Recent years have seen enormous progress in understanding the pathogenesis of rheumatoid arthritis (RA), an autoimmune disorder that primarily affects the joints and leads to their progressive destruction. Advances in molecular biology techniques such as the use of gene transfer and gene silencing technology, the utilization of novel animal models of destructive arthritis—particularly in conjunction with newly established transgenic and knock-out mice—and the observation of very early stages of human disease have provided exciting novel insights into key mechanisms that ultimately lead to the development of established RA in humans and that contribute to joint destruction. It has become increasingly clear that the mechanisms of rheumatoid joint destruction are linked closely to changes that occur predominantly at sites of interaction between the rheumatoid synovium and articular cartilage and bone [1]. Numerous data have shown that cells of the inflamed synovium constitute a highly interdependent network, in which the interaction of stromal cells—specifically synovial fibroblasts—with infiltrating inflammatory cells such as lymphocytes and macrophages creates a unique environment that results in the development of chronic destructive synovitis [2].

Thickening of the RA synovium is largely due to a hyperplasia of the most superficial lining layer that in the course of disease grows from 2–4 layers of cells to more than 10 layers. About two-thirds of the cells in the lining layer express macrophage markers such as CD11b, CD14, CD33, and CD68 as well as major histocompatibility complex (MHC) class II molecules and can thus be identified as macrophages [3,4]. These macrophages constitute a major source of inflammatory factors in the RA synovium, and it is now evident that macrophage-derived cytokines such as TNF-α contribute prominently to the activation of synovial cells in RA. Thus, mice transgenic for human TNF-α (hTNFtg), a major inflammatory cytokine in RA, constitutively develop a chronic inflammatory polyarthritis that is highly destructive [5]. Although treatment of arthritic hTNFtg mice with monoclonal antibodies against hTNF prevents development of disease, there is only a narrow window of time in which anti-TNF-α treatment can inhibit the onset of arthritis entirely, suggesting that chronic exposure of cells to inflammatory mediators may induce a stable activation and alterations in tissue homeostasis that can become independent of the specific trigger. Furthermore, most recent data suggest that activation pathways of synovial cells differ between the various animal models of arthritis and that each of these models reflects only part of human pathology [6]. This notion is supported by clinical data using inhibitors of individual cytokines such as anti-TNF-α agents. Although there has been a breakthrough in the treatment of RA using these novel biologics, response is still limited with respect to both the number of patients going into remission and the degree to which remission can be achieved in individual patients.

As a consequence, there are continuous efforts to identify new molecular targets for anti-inflammatory and anti-resorptive intervention as well as to better understand the mechanisms of known mediators of inflammation and joint destruction. In this context, interest has focused, not only on well-established molecules, such as inflammatory cytokines, chemokines, and transcription factors, but also on molecules that are involved in more basic biologic processes such as...
expression, folding, and degradation of proteins. The investigation of cyclophilins constitutes a prominent example of such approaches.

Cyclophilins constitute a family of evolutionarily conserved proteins that are expressed ubiquitously in eukaryotic cells [7]. They are found mainly in the cytoplasm and have peptidyl-prolyl isomerase activity catalyzing the cis–trans interconversion of peptide bonds N-terminal to proline [8]. The entire spectrum of their functions has not been clarified, but it appears that cyclophilins are involved mainly in the folding of nascent proteins [9]. Cyclophilin A is the prototype of this family and is expressed most widely in mammals. There are at least 15 different cyclophilin genes in the mouse genome, which differ from cyclophilin A mainly by terminal extensions that appear responsible for subcellular localization and protein–protein interactions. Initial interest in cyclophilin A in immunity has come mainly from the fact that cyclophilin A can bind the immunosuppressive agent cyclosporine A with very high affinity [10,11]. Most recent data have supported the functional involvement of cyclophilin A in mediating the effects of cyclosporine A by demonstrating that Ppia−/− (the gene encoding cyclophilin A) mice are resistant to cyclosporine A-mediated immunosuppression and that cyclophilin A is the primary mediator of the immunosuppressive effects of cyclosporine A [12]. However, a growing body of evidence suggests that cyclophilin A is involved also in the pathogenesis of immune-mediated disorders [13–16]. Although Ppia−/− mice show only a slight loss in viability and adult Ppia−/− animals have no obvious decrease in their life spans, they spontaneously develop an allergic condition that is similar to that of IL-4 overexpressing animals and is linked to elevated levels of IL-4 [17]. In addition, CD4+ cells of Ppia−/− mice produce significantly higher amounts of IL-2, and Th2 cells of these animals are hypersensitive to T cell receptor (TCR) stimulation. These data suggest that cyclophilin A is involved in the regulation of Th1–Th2 balance and that overexpression of cyclophilin A is linked to autoimmune diseases. In line with this concept, cyclophilin A has been identified as an inflammatory mediator in different conditions. It has been shown to be produced by macrophages following LPS stimulation and more recently linked to atherosclerosis and endothelial dysfunction [14,15].

Of interest, RA has been the first condition in which a secreted form of cyclophilin A has been demonstrated in extracellular fluids. As shown by Billich and colleagues, cyclophilin A was increased in the synovial fluids of RA patients compared to OA patients and correlated with the total cell counts [13]. However, the precise origin of cyclophilin A in RA, as well as the functional consequences of increased cyclophilin A expression, has remained largely undefined (Fig. 1).

In this issue of Clinical Immunology, Won-Ha Lee and colleagues extend the findings on cyclophilin A in RA by identifying the source of cyclophilin A in the rheumatoid synovium and by demonstrating pro-inflammatory functions of cyclophilin A in macrophage-like cells [18]. As demonstrated in their study, macrophages of the synovial lining layer constitute the major source of cyclophilin A in the RA synovium. In addition, they show that stimulation of monocytes with cyclophilin A results in increased production of inflammatory cytokines, specifically TNF-α, interleukin (IL)-1β, IL-8, and monocyte chemoattractant protein (MCP)-1. Won-Ha Lee and his colleagues suggest further that cyclophilin A is involved in the expression of gelatinase B (matrix metalloproteinase 9, MMP-9) by monocytes and that these stimulatory effects of cyclophilin A on MMP-9 production are mediated through the nuclear factor kappa B (NFκB) transcription factor. These data are of interest because they tighten the links between cyclophilins and key pathological mechanisms of RA and in the light of what is known about cyclophilins have a number of possible implications. At the same time, the major caveat is given by the authors themselves when they state in the title of their
work that “Cyclophilin A may contribute to the inflammatory process in rheumatoid arthritis...” Certainly, their data will encourage further research on the functional relevance of increased cyclophilin A in RA. Such research should take advantage of the availability of the Ppia−/− mice and investigate if these animals—along with their allergic phenotype—exhibit altered susceptibility to models of chronic destructive arthritis. Furthermore, such research will have to clarify whether Ppia−/− macrophages have a deceased ability of autocrine and paracrine stimulation, as well as (due to potentially reduced levels of MMP-9) altered homing into inflamed synovial tissue. Given the aforementioned data on changes in TCR signaling in the Ppia−/− mice, it will also be of interest to see whether cyclophilin A affects the composition of the T cell compartment in the chronically inflamed synovium and/or modulates the reactivity of arthritis-derived versus normal T cells.

Collectively, these data provide further evidence of the complexity of synovial inflammation and point to novel, as yet undiscovered pathways in the interactions of different cells in the RA synovial membrane.

References