Editorial

The 'RASor's' edge: Ras proteins and matrix destruction in arthritis

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Published: 11 December 2009
This article is online at http://arthritis-research.com/content/11/6/136

Arthritis Research & Therapy 2009, **11:**136 (doi:10.1186/ar2840)

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Abstract

The shared characteristics of rheumatoid arthritis (RA) and cancer, particularly their unchecked growth and invasive behaviors, have been apparent for some time. However, the molecular mechanisms underlying these similarities are not clear. In a recent issue of *Arthritis Research & Therapy*, Abreu and colleagues link a well-studied oncogene, Ras, with expression of matrix metalloproteinase-3 (MMP-3) in RA. Their study correlates expression of the Ras guanine nucleotide exchange factor RasGRF1 with MMP-3 expression in RA synovium. They elucidate a potential mechanism of regulation of MMP-3 expression in RA, suggesting a potential target for RA treatment.

In a recent issue of *Arthritis Research & Therapy*, Abreu and colleagues [1] demonstrate that the Ras guanine nucleotide exchange factor (GEF) RasGRF1 regulates production of matrix metalloproteinase-3 (MMP-3) (stromelysin) in synovial cells taken from the joints of patients with rheumatoid arthritis (RA). The data suggest that overexpression of RasGRF1 activates signal transduction pathways that target the MMP-3 gene, thereby contributing to joint destruction in RA. In addition to measuring MMP-3 expression, they measured levels of the interstitial collagenase, MMP-1, and several other genes involved in RA. Interestingly, production of MMP-1 and MMP-3 in RA, but not non-RA (osteoarthritis and reactive arthritis), synovial tissue correlated positively with expression of RasGRF1 and co-localized in cells expressing RasGRF1. In addition, locked nucleic acid (LNA)-mediated knockdown of RasGRF1 abrogated MMP-3 levels but failed to affect MMP-1, thus demonstrating disparate regulation of these two MMPs. The study raises several noteworthy issues, some of which the authors themselves pointed out.

The first is the similarity between the proliferative and invasive characteristics of both RA synovium and cancer [2]. In the present study, the parallel between RA and cancer is further demonstrated by Ras, a classic oncogene, as a signaling molecule in RA fibroblast-like synoviocytes. The Ras superfamily of small GTPases is perhaps best known for linking external mitogenic stimuli to internal signal transduction pathways, leading to changes in gene expression affecting cell proliferation and survival. Upstream signaling events activate GEFs, which mediate the exchange of GDP (on inactive Ras) for GTP, thus causing a conformational change to an active state and interaction with downstream effectors. GTP-bound Ras is inactivated by its intrinsic GTPase capability, which hydrolyzes GTP to GDP, and is aided by GTPase-activating proteins that stimulate the GTPase activity [3].

Increases in the expression or activity of Ras proteins or both are usually associated with transformed cells and thus with cancer. However, as Abreu and colleagues [1] note, altered expression of Ras GEFs has been linked to autoimmune diseases, many of which display increased proliferation and invasion resembling those seen in tumors. The specific documentation of altered expression of a molecule usually associated with malignant cells once again underscores similarities between aspects of cancer and non-malignant proliferative diseases, such as RA [2]. Although these similarities have been noted for at least 30 years at a phenotypic level [2], we are now shedding light on their molecular basis (for example, changes in the expression of tumor suppressor proteins and oncogenes and the activation of certain mitogen-activated protein kinase signal transduction pathways) [4,5]. Abreu and colleagues [1] include the Ras family of proteins, thus reiterating how the phenotypic transformation of RA synovium mimics the genotypic transformation of tumor cells [2].

A second concept that the authors [1] emphasize is the discordant regulation of MMP-1 and MMP-3. Although early studies suggested that expression of these MMPs was co-

GEF = guanine nucleotide exchange factor; MMP-3 = matrix metalloproteinase-3; RA = rheumatoid arthritis.

ordinate, more recent work indicates disparate regulation, suggesting that these MMPs are the downstream targets of different signaling pathways [6-8]. Nonetheless, the promoters of these MMPs share many common cis-regulatory elements that may respond coordinately [6-8]; the present report of differential regulation sheds new light on the mechanisms regulating MMP-3 expression and opens up the possibility of developing targeted therapies directed at MMP-1 or MMP-3.

Interestingly, the authors describe 'spontaneous' MMP production by RA synovial cells. This means that no exogenous stimulating agent, such as interleukin-1-beta or tumor necrosis factor-alpha [4-7], was added to the cultures, so that they appear to 'spontaneously' synthesize MMPs. Primary cultures of RA synovial cells contain a mixture of activated fibroblasts, macrophages, and lymphoid cells (T cells, B cells, and neutrophils), all of which produce a cocktail of cytokines and growth factors capable of increasing MMP production [4,5], thereby making MMP expression appear 'spontaneous'. Regardless of the combination of factors present in their cultures [1], only MMP-3 expression was significantly modulated by RasGRF1. This finding provides an opening for future studies to dissect the roles of various factors present in RA synovium for their ability to differentially regulate MMP-1 versus MMP-3. It will be essential to test combinations of factors for this differential regulation, emphasizing the complex interactions of the potpourri of factors present in RA tissues and their ability to differentially influence synovial cell behavior.

Finally, there is the implication that the upregulation of MMP-3 in RA synovial tissue contributes to joint destruction [1]. Indeed, a role for MMP-3 in escalating joint degradation has been described [9]. MMP-3 activates latent MMP-1 [10] and also degrades non-collagen matrix [6-8]. Furthermore, with a comparatively promiscuous portfolio of matrix substrates [6-8], MMP-3 can be considered a substantial player in RA pathogenesis. The present study supports this role and suggests several avenues of future investigation to determine the mechanism governing the differential expression of MMP-1 and MMP-3 and to elucidate targeted therapies directed at one MMP versus the other. Interestingly, by focusing on MMP-3, there may be indirect suppression of the ability of MMP-1 to destroy the extracellular matrix in RA.

Competing interests

The authors declare that they have no competing interests.

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