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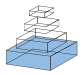

Macrophages in synovial inflammation

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Synovial macrophages are one of the resident cell types in synovial tissue and while they remain relatively quiescent in the healthy joint, they become activated in the inflamed joint and, along with infiltrating monocytes/macrophages, regulate secretion of pro-inflammatory cytokines and enzymes involved in driving the inflammatory response and joint destruction. Synovial macrophages are positioned throughout the sub-lining layer and lining layer at the cartilage–pannus junction and mediate articular destruction. Sub-lining macrophages are now also considered as the most reliable biomarker for disease severity and response to therapy in rheumatoid arthritis (RA). There is a growing understanding of the molecular drivers of inflammation and an appreciation that the resolution of inflammation is an active process rather than a passive return to homeostasis, and this has implications for our understanding of the role of macrophages in inflammation. Macrophage phenotype determines the cytokine secretion profile and tissue destruction capabilities of these cells. Whereas inflammatory synovial macrophages have not yet been classified into one phenotype or another it is widely known that TNFα and IL-l, characteristically released by M1 macrophages, are abundant in RA while IL-10 activity, characteristic of M2 macrophages, is somewhat diminished. Here we will briefly review our current understanding of macrophages and macrophage polarization in RA as well as the elements implicated in controlling polarization, such as cytokines and transcription factors like NFκB, IRFs and NR4A, and pro-resolving factors, such as LXA4 and other lipid mediators which may promote a non-inflammatory, pro-resolving phenotype, and may represent a novel therapeutic paradigm.

Keywords: macrophage, arthritis, inflammation

INTRODUCTION

Macrophages (Mϕ) are one of the resident cell types in synovial tissue, along with fibroblasts. While quiescent in health, Mϕ become activated in the inflamed joint, where they make up around 30–40% of the cellular content, and regulate secretion of pro-inflammatory cytokines and enzymes involved in driving the inflammatory response and joint destruction (Firestein and Zvaifler, 1990). Their position throughout the sub-lining layer and lining layer at the cartilage–pannus junction facilitates their role mediating articular destruction. It is estimated that rheumatoid arthritis (RA) and psoriatic arthritis (PsA) each affects approximately 1% of the population (Firestein, 2003; Gladman, 2009), leading to patient pain and disability as well as contributing to a great economic burden in terms of lost working days and patient health services (Cooper, 2000) and therefore is an area of intense investigation.

As our understanding of inflammation progresses, including the recent concept that resolution of inflammation is an active process rather than a passive return to homeostasis, the role of Mϕ is increasingly appreciated. The inability to resolve acute inflammation may lead to a chronic inflammatory state. Depending on their phenotype, Mϕ can secrete either pro- or anti-inflammatory cytokines and mediate matrix destruction or deposition. Synovial Mϕ participate in many of the events driving inflammation including the stimulation of angiogenesis, leukocyte and lymphocyte recruitment, fibroblast proliferation, and protease secretion leading to eventual joint destruction (Burmester et al., 1997; Vallejo et al., 2003; Abeles and Pillinger, 2006). While RA and PsA are considered more inflammatory than osteoarthritis (OA), it can still contain an inflammatory component, of which Mϕ play a large part. In all of these conditions Mϕ derived mediators can drive inflammation and cartilage destruction. Depletion of Mϕ from OA synovial cell cultures significantly reduced TNFα and IL-1β levels. Depletion of Mϕ from both RA and OA synovial cell cultures leads to reduced synovial fibroblast responses such as cytokine and MMP production (Janusz and Hare, 1993; Bondeson et al., 2010). Both macrophages and fibroblasts display an activated cell phenotype with increased cell surface expression of HLA-DR and leukocyte adhesion molecules (Athanasou et al., 1988; Alvaro-Gracia et al., 1990) participating in T-cell activation. Interaction of Mϕ with T-cells potentiates the expression of several pro-inflammatory mediators such as IL-1α and β and MMPs (McInnes et al., 2000).

