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Matrix Metalloproteinase and G Protein Coupled Receptors: Co-conspirators in the pathogenesis of autoimmune disease and cancer

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Abstract

Similarities in the pathologies of autoimmune diseases and cancer have been noted for at least 30 years. Inflammatory cytokines and growth factors mediate cell proliferation, and proteinases, especially the collagenase, Matrix Metalloproteinase-1 (MMP-1), contribute to disease progression by remodeling the extracellular matrix and modulating the microenvironment. This review focuses on two cancers (melanoma and breast) and on the autoimmune disorder, rheumatoid arthritis (RA), and discusses the activated stromal cells found in these diseases. MMP-1 was originally thought to function only to degrade interstitial collagens, but recent studies have revealed novel roles for MMP-1 involving the G protein-coupled receptors: the chemokine receptor, CXCR-4, and Protease Activated Receptor-1 (PAR-1). Cooperativity between MMP-1 and CXCR4/SDF-1 signaling influences the behavior of activated fibroblasts in both RA and cancer. Further, MMP-1 is a vital part of an autocrine/paracrine MMP-1/PAR-1 signal transduction axis, a function that amplifies its potential to remodel the matrix and to modify cell behavior. Finally, new therapeutic agents directed at MMP-1 and G protein-coupled receptors are emerging. Even though these agents are more specific in their targets than past therapies, these targets are often shared between RA and cancer, underscoring fundamental similarities between autoimmune disorders and some cancers.

Keywords

rheumatoid arthritis; collagenase; CXCR4; PAR-1; synovial fibroblasts; carcinoma associated fibroblasts; endothelial cells

As noted 30 years ago by Sporn and Harris [1], the pathologies of autoimmune diseases and cancer share the concepts of aberrant cell proliferation, remodeling of the extracellular matrix and perturbation of the tissue microenvironment. Specifically, they held that inflammatory

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cytokines and growth factors are important in initiating and maintaining proliferation, and that proteinases, especially the collagenase, Matrix Metalloproteinase-1 (MMP-1), contribute substantially to disease progression by remodeling the matrix and modulating the microenvironment. The authors also noted that as the biochemical mechanisms of disease pathogenesis become identified, new therapeutic targets will emerge. Although gaps in our knowledge of mechanism(s) remain, many of their insights are valid today, and we have a clearer picture of the molecular pathways mediating the pathogenesis of autoimmune disorders and cancers. Sporn and Harris considered seven proliferative diseases: cancer, atherosclerosis, rheumatoid arthritis, psoriasis, pulmonary fibrosis, scleroderma and cirrhosis of the liver.

In this review, we will concentrate on two of these: cancer (melanoma and breast) and the autoimmune disorder, rheumatoid arthritis (RA), and we will focus on the role of MMP-1 in activated fibroblasts and its effects on the behavior of endothelial cells. Many of our studies have centered on the mechanisms controlling MMP-1 expression in the activated synovial fibroblasts (synoviocytes) found in RA. In RA, increased production of MMP-1 is at the end of a cascade of inflammatory/immune mediators, and MMP-1 is now well established as a major mediator of irreversible connective tissue destruction. As our studies progressed, the similarities in the role of MMP-1 in RA and cancer became increasingly evident, leading us to investigate MMP-1 expression in two invasive cancers, breast and melanoma. Interestingly, this work has revealed novel roles for MMP-1 involving the G protein-coupled receptors, the chemokine receptor, CXCR-4, and Protease Activated Receptor-1 (PAR-1), roles which may also be applicable to RA. We will discuss how expression of these receptors on activated stromal cells conspires with MMP-1 to modulate cellular behavior in RA and cancer.

Matrix Metalloproteinase-1 (MMP-1), rheumatoid arthritis (RA), and cancer

MMPs are a family of zinc-dependent endopeptidases that function at neutral pH and that are responsible for the degradation of the extracellular matrix [2–4]. While low levels of these enzymes are essential for normal homeostasis, high levels are implicated in the pathology of several diseases. Although many MMPs are elevated in these conditions, MMP-1 has a particularly prominent role. Collagen (types I, II and III) is the body's most abundant protein, comprising 30% of all protein, and collagen degradation is accomplished primarily by the interstitial collagenases, MMP-1, MMP-8, MMP-13 and MMP-14. The major collagen in joints is type II, which is almost unique to cartilage and which is preferentially degraded by MMP-13 produced by chondrocytes. MMP-8 is predominantly a product of neutrophils, although its expression by other cell types is now noted. MMP-14 is a membrane bound MMP and is constitutively expressed at low levels. In contrast, MMP-1 is expressed robustly by many cell types, and it degrades all three stromal collagens, making it the foremost player in collagen degradation in many diseases, including cancer and RA.

