of 12/15-LO was found to promote the production of resolvin (Rv) D1 (7*S*,8*R*,17*S*-trihydroxy-DHA) and maresin 1 (7,14-dihydroxy-4*Z*,8,10,12,16*Z*,19*Z*-DHA), in addition to LXA_4 and PD1 [179,180]. The expression of 12/15-LO was also up-regulated in mouse macrophages following their incubation with apoptotic cells [17,20], and its bioactivity increases as resolution progresses to yield many of the above-indicated compounds [17,50,181,182]. Importantly, 12/15-LO expression and anti-inflammatory activity were recently identified in eosinophils that infiltrate the peritoneal cavity during the later phase of resolution [183]. Eosinophil 12/15-LO gave rise to a novel EPA-derived lipid mediator termed RvE3 (17,18-diHEPE) that blocked neutrophil migration *in vivo* and *in vitro* [184]. Macrophages from chronic granulomatous disease (CGD) mice display impaired efferocytosis that could be repaired by IL-4 through the expression of 12/15-LO and activation of PPARγ [108]. Hence, efferocytosis and M2 polarization seem to limit inflammation and promote tissue repair through 15-LO-mediated signalling. 15-LO products can then, through several pathways, block excessive ECM deposition and promote the degradation and clearance of surplus fibrous material to restore normal organ architecture and function.

Along these lines, 12/15-LO products, termed specialized pro-resolving lipid mediators, have been shown to be anti-inflammatory and to promote tissue repair, while playing an anti-fibrotic and immunoregulatory role [185]. The major bioactive 12/15-LO products could be produced from arachidonic acid to yield 15-HETE or LXs, or from DHA to generate PD1, resolvins of the D series, and the recently identified macrophage product maresin 1 [185]. While 15-HETE (and 13-HODE) binds PPARγ to mediate its anti-inflammatory actions [161], LXA_4, PD1, and resolvin D1 seem to act through binding to cell surface GPCRs [186], as well as the aryl hydrocarbon receptor (that binds LXA_4) [187] and the oestrogen receptor [188]. All of these 12/15-LO products induce a broad spectrum of anti-inflammatory actions on neutrophils and macrophages, as well as other cell types [186,189], while RvDs and PD1 also enhance *E. coli* clearance by antibiotics [181]. On the other hand, 12/15-LO products also induce unique pro-resolving properties of macrophages and promote regulatory pathways in lymphocytes. LXA_4, PD1, RvD1, and PPARγ agonists were all found to promote efferocytosis and enhance PMN clearance during resolution [108,190–192]. In addition, PD1 and RvD1 were found to promote macrophage departure of resolving inflammation sites [20,191]. 15-LO-produced lipid mediators are also apparently involved in blocking acquired immune responses and promoting tolerance. LXA_4 enhances TGFβ release during resolution of inflammation concomitantly with 12/15-LO expression by macrophages [105]. Moreover, macrophages that migrate to lymphoid tissue during resolution express higher levels of TGFβ and 12/15-LO [20], suggesting that 15-LO products promote immune regulation through TGFβ up-regulation. Along these lines, LXA_4 and PD1 inhibited inflammatory cytokine secretion from T lymphocytes [175,193] and enhanced CCR5 expression on apoptotic PMNs to promote clearance of its pro-inflammatory ligands [105]. Moreover, LXA_4 was recently found to play a role in the generation of myeloid-derived suppressor cells [194]. Although they promote TGFβ-producing efferocytosis and reprogramming in macrophages, lipid mediators are also effective blockers of fibrosis. LXA_4, PD1, and RvD1 are potent inhibitors of fibrosis in the lung, skin, and kidney [174,195–197], and lipoxins and PD1 are produced during epithelial injury in the cornea and mediate wound repair in addition to counteracting inflammation [173,198].