Important pro-inflammatory cytokines like TNFα and IL-l are abundant in the inflamed synovium and are characteristically released by classically activated (M1) Mϕ. These cytokines are

central to joint destruction. The importance of Mϕ in driving the inflammatory response has been highlighted by several quantitative microscopic studies, where they have shown that Mϕ number; correlates with disease activity (Tak et al., 1997), has potential use as a biomarker for disease (Kruithof et al., 2006; Bresnihan et al., 2009) and declines in response to therapy (Goedkoop et al., 2004; Canete et al., 2010). Mϕ can induce angiogenesis (Leibovich et al., 1987), and hypoxia, a prominent feature of the inflamed joint, promotes the survival of monocytes/macrophages and induces their anaerobic adaptations including glycolysis (Roiniotis et al., 2009).

It is long appreciated that Mϕ play an important role in the pathogenesis of arthritis and this observation was supported by studies showing that the number of Mϕ was increased in clinically affected joints compared to non-affected joints (Kraan et al., 1998). Several studies also linked the number of synovial Mϕ to inflammatory cytokine production joint destruction (Mulherin et al., 1996). As the search for a reliable biomarker in RA continued, the role of Mϕ was again highlighted. The culmination of this work has led to sub-lining CD68 positive synovial Mϕ currently being the only validated biomarker for disease severity (Tak et al., 1997) and response to therapy in arthritis (Haringman et al., 2005), further confirming their importance in the pathogenesis of this disease, a finding which is independent of treatment type (Haringman et al., 2005; Thurlings et al., 2008). Considering the similarities between synovial inflammation in RA and PsA, Mϕ have also been proposed as a biomarker for response to therapy in PsA. Several studies have concluded that Mϕ number is decreased in PsA synovial tissue following therapy (Goedkoop et al., 2004; Kruithof et al., 2006; Canete et al., 2010).

ACTIVATION OF SYNOVIAL MACROPHAGES

Besides the abundant pro-inflammatory cytokines and chemokines present in inflamed synovial tissue, activation, and survival of Mϕ can be achieved through acetylation or de-acetylation of histones. Downstream effects of TNFα and other molecules results in the induction of histone acetyltransferase (HAT) activity in Mϕ which causes acetylation of histones and subsequent modulation of transcriptional activity. HAT activity is counteracted by histone deacetylases (HDAC). Two recent studies have found evidence of depressed HDAC activity in RA, particularly in synovial macrophages and fibroblasts. The ratio of HDAC:HAT activity was significantly lower in RA synovial tissue compare to healthy controls. In combination with this, HDAC inhibition decreases IL-10 production from whole tissue synovial explants cultures, indicating a negative effect on anti-inflammatory pathways, which would lead us to believe that a lack of HDAC may contribute to perpetuation of inflammation (Huber et al., 2007; Grabiec et al., 2008, 2010). Despite this, HDAC inhibition is showing promise for inflammatory diseases. HDAC inhibitors reduced IL-6 production from TNFα stimulated Mϕ and induced apoptosis of RA synovial fluid (SF) Mϕ, even in the presence of a pro-inflammatory stimulus (Grabiec et al., 2010). This is of interest considering the ability of synovial cells and infiltrating cells to evade apoptosis during joint inflammation contributing to synovial hypercellularity (Salmon et al., 1997; Perlman et al., 2001). The potential use of HDAC inhibitors has been further promoted by their success in suppressing synovial inflammation and cartilage destruction in a CIA mouse model (Nasu et al., 2008).

Toll like receptors (TLR) are pattern recognition receptors that mediate response to infection. However, it is becoming apparent that some of these receptors may become activated by non-infectious agents from within the body and may therefore play a role in autoimmune conditions such as RA. Engagement of TLRs induces signaling through a well defined pathway involving MyD88 that leads to transcriptional activation (Joosten et al., 2003). TLR2 and TLR4 appear to be particularly associated with RA. TLR knockout and arthritis mouse models, or a combination of both, have highlighted the position of TLRs in the pathogenesis of arthritis. In a model of spontaneous arthritis due to IL-1 receptor antagonist knockout, simultaneous knockout of TLR4 attenuated inflammation while TLR2 knockout produced a more severe arthritis. Knockout of TLR9 had no effect (Abdollahi-Roodsaz et al., 2008). This clearly indicates a potential benefit for TLR4 antagonism in RA. However the role of TLR2 seems less defined as other studies have shown that knockdown of TLR2 produces beneficial effects in arthritis (Joosten et al., 2003). Further to this, many TLR ligands have been identified in synovial inflammation (Okamura et al., 2001; Park et al., 2004). Acute serum amyloid A (SAA), which is significantly upregulated in arthritis and propagates pro-inflammatory effects similar to TNFα (O'Hara et al., 2000; Mullan et al., 2006; Connolly et al., 2011), is a functional ligand for TLR2 and may contribute to the deleterious effects of SAA in arthritis (Cheng et al., 2008). RA Mϕ are more responsive to stimulation than Mϕ from other forms of inflammatory arthritis, despite no difference in Mϕ number (Huang et al., 2007). Therefore, engagement of TLR2 and 4 may contribute to Mϕ activation and a sustained Mϕ response in RA.