RA is an autoimmune disease, which affects numerous joints throughout the body. It is characterized by chronic inflammation of the synovial cells lining the joints and by irreversible destruction of the cartilage, tendons and bone that comprise joint structure [5,6]. Although the cause of RA remains elusive, a genetic predisposition related to HLA genotype and some inciting event are thought to trigger the disease by inducing an initial immune/inflammatory response in the joint tissues. This local reaction then recruits additional inflammatory cells (neutrophils and macrophages) to the inflamed joints, and these cells release cytokines [e.g., Interleukin-1 β (IL-1 β) and tumor necrosis factor- α (TNF- α)], exacerbating inflammation and the immune response. Further, these cytokines activate the synovial fibroblasts within the joint, increasing cell proliferation and expression of matrix-degrading enzymes, especially the MMPs. The increased cell proliferation produces a mass of activated fibroblasts (pannus), with ensuing destruction of type II collagen in cartilage and type I collagen in tendon and bone. This inflammatory/cytokine/MMP loop is self-sustaining until the connective tissues are destroyed,

resulting in chronic pain and subsequent loss of joint function. Because of their singular ability to cleave the collagen triple helix, the over-expression of MMP-1 and MMP-13 by synovial fibroblasts and chondrocytes is critical in the pathogenesis of RA [5,6].

Similar to RA, the hallmark of cancer, cell proliferation, is also accompanied by the aberrant expression of MMPs, which are classically linked to invasion and metastasis due to their ability to degrade the extracellular matrix [2,7]. In particular, the destruction of type IV collagen in basement membrane by MMP-2 and MMP-9, and the degradation of the interstitial collagens, types I and III, in the stromal tissues by the collagenases, are essential components of metastasis. Although the tumor cells may mediate this tissue destruction, adjacent stromal cells (i.e., fibroblasts and endothelial cells) in the tumor microenvironment also degrade and remodel the matrix. However, these resident stromal cells must become activated through the engagement of signal transduction pathways. This occurs through interactions with the tumor cells, creating a population of stromal cells that shares many characteristics with the activated synovial fibroblasts in RA. In addition to degrading the extracellular matrix, MMPs can also mediate cell behavior by liberating peptides and growth factors anchored in the extracellular matrix, and by activating receptors to induce signal transduction pathways. Thus, by directly mediating cell behavior, MMPs can influence physiology and disease pathology, emphasizing the need to understand mechanisms regulating their expression.

Regulation of MMP-1 gene expression

MMP expression is tightly regulated and occurs primarily at the level of transcription [2–4, 7]. In normal tissues, basal/constitutive expression is low, but is induced in response to growth factors and cytokines that activate signal transduction pathways (Figure 1). The molecular mechanisms of transcriptional activation of several MMPs, including MMP-1, at the promoter are well characterized and comprise the Activator Protein-1 (AP-1) element in the proximal region of the promoter ~ -70 bp, several ETS sites, and a Nuclear Factor kappa B (NFkB)-binding site located upstream. Chromatin remodeling is also an essential, often involving histone acetylation in response to inductive stimuli [8,9]. In many cancers increased expression of several MMPs, again including MMP-1, is constitutively high, due to either aberrant activation of signal transduction pathways and/or continuous stimulation of growth factor receptors, which target the MMP-1 promoter [7].

Although MMP expression is controlled primarily at the transcriptional level, mRNA stability also contributes. In addition, post-translational mechanisms are important, since MMPs are secreted as a zymogen, and require proteolytic cleavage for enzymatic activity. MMPs are subject to inhibition of their enzyme activity by a group of molecules called tissue inhibitors of metalloproteinases (TIMPs). TIMPs inhibit MMP enzyme activity on a 1:1 molar basis, but the high levels of MMPs seen in pathological conditions exceed TIMPs, and net tissue destruction continues [2–4].

