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TARGETING THE MYDDOSOME IN SYSTEMIC AUTOIMMUNITY- READY FOR PRIME TIME?

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Innate immune responses play key roles in the initiation and perpetuation of a variety of systemic autoimmune diseases, including rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).(1) While effective biologics and small molecules targeting innate and adaptive immune responses in these diseases are currently available, there are still significant gaps in the development of therapies that can hamper innate immune dysregulation in certain subgroups of patients where this pathway may play crucial pathogenic roles. Cellular receptors belonging to the Toll (TLR)/Interleukin-1 receptor (IL1R) superfamily play fundamental roles in innate immune responses. TLRs sense pathogen-associated molecular patterns but are also implicated in detecting endogenous stimuli involved in immune dysregulation in autoimmune diseases, while members of the IL-1R are stimulated by cytokines such as IL-1 α and IL-1 β (2). TLRs share with the IL-1R a carboxyterminal intracellular (TIR) domain that acts as a platform to recruit downstream signaling molecules. Upon activation with respective ligands, the intracellular Toll/IL-1R domains of TLR dimers initiate oligomerization of a multiprotein signaling platform comprising myeloid differentiation primary response 88 (MyD88) and members of the interleukin-1 receptor-associated kinase (IRAK) family(3). Formation of this so called Myddosome complex initiates signal transduction pathways, leading to the activation of transcription factors and the production of various important inflammatory cytokines(4). In this context, IRAK-4 has a pivotal role as the master IRAK in TLR/IL-1R-triggered responses, as it functions upstream of other IRAK molecules. IRAK-4 has roles as both a structural protein and a kinase, and both functions are required for the Myddosome complex formation. Switching on IRAK-4 promotes the activation of nuclear factor kappa-light-chain-enhanced of activated B cells (NF- κ B), Interferon Regulatory Factor-5 (IRF-5) and the signaling pathways that lead to mitogen-activated protein kinase (MAPK) activity. Therefore, proper activation of this pathway leads to the synthesis of Interferons and various proinflammatory cytokines including TNF, IL-1 and IL-6. While IRAK-4 has been implicated in the pathogenesis of several autoimmune diseases, clinical development of IRAK-4 inhibitors has been difficult, due to conflicting effects on downstream inflammatory pathways related to inhibition of kinase activity versus scaffolding functions, as well differences among species studied in the responses to the inhibitory effects of these compounds. Indeed, the selective

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utilization of IRAK kinases has been reported to differ substantially in mouse and human cells(5).

In this issue of *Arthritis & Rheumatology*, Winkler et al report that an IRAK-4 specific inhibitor, called PF-06650833, suppresses inflammation in preclinical models of RA and SLE and in phase 1 healthy volunteer studies(6). The authors showed that PF-06650833 is highly selective as an inhibitor of the kinase activity of IRAK-4. Using *in vitro* approaches, the compound blocked specific downstream effects of disease-relevant stimuli in RA (inflammatory responses in synovial fibroblasts and immune-complex induced TNF production in macrophages) and in SLE (nucleic acid release from neutrophils and nuclear localization/activation of IRF-5 in monocytes, in response to TLR-7 agonists and/or lupus sera). Also relevant to SLE, the compound inhibited B cell cytokine synthesis and differentiation into plasma cells in response to IFNs and/or TLR-7 agonists, and hampered type-I IFN release by plasmacytoid dendritic cells and PBMCs in response to immune complexes. Using *in vivo* systems, the compound inhibited various clinical and immunologic features of the RA model of rat collagen induced arthritis and of two lupus models (the pristane-induced model and the genetically-prone MRL/lpr model). In two previous studies, PF-06650833 had been well tolerated and showed sustained decrease in serum high-sensitivity C reactive protein in healthy volunteers (7). Moving further into human *in vivo* studies, the authors performed two randomized, double-blind ascending dose, phase 1 studies to assess the safety of this compound in healthy volunteers. The compound was well tolerated and showed a decrease in the type I IFN gene signature by almost a third. As this inhibitory effect was tested in healthy people in steady state conditions, it will be important to determine whether a significant inhibitory effect of the type I IFN gene signature that is enhanced in many SLE patients(1) can be achieved, and how the degree of inhibition will compare to other currently used anti- type I IFN strategies(8).

Overall, this multimodal assessment of the potential efficacy of targeting IRAK-4 activity in RA and SLE demonstrates promising effects on targeting multiple innate inflammatory pathways relevant to a variety of chronic inflammatory conditions. These observations are supported by previous publications that suggest an anti-inflammatory role of IRAK-4 inhibition in crucial aspects of RA and SLE disease pathogenesis. This includes end-organ complications, such as bone damage in the context of RA(9), as well as previous evidence from murine systems that IRAK-4 is essential for autoimmune traits of various lupus-prone mouse models(10–12).

Although this study presents us with many provocative findings, there are some limitations on the interpretation of the results. The renal phenotype of the pristane-induced lupus model on Balb/c background was surprisingly mild and did not allow for full assessment of the role of an IRAK-4 inhibitor in lupus clinical kidney involvement, although the findings in the MRL/lpr mouse model do support that IRAK-4 inhibition could target lupus nephritis. The assessment of IRAK-4 inhibition in the IFN signature of healthy volunteers under conditions of homeostasis is unlikely to adequately reflect the potential effects on dysregulated IFN pathways in SLE and other autoimmune diseases, which may not be entirely TLR-dependent(13).

Safety will be a key issue to monitor in future human studies. Animals that lack IRAK-4 are resistant to lipopolysaccharide challenge, display severe impairments in ability to synthesize proinflammatory cytokines and are more susceptible to certain viral and bacterial infections(14). Of interest, despite the fundamental role of IRAK-4 in innate immune signaling and danger sensing, patients with autosomal recessive amorphic mutations in *IRAK4* display an immunologic syndrome with defective immunity in response to IL-1, IL-8 and various TLR ligands, effects on B cell subsets and IgM synthesis(15) but restricted effects on increased susceptibility to certain bacterial pyogenic infections, which occur earlier, but not later, in life(16). These observations may suggest that, especially in adults, IRAK-4 inhibition may provide benefits in autoimmune disorders without significantly hampering antimicrobial responses. Future studies will need to assess the safety effects of longer-term treatment with this compound in individuals with systemic autoimmunity.

The last few years have seen an increased number of IRAK-4 inhibitors being developed and tested(5). While phase 2 and 3 studies will be needed to assess the role of these compounds in inhibiting various chronic inflammatory diseases, the results of the study by Winkler et al suggest a promising novel avenue that may be added to the armamentarium of drugs involved in hampering innate immune dysregulation in the context of systemic autoimmune diseases. It will also be important to assess if the targeting of IRAK-4 could be used in combination with other drugs (DMARDs or biologics) in patients that may be resistant to more limited immunomodulatory therapy. Overall, identifying those patients with systemic autoimmunity where Myddosome activation is a key dysregulated pathway in their specific syndrome and clinical presentation will be a key feature to select those individuals that may be more likely to benefit from such a targeted therapy.

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