Rheumatoid factor (RF) is one of the diagnostic criteria for RA and can help to distinguish RA from similar arthropathies like PsA. Classification of RA as an autoimmune disease came initially from the discovery of IgG auto-antibodies in the blood of patients (Waaler, 1940; Franklin et al., 1957). RF is mostly IgM-RF, but IgG-RF and IgA-RF can also be detected in some patients. The cellular receptors for IgG are the Fcγ receptors, FCγRI (CD64), FcγRII (CD32), and FcγRIII (CD16). All three receptors are expressed on synovial Mϕ (Laurent et al., 2011) as well as lymphocytes. FcγRIII has been demonstrated to play a role in the development of arthritis through animal models. Mice deficient in FcγRIII are protected from the development of collagen induced arthritis without alteration of their humoral response, and therefore the protection is not due to alterations in T-cell responses (Ståhl et al., 2002; Andrén et al., 2006). Polymorphisms in Fcγ receptors are associated with incidence of RA as well as response to therapy (Morgan et al., 2006; Canete et al., 2009; Thabet et al., 2009; Morales-Lara et al., 2010).

ARE SYNOVIAL MACROPHAGES POLARIZED?

In the immune system Mϕ are effective antigen presenting cells with phagocytic activity which respond to lymphocyte derived cytokines. However, the responses elicited by Mϕ are variable and depend entirely on the tissue environment. We now know these responses can be either pro- or anti-inflammatory. Dedicated reviews on this topic discuss in more detail the cytokines and chemokines involved in promoting one phenotype over another

(Mantovani et al., 2004; Murray and Wynn, 2011) but an overview of the main components are outlined in **Figure 1**. Classically activated M1 Mϕ have a pro-inflammatory phenotype, producing high levels of TNFα, IL-1, IL-6, IL-12, IL-23, reactive oxygen species, and low levels of IL-10. Alternatively activated Mϕ, of which there are three subsets (Mantovani et al., 2004; Martinez et al., 2008), display and anti-inflammatory phenotype, producing high levels of IL-10, IL-1 receptor antagonist, decoy IL-1RII, TGFβ, and low levels of IL-12. Both types are necessary for correct resolution of inflammation. An interesting, and potentially useful, property of these Mϕ is that they remain plastic and polarization into one phenotype does preclude re-polarization (Stout et al., 2005). Therefore, if we could elucidate the exact pathways and transcription factors involved in promoting one phenotype over the other *in vivo*, this system could be exploited for therapeutic gain.