Carcinoma Associated Fibroblasts (CAFs), MMP-1 and CXCR4

While cancer research has traditionally focused on the tumor cells, host/tumor cell interactions in the tumor microenvironment are increasingly recognized as critical components of tumor development and progression [10,11]. These interactions between the tumor and adjacent stromal cells result in the production of stromal factors, such as growth factors, chemokines, cytokines, proteases, and vascular-stimulating factors [12,13], all of which can contribute to the growth of the primary tumor and its dissemination to distant sites. The stromal fibroblasts found within carcinomas are termed carcinoma-associated fibroblasts (CAFs). Just as a tumor has been equated to a “wound that never heals” [14], CAFs have been compared to “activated fibroblasts” or myofibroblasts, which are present in inflammatory environments, including RA, where they are a major components of the proliferating pannus, and where they contribute to

angiogenesis and matrix remodeling [12,13]. In breast cancer, CAFs also constitute the major cellular component of the tumor microenvironment [10,15]. As in RA, myofibroblasts, which selectively express alpha smooth muscle actin (α SMA), are believed to comprise the majority of CAFs [16,17]. However, others have suggested that not all CAFs within the tumor microenvironment are myofibroblasts [18]. Still others report that CAFs express elevated levels of the chemokine, stromal derived factor-1 (SDF-1), also known as CXCL12 [19,20]. The commonly used “CAF-markers”, such as α SMA, vimentin, and fibroblast activation protein (FAP) do not, therefore, necessarily overlap with each other. Consequently, CAFs can be considered as a heterogeneous population [21]. Although the importance of CAFs in tumor progression has been acknowledged, the identity, origin and common characteristics of CAFs have not been clearly defined.

Orimo and Weinberg have proposed three models for the derivation of CAFs in human carcinomas: (1) transdifferentiation of normal resident stromal fibroblasts, without genetic alterations; (2) clonal selection of a group of fibroblasts or progenitors with genetic alterations; and (3) differentiation of stromal fibroblasts recruited from bone marrow progenitor cells [22]. Based on their model, we have hypothesized that normal resident human mammary fibroblasts (HMFs) can transition to CAF-like cells or to *bone fide* CAFs by exposure to factors secreted by the breast cancer cells. We further hypothesized that as these normal quiescent cells transition to CAFs, they become activated and express many characteristics seen in the fibroblasts found at sites of inflammation, such as the synovium of RA joints (Figure 2) [20, 23,24]. Indeed, we found that soluble factors produced by breast cancer cells induced expression of two tumor-enhancing and inflammatory related factors in HMFs: MMP-1 and the G protein-coupled receptor, CXCR4, [25] two markers linked to a poor prognosis in breast cancer and also seen in RA synoviocytes.

Expression of the chemokine receptor, CXCR4, is well documented in breast cancer tumorigenesis [26]. CXCR4 is a seven-transmembrane G protein-coupled receptor with SDF-1 as its only known ligand. CXCR4 is often upregulated on breast cancer cells, and can induce targeted migration to distant organs containing cells that secrete SDF-1 [27], a process that may contribute to breast cancer metastasis. Importantly, elevated expression of CXCR4 has also been documented in synovial fibroblasts in RA. In tissue samples from RA patients, SDF-1 signaling through CXCR4 on fibroblasts results in their activation, migration and proliferation, as well as matrix remodeling due to increases in MMP-1 [28,29]. Since the breast cancer microenvironment has been compared to a site of chronic inflammation [14], our findings support the concept that similar to activated fibroblasts in autoimmune/inflammatory conditions such as RA, CXCR4 expression in CAFs identifies them as activated stromal cells.

In addition to cell migration, invasion of the extracellular matrix by malignant cells also requires degradation of the extracellular matrix [30]. We used short hairpin RNA (shRNA) technology to demonstrate that MMP-1 derived from breast cancer cells is necessary for tumor growth and invasion at the primary tumor site [31,32]. Since MMP-1 is a secreted protein, it is reasonable to propose that stromal-derived MMP-1 functions similarly to that produced by the breast cancer cells. For example, MMP-1 produced by stromal cells induced growth and invasion of breast cancer cells that did not express MMP-1 [32]. Furthermore, not all breast cancer cells produce MMP-1 [33], thereby increasing the significance of CAF-derived MMP-1 in tumor progression, and relating it to MMP-1 derived from synovial fibroblasts. Thus, MMP-1 and CXCR4 are phenotypically linked in activated HMFs in cancer and in synovial cells taken from RA pannus, where in both conditions, they are important mediators of disease pathology.