Monohydroxy products of 15-LO from ODA, ETA, and DHA, namely 13-HODE, 15-HETE, and 17-HDHA, were found to bind a different type of receptor than pro-resolving lipid mediators [161,199]. This nuclear transcription factor, termed PPARγ, is highly involved in macrophage alternative responses and reprogramming and exerts significant anti-inflammatory actions in various inflammatory and metabolic settings [107,199–201]. Importantly, PPARγ expression in macrophages was found to be essential for the resolution of inflammation [202] and efferocytosis in CGD and *in vitro* cultures [106,203]. Of interest, PPARγ ligands can also hamper fibrosis in various models through their actions on fibroblasts, macrophages, and other cells [109,110,204–206], and interfere with lymphocyte activation and proliferation [200]. Overall, 15-LO products can be generated by macrophages following their interaction with apoptotic cells and/or polarization to the M2 phenotype (Figure 3). In turn, these products not only block inflammation, but can also shift the macrophage healing balance from tissue repair/fibrosis to pro-resolution, anti-fibrotic, and regulatory functions. The exact mode of production and action for the different 15-LO products is probably dependent on substrate availability, the concentration formed in the healing tissue, and additional cues from the resolving environment. Nevertheless, they seem to act in concert to antagonize TGFβ-driven matrix deposition and tissue destruction and rather promote post-inflammation tissue healing and return to homeostasis.