There appears to be a lack of evidence for Mϕ polarization in either direction in the inflamed joint. It has been suggested that spondyloarthropathies such as PsA display a more M2 profile compared to RA patients and that M1 mediators correlate with joint inflammation in RA (Vandooren et al., 2009). However, in general, most studies of Mϕ in arthritis focus on important Mϕ functions and not polarization. The mediators that can control Mϕ polarization are indeed present in the synovium and some show potential as therapeutic targets. Synovial lining layer thickness is greater in RA, compared to PsA or healthy control subjects, which is associated with an increase in synovial Mϕ and fibroblasts. PsA patients tend to have less lining layer Mϕ than RA patients. This has been observed in many comparative studies. Danning et al. (2000) also found similar levels of IL-10 in RA and PsA synovium, despite the difference in synovial lining layer Mϕ numbers, however levels were described as being quite low. It is difficult to determine if this lack of IL-10 is a contributor to or consequence of the overwhelming inflammation in the joint. A study by Mottonen et al. (1998) found that 68% of Mϕ isolated from RA SF were CD86 positive and that SF Mϕ can take on a dendritic cell phenotype when exposed to a combination of IL-4 and GM-CSF and that these cells were more effective at activating T-cells than control or TNFα stimulated Mϕ. The effects of IL-4 + GM-CSF were mediated through CD86, a marker of classically activated Mϕ. IL-10 was able to inhibit the observed effects with IL-4 + GM-CSF as it downregulated the expression of CD86, as well as CD-40 and HLA-DR which also participate in Mϕ mediated T-cell activation. This is consistent with the classification that M2c Mϕ, which are driven by IL-10 are involved in suppression of the immune response (Mantovani et al., 2004). These results may appear confusing as IL-4 along with IL-13 drive the M2a or alternative Mϕ phenotype which should be involved in anti-inflammatory responses. However GM-CSF drives the M1 phenotype in monocyte derived macrophages so this may be the driving force for inflammatory responses in these experiments.

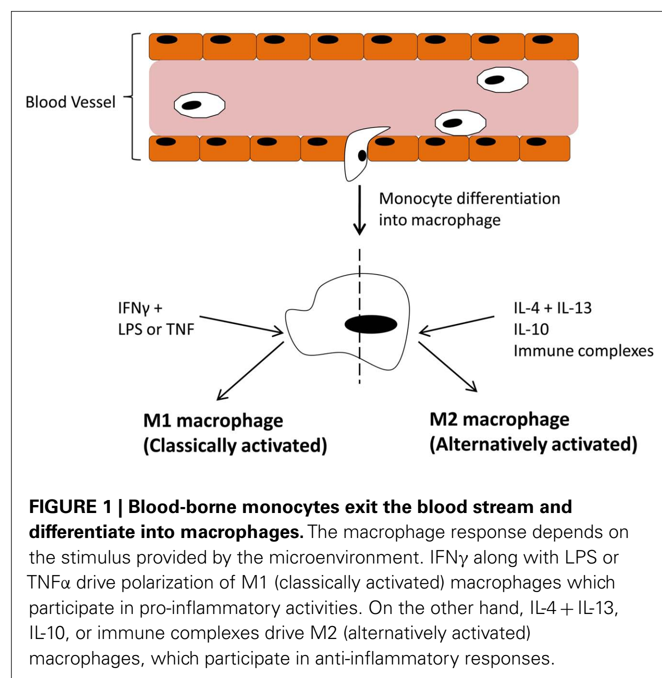

FIGURE 1 | Blood-borne monocytes exit the blood stream and differentiate into macrophages. The macrophage response depends on the stimulus provided by the microenvironment. IFNγ along with LPS or TNFα drive polarization of M1 (classically activated) macrophages which participate in pro-inflammatory activities. On the other hand, IL-4 + IL-13, IL-10, or immune complexes drive M2 (alternatively activated) macrophages, which participate in anti-inflammatory responses.

WHAT REGULATORS IN SYNOVIAL INFLAMMATION COULD POTENTIALLY INFLUENCE MACROPHAGE POLARIZATION?