Endothelial cells, Protease Activated Receptor-1 (PAR-1) and MMP-1

The function of another G protein-coupled receptor, PAR-1, is directly linked to the enzymatic activity of MMP-1. Among all the MMPs, MMP-1 has the unique ability to cleave PAR-1 [34], with subsequent activation of signal transduction pathways and alterations in the expression of downstream genes. This unique ability to cleave PAR-1 gives MMP-1 a powerful role in controlling cell behavior.

As an example, we found that by silencing MMP-1 expression in a human melanoma cell line with shRNA technology reduced metastasis from the primary orthotopic (skin) site to the lung in a xenograft model [35]. In contrast, cells with a control shRNA (and, therefore, expressing high levels of MMP-1) readily metastasized. At first blush, the absence of metastatic ability would seem to be due to the absence of collagenolytic activity and the inability to degrade stromal collagens. However, successful metastasis requires to the coordinated expression of several genes and pathways in the both tumor cells and cells within the adjacent microenvironment [7,12,15]. Thus, the simple absence of MMP-1 was a naïve explanation. We noted a striking reduction of vasculature surrounding the primary melanomas in which MMP-1 expression was silenced, and this observation lead us to examine a potential link between MMP-1 expression and angiogenesis.

Indeed, when the human tumor cells were injected interdermally into nude mice, MMP-1 expression by the melanoma cells was associated with increased angiogenesis [35]. Since increased vessel formation has been linked to the ability of a tumor to metastasize [34–36], we hypothesized that MMP-1 was inducing angiogenesis, which is a critical aspect of neoplastic progression. Our work demonstrated that MMP-1 is a proangiogenic factor within the tumor microenvironment, and importantly, these proangiogenic activities resulted from the ability of MMP-1 to activate the G protein-coupled receptor, Protease Activator Receptor-1 (PAR-1) on the endothelial cells [35,36].

PAR-1 is one of four proteolytically activated PARs, which are expressed by several types of cells, including tumor cells, by endothelial cells, platelets, activated fibroblasts, and some types of tumor cells [37]. PAR receptors are unique in that their ligand is embedded and masked N-terminally under resting conditions. The serine protease, thrombin, is the classic activator of PAR-1, and when the ligand is exposed by proteolytic cleavage, it binds to the extracellular active site and activates PAR-1 intramolecularly [38,39]. Activated PAR initiates signal transduction pathways, with downstream consequences that lead to changes in cellular morphology and behavior under many circumstances, including tumor progression and inflammation [40]. Because the tumor microenvironment resembles chronic inflammation [14], the activation of PAR-1 on stromal cells in the tumor microenvironment may induce changes similar to those seen in stromal cells in RA [39,41]. PAR-1 is expressed on rheumatoid synovial fibroblasts [42,43] and on human chondrocytes [44]. Further, compared to wild type controls, experimental arthritis is ablated in PAR-1 $-/-$ mice, and MMP-13 gene expression is reduced [45], thereby linking PAR-1 to MMP expression and indicating that PAR-1 plays a significant role in this model of arthritis.

Thus, it is potentially significant that MMP-1 and PAR-1 are highly expressed by both tumor and activated stromal cells in both tumor and inflammatory microenvironments. The first report of MMP-1 mediated activation of PAR-1 used MMP-1 derived from activated fibroblasts to cleave PAR-1 on tumor cells [34]. Subsequent studies demonstrated that MMP-1 could also activate PAR-1 on endothelial cells [46]. However, it was not known if PAR-1 cleavage by MMP-1 vs. thrombin on endothelial cells was redundant or resulted in distinct changes within the endothelial cells. A cell-free system demonstrated that MMP-1 and thrombin have different cleavage sites within the PAR-1 active site, with thrombin producing the hexapeptide,

S₄₂FLLRN₄₇, and MMP-1 giving a truncated cleavage product, L₄₄RN₄₇, with low affinity for PAR-1 [47]. This differential cleavage of PAR-1 suggests that these proteases could have differential effects on endothelial cell gene expression [47]. To examine this possibility, we used the model system of stromal human microvessel endothelial cells (HMVECs) in which PAR-1 was activated by purified thrombin or MMP-1 [36].

