Commentary

MAPK signalling in rheumatoid joint destruction: can we unravel the puzzle?

Lars-Henrik Meyer and Thomas Pap

Division of Molecular Medicine of Musculoskeletal Tissue, Department of Orthopaedics, University Hospital of Munster, Munster, Germany

Corresponding author: Thomas Pap, thomas.pap@uni-muenster.de

Published: 16 August 2005
This article is online at http://arthritis-research.com/content/7/5/177
© 2005 BioMed Central Ltd

Arthritis Research & Therapy 2005, **7**:177-178 (DOI 10.1186/ar1810)

See related research by Goertz *et al*. in this issue [http://arthritis-research.com/content/7/5/R1140]

Abstract

Mitogen-activated protein kinases (MAPKs) have been associated with the pathogenesis of rheumatoid arthritis (RA), but the individual contributions of the three MAPK family members are incompletely understood. Although previous data have established a role for c-Jun N-terminal kinase (JNK) and extracellular signal-related kinase (ERK) in different animal models of arthritis, most recent data indicate that the stable activation of p38 MAPK and in part of ERK significantly contributes to destructive arthritis in mice transgenic for human tumour necrosis factor-α. These data highlight the complexity of MAPK signalling in arthritis and provide a basis for the design of novel strategies to treat human RA.

Although all three mitogen-activated protein kinase (MAPK) families – p38, extracellular signal-related kinase (ERK) and c-Jun N-terminal kinase (JNK) – seem to be involved in the activation of synovial cells in rheumatoid arthritis (RA), the main pathways involved in the regulation of joint destruction are incompletely understood. In this issue of *Arthritis Research & Therapy*, Goertz and colleagues report some important novel data on MAPK activation in arthritic mice transgenic for human tumour necrosis factor-α (hTNFtg mice) [1]. With the use of Western blotting and immunohistochemistry, they show that p38 MAPK and ERK are the primarily activated MAPKs. Although activation of p38 MAPK is more dominant in synovial macrophages, phosphorylated ERK is also found at increased levels in synovial fibroblasts. JNK activation is induced much less by chronic exposure to tumour necrosis factor (TNF)-α. Applying cytokine blockers to inhibit TNF-α-induced MAPK activation, the authors show a significantly reduced activation of p38 MAPK and ERK in the synovial membrane by antibodies against TNF-α.

Expression of MAPKs has previously been described at elevated levels in the RA synovium, and data from different animal models suggest important yet distinct roles of the three MAPKs in destructive arthritis. However, several questions about the regulation of joint destruction by MAPKs remain unanswered. Thus, the predominant regulation of collagenases (particularly matrix metalloproteinase (MMP)-13) by JNK as suggested by Han and co-workers [2] seems to contrast with previous studies by Mengshol and colleagues from the group of Constance Brinckerhoff. The latter have demonstrated a pivotal role of p38 MAPK in the regulation of MMP-13 in human chondrocytes [3]. The differences have been attributed in part to the peculiarities of the rodent system. It has been suggested that, because of the lack of a homologue to the human MMP-1 in rat and mice, the regulation of collagenases is different in rodents and results in a greater dependence on JNK, whereas p38 may be of greater importance in humans [4]. However, few functional data on the specific contribution of p38 MAPK to cytokine-mediated joint destruction in comparison with other MAPKs are available.

In this context, TNF-α is of importance. It can activate all three members of the MAPK family, but p38 MAPK has been suggested to be a key molecule mediating the response of mesenchymal cells to TNF-α [5]. The pivotal role of TNF-α in RA is highlighted not only by *in vitro* data but also by different animal models, in which the overexpression of TNF-α results in the development of chronic destructive arthritis [6].

The present data by Goertz and colleagues are interesting mainly for two reasons. First, they shed new light on the balanced activation of MAPKs during destructive arthritis and underline the complexity of MAPK signalling. The results confirm the notion that macrophages and synovial fibroblasts are the major targets of TNF-α-induced MAPK activation, yet

ERK = extracellular signal-related kinase; IL = interleukin; JNK = c-Jun N-terminal kinase; MAPK = mitogen-activated protein kinase; MMP = matrix metalloproteinase; RA = rheumatoid arthritis; TNF = tumour necrosis factor.

at the same time they strengthen the concept of p38 and ERK as important MAPKs in the inflamed synovium. In line with previous data, the results of Goertz and colleagues also emphasise the role of ERK1/2 as a key integrator of activation signals in synovial fibroblasts. In contrast, the data may be interpreted to suggest that chronic destructive arthritis does not require JNK activation. This notion is supported by other recent data of Georg Schett's group demonstrating that JNK1 is not required for destructive joint disease in the hTNFtg mouse model of RA [7]. The data seem to contradict the aforementioned results in rat adjuvant arthritis [2], but given the multitude of data on JNK activation in human RA they more probably illustrate the complexity of human disease in comparison with the hTNFtg model, which focuses on only one, although central, pathway of human disease. Thus, in human RA as well as in other animal models of RA, the activation of JNK may be caused by another disease-relevant signalling pathway such as IL-1, which is a potential inducer of JNK phosphorylation in RA synovial cells. In addition, growth factors such as epidermal growth factor, in concert with cell–cell and cell–matrix interactions, may contribute to JNK activation in human RA, namely by processes that seem less prominent in the hTNFtg mouse model. This hypothesis is supported by most recent research on upstream MAPK kinases (MKKs), which largely determine the balance of MAPK activation in response to inflammatory stimuli [8,9].