Figure 1 has outlined the cytokines and regulators that promote M1 or M2 polarization. The extent of expression of these factors in the joint varies. The M1 Mϕ phenotype is induced by interferon-γ (IFNγ) in combination with either lipopolysaccharide (LPS) or TNFα. IFNγ is highly expressed in RA synovial tissue and its levels significantly correlate with disease severity (Milman et al., 2010). Exposure to INFγ increases the response of Mϕ exposed to other stimuli by either upregulating pro-inflammatory cytokines, like TNFα, or downregulating anti-inflammatory cytokines, like IL-10 (Erwig et al., 1998; Wallet et al., 2010). TNFα is a master cytokine in inflammation and as such is a potent inducer of other pro-inflammatory cytokines (Nawroth et al., 1986; Butler et al., 1995), is chemotactic for leukocytes, is a potent inducer of angiogenesis (Leibovich et al., 1987), stimulates adhesion molecule expression in SFC *in vitro* (Marlor et al., 1992), and lymphoid migration into inflamed synovial tissue *in vivo* (Wahid et al., 2000). Within the inflamed joint macrophages, fibroblasts, lymphocytes, and endothelial cells produce TNFα. An important role for TNFα in arthritis was confirmed by studies which showed its potential to degrade both cartilage (Dayer et al., 1985) and bone (Bertolini et al., 1986). Further rationale for the involvement of TNFα in the progression of inflammatory arthritis was provided when transgenic mice expressing a modified human TNFα gene spontaneously developed arthritis which exhibited increased human TNFα protein, joint inflammation, bone erosion, and cartilage destruction. In this study, antibodies specific for human, but not mouse TNFα reduced disease severity (Keffer et al., 1991). In subsequent studies administration of a monoclonal antibody to TNFα ameliorated inflammation and joint damage after disease onset in a CIA model of arthritis (Williams et al., 1992). TNFα cytokine targeted therapies have now been developed for inflammatory arthritis. The first clinical trial was undertaken in the UK in 1992 and demonstrated that targeted biologic therapy decreased serum IL-6 levels, swollen joint numbers and levels of the acute phase proteins CRP and A-SAA which are markers of inflammation (Elliott

et al., 1993). Alternatively, anti-inflammatory and M2 polarizing cytokines like IL-10 are lowly expressed in arthritis as its signaling is blocked during FCγ receptor ligation (Ji et al., 2003), and treatment with the pro-resolving mediator annexin A1 stimulates release of IL-10 (Ferlazzo et al., 2003). Treatment of PBMC with IL-10 caused a change in the ratio of T_h17:Treg cells in favor of Treg cells and decreased production of the pro-inflammatory cytokine IL-17 (Heo et al., 2010). Animal models of arthritis have also demonstrated how treatment with IL-10 can suppress the development and progression of joint inflammation, even in established disease (Walmsley et al., 1996; Whalen et al., 1999; Mauri et al., 2003).

The cytokines involved in promoting polarization are well defined, however less is known about which transcription factors are utilized to induce polarization. IRF5 (interferon regulatory factor 5) has been implicated in driving the M1 phenotype as well as actively suppressing M2 polarization and driving T_h1 and T_h17 responses (Krausgruber et al., 2011). While the study by Krausgruber et al. (2011) was not performed in synovial Mϕ, animal studies suggest that inflammation in RA is driven by T_h1 cytokines such as IFNγ, which is upregulated early in the disease process (Miltenburg et al., 1992; Schulze-Koops and Kalden, 2001) and a rapid growth in interest in the T_h17 pathway and indeed IL-17 itself in the last few years would suggest that this would warrant investigation in the inflamed joint. Recent reports confirm that alterations in the IRF5 gene confers susceptibility to RA (Dieguez-Gonzalez et al., 2008; Han et al., 2009; Dawidowicz et al., 2011) as well as many related illnesses such as inflammatory bowel disease, Sjogrens syndrome, and systemic lupus erythematosus (Dideberg et al., 2007; Graham et al., 2007; Miceli-Richard et al., 2007). Other transcription factors in the IRF family, like IRF3 (Biswas et al., 2006) and IRF4 (Satoh et al., 2010) have been implicated in promoting Mϕ polarization in other disease settings, and IRF family members contribute to determination of dendritic cell fate (Tamura et al., 2005). These findings make the IRF family attractive candidates to study in the context of Mϕ's in arthritis.