We found that the MMP-1/PAR-1 signaling axis in endothelial cells activated Mitogen Activated Protein Kinases (MAPKs), resulting in the induction of a panel of pro-angiogenic genes, while thrombin activated another panel of genes. Consequently, PAR-1 activation by MMP-1 vs. thrombin could differentially influence cell behavior and pathological outcome. In addition, we proposed that the two proteinases could cooperate in the tissue microenvironments to promote both tumor progression and inflammation [36]. Since MMP-1 produced by activated fibroblasts in response to cytokines and growth factors is present in both RA and cancer, MMP-1 has the potential to activate PAR-1 on several types of cells, amplifying the role of fibroblast-derived MMP-1 as a collagenolytic enzyme and also as a critical signaling molecule.

Our studies with MMP-1 and endothelial cells describe a MMP-1/PAR-1 signaling axis that acts in a paracrine manner, whereby MMP-1 produced by tumor cells or activated fibroblasts modulates gene expression in endothelial cells [34,36] (Figure 3). Our more recent observations indicate that melanoma cells possess an autocrine MMP-1/PAR-1 signaling axis (Figure 3) in which tumor –produced MMP-1 signals through PAR-1 on the tumor cells to induce expression of a panel of genes associated with invasive behavior [48]. We propose a similar scenario for activated synovial fibroblasts in RA. Indeed, since PAR-1 is also expressed on RA synovial fibroblasts [42,43], it is reasonable to speculate that this signaling axis is operational in RA: MMP-1/PAR-1 signaling in activated synovial fibroblasts modulates gene expression in these cells and/or on neighboring chondrocytes. This would imply a broader and more significant role for MMP-1 in RA, one that mirrors that seen in tumor biology. Given the potential of MMP-1 for mediating joint destruction in RA, this new role would assign even more importance to defining therapeutic strategies that are targeted at reducing MMP-1 gene expression.

Therapeutic strategies that target MMP-1 and G protein-coupled receptors

RA and cancer share several therapeutic strategies, including the use of chemotherapeutic agents such as methotrexate, antibodies directed at cytokines/growth factors and their receptors, and/or small molecule inhibitors of signal transduction pathways ([3,4,49–51]; www.Cancer.org). In cancers, these treatments are often successful, but they may also eventually fail, resulting in relapse as tumors mutate and become resistant. Since stromal cells are recognized as critical contributors cancer pathogenesis, and since these cells are more genetically stable than the tumor cells and are less likely to develop drug resistance, they have been suggested as appropriate therapeutic targets [52,53]. In arthritis, many of these same types of treatments with chemotherapeutic agents and targeted antibodies reduce inflammation and cytokine production, with the downstream effect of reducing joint destruction. However, despite their efficacy, there is the potential for serious side-effects, particularly since the antibodies directed at the cytokines/receptors are immunosuppressive, increasing the possibility of infection and even leukemias/lymphomas [51]. Therefore, in RA there is a need for therapies targeted at reducing joint destruction, and in cancer, for therapeutics that are directed at the stromal cells in the microenvironment.

Inhibiting MMP-1 gene expression

Directly inhibiting the effects of MMPs has been a therapeutic goal in the treatment of RA and cancer for a long time [2,3,49], since this approach has the potential to limit (or even prevent)

invasion/metastasis and irreversible joint destruction. Many studies have focused on blocking enzymatic *activity* of MMPs with small molecule chemical inhibitors. Numerous compounds have been tested, including some phase I trials [2,3,54]. Unfortunately, these studies were fraught with difficulties due to lack of specificity and problems with drug delivery and toxicities.

Inhibition of MMP *gene expression* has been an alternative approach, and has focused on the retinoids, a class of vitamin A derivatives [2,4,49] that are ligands for a family of nuclear hormone receptors, the retinoic acid receptors (RAR α , β , and γ). Retinoids inhibit MMP production primarily by affecting the levels of Activator Protein-1 (AP-1) proteins, i.e., members of the Fos and Jun families of transcription factors [55], but unfortunately, these compounds also lack specificity, affecting the expression of many genes and leading to undesirable side effects. Compounds targeting a related group of nuclear hormone receptors, the retinoid X receptors (RXR α , β , and γ) appear to be more selective and less toxic. These compounds, termed “rexinoids” [49] and bind as RXR:RXR homodimers to DNA in the promoter regions of responsive genes to reduce transcription. Among the new experimental rexinoids is LG268, which selectively inhibits MMP-1 and MMP-13 mRNA and protein [8].