The second interesting observation by Goertz and colleagues is the inability of TNF-α blocking agents to completely reverse the activation of p38 and ERK in hTNFtg mice. In the light of this and previous data, it seems that there is only a narrow window of time in which anti-TNF-α treatment can entirely prevent the onset of arthritis and the activation of disease-relevant MAPKs. Consequently, the results suggest that chronic exposure of synovial cells to TNF-α may result in their stable activation. This may be true particularly for synovial fibroblasts, which have been assigned a key role in rheumatoid joint destruction and have been imbued with tumour-like stable activation in RA [10]. Although a detailed analysis of synovial fibroblasts in the hTNFtg mouse model is lacking and it is as yet unclear to what degree the activation of synovial fibroblasts in these mice resembles the specific features of human RA synovial fibroblasts, the present data suggest that chronic exposure of synovial cells in hTNFtg mice results in an activation pattern that is maintained if TNF-α is inhibited.

Conclusion

MAPKs contribute to the activation of synovial cells in RA, and several lines of evidence suggest that there is a stable activation of distinct MAPK family members in chronic destructive arthritis. Research on MAPKs is complicated by the fact that different animal models of RA reflect distinct features of human disease. Recent data on the involvement of MAPKs provide a basis for the development of novel therapeutic strategies for human RA.

Competing interests

The author(s) declare that they have no competing interests.

References

1. Goertz B, Hayer S, Tuerk B, Zwerina J, Smolen J, Schett G: **Tumour necrosis factor activates the mitogen-activated protein kinases p38a and ERK in the synovial membrane *in vivo.*** *Arthritis Res Ther* 2005, **7:**R1140-R1147.
2. Han Z, Boyle DL, Chang L, Bennett B, Karin M, Yang L, Manning AM, Firestein GS: **c-Jun N-terminal kinase is required for metalloproteinase expression and joint destruction in inflammatory arthritis.** *J Clin Invest* 2001, **108:**73-81.
3. Mengshol JA, Vincenti MP, Coon CI, Barchowsky A, Brinckerhoff CE: **Interleukin-1 induction of collagenase 3 (matrix metalloproteinase 13) gene expression in chondrocytes requires p38, c-Jun N-terminal kinase, and nuclear factor kappaB: differential regulation of collagenase 1 and collagenase 3.** *Arthritis Rheum* 2000, **43:**801-811.
4. Vincenti MP, Brinckerhoff CE: **The potential of signal transduction inhibitors for the treatment of arthritis: Is it all just JNK?** *J Clin Invest* 2001, **108:**181-183.
5. Suzuki M, Tetsuka T, Yoshida S, Watanabe N, Kobayashi M, Matsui N, Okamoto T: **The role of p38 mitogen-activated protein kinase in IL-6 and IL-8 production from the TNF-α- or IL-1β-stimulated rheumatoid synovial fibroblasts.** *FEBS Lett* 2000, **465:**23-27.
6. Keffer J, Probert L, Cazlaris H, Georgopoulos S, Kaslaris E, Kioussis D, Kollias G: **Transgenic mice expressing human tumour necrosis factor: a predictive genetic model of arthritis.** *EMBO J* 1991, **10:**4025-4031.
7. Koller M, Hayer S, Redlich K, Ricci R, David JP, Steiner G, Smolen JS, Wagner EF, Schett G: **JNK1 is not essential for TNF-mediated joint disease.** *Arthritis Res Ther* 2005, **7:**R166-R173.
8. Inoue T, Hammaker D, Boyle DL, Firestein GS: **Regulation of p38 MAPK by MAPK kinases 3 and 6 in fibroblast-like synoviocytes.** *J Immunol* 2005, **174:**4301-4306.
9. Sundarrajan M, Boyle DL, Chabaud-Riou M, Hammaker D, Firestein GS: **Expression of the MAPK kinases MKK-4 and MKK-7 in rheumatoid arthritis and their role as key regulators of JNK.** *Arthritis Rheum* 2003, **48:**2450-2460.
10. Pap T, Muller-Ladner U, Gay RE, Gay S. **Fibroblast biology. Role of synovial fibroblasts in the pathogenesis of rheumatoid arthritis.** *Arthritis Res* 2000, **2:**361-367.