NR4A is part of the orphan nuclear receptor superfamily which have roles in lipid metabolism and inflammation (Desreumaux et al., 2001; Oosterveer et al., 2010; Hong et al., 2011). Receptors in the same superfamily as NR4A are downregulated in arthritic tissue and their activation appears to play a role in inhibiting disease progression (Bonnelye et al., 2008; Park et al., 2010). However members of the NR4A subfamily appear to have less clearly defined effects to the anti-inflammatory family members liver X receptor and peroxisome-proliferator-activator receptor and drive inflammation in human synovial tissue (Murphy et al., 2001). The role of NR4A receptors specifically in Mϕ polarization has not yet been elucidated, however, any role for NR4A in Mϕ polarization would be an interesting finding due to the modulation of NR4A by both dexamethasone and methotrexate, which are effective treatments for joint inflammation in some patients. NR4A receptors can also activate NFκB in murine Mϕ (Pei et al., 2006) where it promotes transcription of pro-inflammatory genes. In arthritis, and inflammation in general, NFκB can be considered a master transcription factor as it is utilized by many ligand–receptor complexes to modulate gene transcription. TNFα and IL-1β which are abundant in the inflamed joint employ this transcription factor and in turn can be regulated by it. NFκB activation has been detected prior to the clinical onset of arthritis in animal models (Tsao et al., 1997; Han et al., 1998) and the NFκB pathway has been directly targeted as a treatment method for RA confirming its essential role in the pathogenesis of this disease (Wakamatsu et al., 2005). Immunohistochemical staining has confirmed nuclear expression of NFκB subunits in synovial Mϕ (Handel et al., 1995). The NFκB family consists of five proteins; p50, p52, RelA (p65), RelB, and c-Rel. These proteins form homo or heterodimers to determine gene transcription. RelA, RelB, and c-Rel contain a transcriptional activation domain and therefore upregulate gene expression, however p50 and p52 do not contain the transcriptional activation domain and homodimers of these proteins can sometimes have a repressing function (Bohuslav et al., 1998). NFκB p50 activation has been linked to promoting M2 polarizing genes in Mϕ (Porta et al., 2009). This study found that knockout of the NFκB p50 subunit prevented the development of tolerance in LPS challenged Mϕ by restoring M1 mediators and inhibiting M2 cytokines. Similarly, Saccani et al. (2006) found that accumulation of the p50 homodimer occurred in the nuclei of tumor associated Mϕ and that these Mϕ expressed an M2 phenotype. Therefore due to the prominence of the NFκB pathway in RA it remains an interesting candidate for influencing Mϕ polarization. A summary of all factors discussed here are outlined in **Table 1**.

MACROPHAGES AND RESOLUTION OF INFLAMMATION

There is a growing understanding of the molecular drivers of inflammation and an appreciation that the resolution of inflammation is an active process rather than a passive return to homeostasis. Endogenously produced mediators that actively promote the resolution of inflammation are now under investigation

Table 1 | Description of the regulators in synovial inflammation that could potentially influence macrophage polarization.

Polarizing factors	Mϕ subset promotion	Reference
CYTOKINES		
IFNγ + (LPS/TNFα)	M1	Erwig et al. (1998), Wallet et al. (2010)
IL-4 + IL-13	M2	See review Mantovani et al. (2004)
IL-10	M2	See review Mantovani et al. (2004)
Immune complexes	M2	See review Mantovani et al. (2004)
TRANSCRIPTION FACTORS		
IRF3	M2	Biswas et al. (2006)
IRF4	M2	Satoh et al. (2010)
IRF5	Promotes M1, actively inhibits M2	Krausgruber et al. (2011)
NFκB p50	M2	Porta et al. (2009), Biswas et al. (2006)
NR4A	Not yet investigated in Mϕ polarization	

for their therapeutic use. These are molecules such as lipoxins, resolvins, protectins, and annexins. Lipoxin A4 (LXA4) is an eicosanoid produced by the transcellular metabolism of arachidonic acid by 15/5- or 5/12-lipoxinagese (Serhan et al., 1984). Its biosynthesis is co-incident with the resolution phase of inflammation and many of its bioactions are mediated through ligation of its receptor, ALX/FPR2 (Fiore et al., 1994). LXA4 is produced in inflamed synovial tissue (Thomas et al., 1995) where it can downregulate pro-inflammatory activities of activated fibroblasts and upregulate anti-inflammatory activities, even in the presence of a pro-inflammatory stimulus which acts through the same receptor (Sodin-Semrl et al., 2004; Kronke et al., 2009; Chan and Moore, 2010). In other disease models, LXA4 has been shown to induce anti-inflammatory/pro-resolving actions such as inhibition of neutrophil recruitment and activation (Filep et al., 1999), regulation of NFκB activation (Decker et al., 2009), and the clearance of apoptotic cells by Mϕ (Godson et al., 2000). Neutrophils are the first effector cells at the site of inflammation. Once these cells have carried out their functions in regard to host defense they are programmed to die by apoptosis. Resolution of inflammation and return to homeostasis involves phagocytosis of apoptotic neutrophils to prevent the persistence to necrosis and leakage of cellular contents, which may itself begin an inflammatory reaction. Despite the lack of apoptosis occurring in all cell types in the inflamed synovium, resident synovial Mϕ retain the capacity to phagocytose apoptotic cells, even at an early timepoint after arthritis induction (van Lent et al., 2001). If normal apoptosis and phagocytosis could be induced in the inflamed synovium, possibly by native LXA4 or its stable analogs, this process may trigger a normal resolution of inflammation.