Another group of nuclear hormone receptors are the peroxisome proliferator-activated receptors (PPAR) (α , δ and γ). Substantial data link specific ligands for PPAR γ , the thiazolidinediones, with reduced MMP production, lower inflammation and therapeutic efficacy in cell cultures and in animal models of arthritis [57–61]. RXR is an obligate partner for PPAR γ , resulting in RXR:PPAR γ heterodimers that bind to specific PPAR γ response elements (PPREs), also known as Direct Repeat-1 (DR-1 sites) in promoter DNA [9,49,59]. Rosiglitazone, one of the thiazolidinediones, inhibits IL-1 β -induced MMP transcription in chondrocytic cells, and this inhibition is selective for MMP-1 and MMP-13 [9]. In keeping with reports describing cooperativity between RXR and PPAR γ ligands [62–64], combined treatment with LG268 and rosiglitazone increases the inhibition of MMP-1 and MMP-13 [9], implying that doubly liganded RXR: PPAR γ heterodimers increase efficacy.

In considering how the nuclear hormone receptors and their respective ligands exert their effects, it is noteworthy that the MMP-1 and MMP-13 promoters lack canonical DR-1 nuclear hormone response elements [59]. This suggests that LG268 and rosiglitazone maybe be reducing transcription through non-classical mechanisms to inhibit these genes. Since LG268 does not modulate IL-1 β -induced activation of NF- κ B or a major signal transduction cascade [8], the rexinoid may be acting through a mechanism other than suppression of a general inflammatory pathway. In contrast, rosiglitazone, and other thiazolidinediones, have anti-inflammatory effects that include suppression of signaling cascades and transcription factors such as AP-1 and NF κ B [65]. Therefore, some of the additive/synergistic effects of LG268 and rosiglitazone may be mediated by different mechanisms.

It has been suggested that both RXR:PPAR γ heterodimers (and possibly RXR:RXR homodimers) bind to a non-traditional DNA response element in the MMP-1 and MMP-13 promoters (Figure 4). This suggestion is supported by our work [8,9] and by the work of François *et al.* [59], both of which implicate the AP-1 site in the inhibitory mechanism of each drug. François *et al.* identified a degenerate DR-1 site [59] in the rabbit MMP-1 promoter, which overlaps the AP-1 site (Figure 4). Their model states that the rosiglitazone-liganded RXR:PPAR γ dimer binds to this degenerate site and sterically prevents the binding of AP-1 proteins, thereby decreasing rabbit MMP-1 gene expression. A similar degenerate DR-1 site overlapping the proximal AP-1 site exists in both the human MMP-1 and MMP-13 promoters, thus providing a possible mechanism for some of the inhibitory effects of LG268 and rosiglitazone.

Chromatin remodeling is recognized as an essential component of gene regulation [66,67]. The acetylation of histones by histone-modifying enzymes and chromatin remodeling complexes mediate changes in transcription in response to inducers or repressors [66,67]. We found that changes in histone acetylation play an important role in up-regulating MMP-1 and MMP-13 gene expression [8,9]. IL-1 β treatment leads to increases in the acetylation of histone subunit H4 at the proximal AP-1 site of MMP-1 and MMP13, while LG268 and rosiglitazone block this increase in acetylation [8,9]. Thus, these data show that the PPAR γ ligand, rosiglitazone, and the experimental RXR ligand, LG268, inhibit MMP-1 (and MMP-13) gene expression in cytokine-stimulated cells. This inhibition appears to be mediated through multiple mechanisms operating at a transcriptional level.