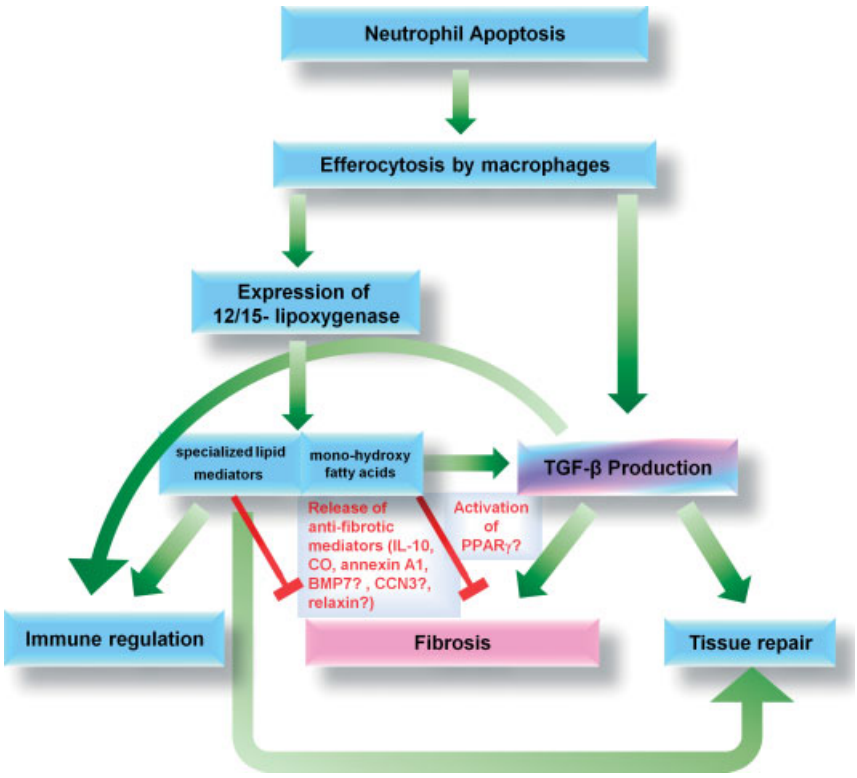

Figure 3. Products of 15-lipoxygenase in the balance between tissue repair, immune regulation, and fibrosis. The engulfment of apoptotic PMNs by macrophages during the resolution of inflammation leads to up-regulation of 15-LO expression and activity, resulting in the generation of mono-, di-, and tri-hydroxy products from ω-6 and ω-3 fatty acids. In addition, this engulfment leads to the release of high levels of TGFβ from macrophages, the major source of this cytokine during tissue repair. TGFβ is essential for tissue repair and immune regulation, which are both instrumental in the return to homeostatic conditions and healthy functioning of the organism. Nevertheless, excessive amounts of this cytokine induce fibrosis and can lead to tissue destruction and loss of function in vital organs, such as the liver, kidney, and lung. The di- and tri-hydroxy products of arachidonic acid and docosahexaenoic acid belong to several series of specialized pro-resolving lipid mediators, namely lipoxins, resolvins, protectins, and maresins. Some of these mediators promote TGFβ production during the resolution of inflammation, but at the same time prevent fibrosis in several experimental models. Importantly, these lipid mediators are also immunoregulatory and possibly play a role in the termination of lymphocytic responses and long-term immunity. Several endogenous mediators, such as IL-10, CO, annexin A1, BMP7, CCN3, and relaxin, have been shown to antagonize the pro-fibrotic activity of TGFβ directly or indirectly and thus might be induced by pro-resolving lipid mediators concomitantly with the production of TGFβ to limit its deleterious actions. Of note, monohydroxy products of 15-LO were found to bind and activate PPARγ, an anti-fibrotic transcription factor, hence suggesting another mode of action for 15-LO in the balance of tissue repair and fibrosis.

Future directions

In this review, we have brought together evidence from the literature to indicate that the delicate balance that exists in tissues that heal from an inflammatory insult is significantly affected by endogenous anti-inflammatory mediators. These mediators not only block additional inflammatory cell infiltration and activation resulting in unwanted tissue damage, but also promote resolution and contained repair of the inflamed tissue, thereby preventing excessive ECM deposition and scar formation. Some well-established anti-inflammatory, pro-resolving, and wound-repairing mediators, such as TGFβ and adenosine, fail to stop the repair process short of fibrotic outcomes, and therefore curtailing their disproportionate activity is essential and can be taken upon by mediators that interfere with TGFβ signalling, block myofibroblast activity, or promote matrix degradation. The 12/15-LO pathway has been found to produce resolution- and healing-promoting lipid mediators that counteract TGFβ in several pathways. While the monohydroxy products of various fatty acids seem to inhibit fibrosis and metabolic consequences of inflammation through binding to PPARγ, the exact mode of anti-fibrotic activity induced by resolution-promoting lipid mediators is still under investigation. Importantly, some of the anti-fibrotic mediators pointed out in this review, such as IL-10, annexin A1, and heme oxygenase-1, were found to be involved in mediating the bioactions of LXA_4. Nevertheless, the elucidation of additional modes of action for endogenous anti-inflammatory mediators in wound repair and prevention of fibrosis will underscore their potential as therapeutic targets and could pave the way for new therapies that will shift the balance in tissue repair towards tissue return to homeostatic functioning.

Acknowledgments

This work was supported by grants from the Israel Science Foundation (grant number 534/09), the Nutricia

Research Foundation, and the Marc Rich Foundation (to AA). AA is a recipient of the Young Scientist Award from Teva Pharmaceuticals Ltd.

Author contribution statement

OT drew the figures and contributed to the literature search. AA designed and wrote the manuscript.

Abbreviations

15-HETE, 15-hydroxyeicosatetraenoic acid; α-SMA, α-smooth muscle actin; ALXR, A4 lipoxin receptor; BMP, bone morphogenic protein; CCN, CYR61-CTGF-NOV; CGD, chronic granulomatous disease; CO, carbon monoxide; Col I, collagen I; COPD, chronic obstructive pulmonary disease; DHA, docosahexaenoic acid; EAE, experimental autoimmune encephalitis; ETA, eicosatetraenoic acid; FOXP3, forkhead box 3; FPRL1, formyl peptide receptor-like 1; GC, glucocorticoid; H_2S, hydrogen sulphide; HMGB1, high mobility group protein B1; iTregs, inducible regulatory T cells; LAP, latency-associated protein; LO, lipoxygenase; LX, lipoxin; LXR, liver X receptor; MFG-E8, milk fat globule-EGF factor 8 protein; Mres, resolution macrophages; PD, protectin D; PMNs, polymorphonuclear cells; PS, phosphatidylserine; Rv, resolvin; TIMP-1, tissue inhibitor of metalloproteinases; TNBS, trinitrobenzene sulphonic acid

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