In order to encourage phagocytosis, apoptotic cells release mediators that attract phagocytes toward them, essentially flagging themselves for engulfment. One such mediator is the anti-inflammatory compound annexin A1 (Arur et al., 2003; Scannell et al., 2007). Annexin A1 is a 37-kDa protein of the annexin superfamily where all family members contain a similar core region and a distinct N-terminal region which confers specificity of function. Generally annexin A1 is localized to the cytoplasm where, upon stimulation, it is mobilized to the cell membrane and secreted (for an extensive review on annexin A1 see Perretti and Dalli, 2009). Interestingly annexin A1 also signals through ALX/FPR2, the same receptor utilized by LXA4 and SAA. Annexin A1 is widely expressed in many cell types including Mϕ. Immunohistochemical analysis has demonstrated an increased expression of annexin A1 in the RA synovial lining layer macrophages and fibroblasts compared to OA and normal joints. This may, however, be due to the increased lining layer thickness in this condition (Goulding et al., 1995) as other studies have shown decreased binding of annexin A1 to several cell types in RA (Goulding et al., 1992; Sampey et al., 2000). Glucocorticoid stimulation causes annexin A1 mobilization to the cell surface and secretion where it mediates glucocorticoid induced anti-inflammatory effects. This is of particular interest in arthritis as glucocorticoid therapy is one of the current treatments for this condition (Flower, 1988; Podgorski et al., 1992; Yang et al., 1998, 1999; Maderna et al., 2005). However, as is increasingly the case for many mediators, the role of annexin A1 may not be as unambiguous as initially described and it may also potentiate pro-inflammatory actions in arthritis. An investigation by Tagoe et al. (2008) has revealed synergistic actions with TNFα and annexin A1 in terms of MMP production from synovial fibroblast cells. They saw firstly that TNFα can induce expression of endogenous annexin A1 and secondly that TNFα along with the annexin A1 mimetic peptide Ac2-26 enhanced secretion of MMP-1 which was dependent on FPR2/ALX, Erk, Jnk, and NFκB (Tagoe et al., 2008). As mentioned, this study was not performed in synovial Mϕ, but as they have similar actions to synovial fibroblasts, the same results may be produced by these cells once investigated. Further to this, it has also been shown that administration of human recombinant annexin A1 during the immunization phase of the collagen induced arthritis model perpetuated the development of the signs and symptoms of arthritis. This may have been due to the increased T-cell activation and skewing toward a T_h1 phenotype by annexin A1 acting through FPR2/ALX (D'Acquisto et al., 2007). T-cells from RA patients 48 h post steroid therapy demonstrated depressed expression of annexin A1 (D'Acquisto et al., 2008) further lending support to the possibility that annexin A1 may also mediate pro-inflammatory actions. However we must be careful to acknowledge the actions of specific cleavage products from full length annexin. One such cleavage product has been identified as causing neutrophil extravasation, an important event in inflammation, where other truncated forms of annexin cannot (Williams et al., 2010).

CONCLUSION

In the study of inflammation and our efforts to promote its normal resolution, Mϕ remain to the fore of our interest. In the inflamed joint, Mϕ will continue to be a focal point for therapeutic intervention which, currently, centers around cytokine blockade but now has the possibility of extending into Mϕ re-programming. This remains an interesting and a yet to be fully explored option in terms of treatment for synovial inflammation.

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