Given the link between increased MMP-1 (and MMP-13) gene expression and RA, these classes of compounds could be useful as therapeutic agents. Since combined treatment with ligands for both RXR and PPAR γ leads to additive inhibition of MMP-1 and MMP-13 production [9], perhaps these compounds could be used together to reduce or block joint destruction in arthritis, and in lower doses than single-drug treatment to thus minimize the risk of adverse side-effects. Importantly, clinical investigations with these classes of drugs are already underway in diseases such as diabetes and cancer. For example, rosiglitazone and another thiazolidinedione, pioglitazone, are currently in clinical use as insulin-sensitizing agents in diabetes [68]. In addition, the rexinoid, bexarotene (Targretin®), is a treatment for several cancers [69,70]. Finally, another study has reported the combined use of bexarotene and rosiglitazone in patients with refractory cancers [71]. There is, therefore, clinical precedent for the appropriate concentrations to be tested and for combinatorial use of these compounds in both cancer and RA, again illustrating some of the molecular similarities between RA and cancer.

G protein-coupled receptors

Our studies have documented links between expression of two G protein-coupled receptors, CXCR4 and PAR-1, and MMP-1 expression in RA and cancer. Although we have focused on activated stromal cells in the tumor microenvironment, our data are directly applicable to the activated stromal environment within RA joints. Other investigators have demonstrated the potential importance of therapies directed at blocking the signaling ability of these two G protein-coupled receptors.

The CXCR4/SDF-1 signaling axis is becoming a therapeutic target, as its roles in cancer and chronic inflammatory/autoimmune diseases are increasingly documented [72–74]. Most studies have concentrated on understanding the structure/function relationships between the receptor and putative antagonists, and new agents are emerging. For example, selective CXCR4 antagonists, T22 and T140, were initially developed as anti-HIV agents, but have been effective in blocking migration of several types of cancer cells [72], and a bio-stable form of T140 significantly repressed pulmonary metastases of breast cancer cells and melanoma cells in mice. Although cell culture experiments have established efficacy against the tumor cells, themselves, one wonders if some of the *in vivo* efficacy of these antagonists is due to their ability to modulate the behavior of activated stromal cells in the tumor microenvironment. An extension of this concept is the potential application of these inhibitors to the treatment of RA, since CXCR4 modulates the migration, proliferation and MMP-1 production by human synovial fibroblasts taken from patients with RA [28].

Likewise, the MMP-1/PAR-1 signaling axis is gaining interest as a therapeutic target. The initial studies on this topic have been in cancer models, where xenografts of advanced ovarian cancer delineated an MMP cascade, which culminated in MMP-1 activation of PAR-1 [75]. In this model, activated PAR-1 mediated angiogenesis, ascites formation and metastases, all of which were effectively inhibited by intraperitoneal administration of pepducins. These novel

cell-permeable peptides, derived from the third intracellular loop of PAR-1 or PAR-4, disrupt signaling between the receptor and G proteins and inhibit activation of downstream pathways [75].

Several more classical PAR-1 antagonists have been described (reviewed in [76]). These act by interacting with the extracellular domain of PAR-1 and blocking its activation by proteolytic cleavage. Of these, SCH79797 is often used in laboratory experiments, both *in vitro* and *in vivo*, where it is anti-angiogenic. Other compounds, SCH53048 and E5555, are further along in development and clinical testing. SCH53048 is a reversible and orally administered compound derived from himbacine, which is found in the bark of the Australian magnolia tree. It is also anti-angiogenic, and in clinical trials, it has shown more than 80% inhibition of platelet aggregation within 60 minutes, with no apparent adverse effects. E5555 is currently undergoing phase 2 trials. These compounds may have a future as an important and effective anti-coagulants during some therapeutic procedures, and other application may well emerge [76].

Lastly, the emerging potential of RNA interference (RNAi) therapy cannot be ignored (reviewed in [77]). These short (~ 20 nt) of RNA are directed at specific sequences within the mRNA of choice, and upon binding, they efficiently silence expression of the target gene. Despite the difficulties associated with targeted delivery to the desired site and issues related to stability/clearance *in vivo*, these small molecules have exquisite specificity and are continuing to garner interest as therapeutics. Indeed, clinical trials with siRNAs against VEGF for age-related macular degeneration and against respiratory syncytial virus (RSV) infection are ongoing (reviewed in [77]). More immediately relevant to this discussion is the efficacy of stably expressed short hairpin RNAs (shRNA) against MMP-1 in breast cancer and melanoma in reducing primary growth and preventing metastasis [32,35]. Further, the successful *in vivo* delivery of PAR-1 siRNA in neutral liposomes in a melanoma model in nude mice [78] suggests that practical technical problems may be overcome [77].

Concluding Comments

As predicted by Sporn and Harris three decades ago, our knowledge of the precise molecular mechanisms that are driving non-malignant proliferative diseases (such as RA) and malignancies (such as breast cancer and melanoma) has grown enormously. This new information has re-enforced the original concept that these two seemingly disparate categories of diseases share many common properties, and the analogy between the reactive stroma in the tumor microenvironment and the pannus of RA has become solidified. We have focused on MMP-1, a collagenase once thought to function only as one of a few enzymes capable of initiating the degradation of the interstitial collagens. However, recent data document its role as a vital part of an autocrine/paracrine MMP-1/PAR-1 signaling axis, a function that amplifies its dual potential to remodel the extracellular matrix and to modulate cell behavior. In addition, the cooperativity between MMP-1 and the signaling of the chemokine receptor CXCR4/SDF-1 in modulating the behavior of activated fibroblasts again emphasizes the importance of MMP-1 as a pathological mediator in RA and cancer. Finally, also as predicted, new therapeutic agents are emerging. Interestingly, although they are more specific in the molecules that they target than past therapies, these targets are often shared between RA and cancer, again underscoring fundamental similarities between autoimmune disorders and some cancers. The similarity between autoimmune diseases and cancer have been noted for three decades and it is particularly noteworthy that Dr. Noel Rose has contributed throughout these same three decades and indeed even longer.

It is thus a pleasure to contribute to this special issue that recognizes Dr. Rose's career, his work in serology, in epidemiology, and in multiple other areas of autoimmunity, including the development of the American Autoimmune Related Diseases Association [79–86]. This issue

is part of the Journal's series that recognizes the extraordinary contributions of scientists in the field of autoimmunity [87–89].

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Figure 1. Major signaling pathways for cytokines and growth factors in synovial cells

Upon binding to its receptor, cytokines, such as IL-1 β , and growth factors, such as basic fibroblast growth factor, stimulate several signaling pathways: NF κ B, p38, JNK and MEK/ERK. These pathways target DNA sequences in the promoter of the MMP-1 gene, increasing transcription. P50/p65 proteins bind to the NF κ B site and cFos/cJun proteins bind to the AP-1 site. TNF α and other growth factors, such as VEGF, activate similar pathways, and target these same sites in the MMP promoters [3,4].

Figure 2. Similarities between the activated fibroblasts in Rheumatoid Arthritis and the Carcinoma-Associated Fibroblasts in cancer

In both cell types, CXCR4, SDF-1, and MMP-1 are up-regulated compared to normal fibroblasts. Signaling through CXCR4 leads to activation of the ERK1/2 pathway, which is a component of the MAPK pathway, in CAFs and the MAPK pathway in activated fibroblasts. Both the MAPK and ERK1/2 pathways are known to stimulate MMP-1 and SDF-1 levels in other cell types [3,4,25].

Figure 3. MMP-1 has multiple functions within the tumor microenvironment

MMP-1 is secreted at high levels by melanoma cells, where it degrades collagen within the extracellular matrix surrounding the tumor cells to facilitate tumor cell invasion. MMP-1 also proteolytically activates PAR-1, expressed by multiple cell types within the microenvironment, to promote tumor progression. For example, MMP-1/PAR-1 signaling on endothelial cells induces pro-angiogenic gene expression, which may contribute to tumor metastasis, and autocrine MMP-1/PAR-1 signaling in melanoma cells induces pro-tumorigenic gene expression, which may contribute to several aspects of tumor progression, including proliferation, invasion and metastasis [34,36,48]. Both the collagenolytic and PAR-1 activating functions of MMP-1 also likely play a role in RA pathology.

Figure 4. Proposed steric hindrance model for inhibiting MMP-1

Overlapping degenerate DR-1 and AP-1 binding sites in promoter DNA. Numbers show distance from transcriptional start site in the rabbit MMP-1 gene [59]. In the model, IL-1 β induces AP-1 proteins, which bind to their cognate element and increase transcription. However, if rosiglitazone or LG268 is present, the liganded RXR:PPAR γ dimer binds to the degenerate DR-1 site, and physically blocks AP-1 and transcriptional activation by IL-1 β .