Editorial

Soluble FcγRIIIa as a Marker for Rheumatoid Arthritis: The Use of Genetics in Selected Populations to Study Pathogenetic Pathways


Several sources of data are available to enhance our understanding of the pathophysiology of rheumatoid arthritis (RA). Studying the involvement of the various cell lineages in the pathogenesis of RA has been possible in mouse models of arthritis, in which lineage-specific ablation was achieved by genetic manipulation or by using depleting antibodies. The impossibility of using these methods in humans forced researchers to assess the involvement of various cell types in the pathophysiology of RA by studying their specific accumulation and/or activation in cells or tissues from patients with RA. In this issue of *The Journal*, Masuda, *et al* present evidence that the serum concentrations of soluble FcγRIIIa are specifically increased in RA patients, suggesting that macrophages/natural killer (NK) cells are locally activated in this disease[1]. Their study confirms the unequivocal data that have been generated in animals that were genetically engineered to miss a gene (a knockout animal) or to overexpress a gene (a transgenic animal). These data indicate that the activation of cells of the myeloid lineage is critical in the pathogenesis of RA.

The evidence for involvement of the myeloid lineage in RA originates from different animal models. Mice that have a specific deletion in the myeloid lineage of the HiF-1α gene (encoding a transcription factor induced by hypoxia) cannot activate myeloid cells in hypoxic conditions of joint inflammation. Using a serum transfer model of arthritis, it was demonstrated that arthritis induced in these animals was strongly reduced[2]. Using this same model of arthritis, it was demonstrated that mast cells and neutrophils, as well as the alternative pathway of the complement system and FcγRIII, are critically involved in the effector phase of the disease[3-5]. Moreover, it has been demonstrated in a different mouse model of arthritis that the absence of FcγRI, specifically expressed by monocytes/macrophages and dendritic cells, results in a strong decrease in the severity of arthritis[6]. Altogether, these results strongly support that cells from the myeloid lineage have a pivotal role in inflammation of joints. These models point to the relevance of monocyte/macrophages and neutrophils in the pathogenesis of RA.

From a more clinical perspective, intervention strategies directed against the activation products of these cells, such as tumor necrosis factor (TNF) blocking agents, have been shown to be highly effective, implying the relevance of the myeloid lineage in human RA as well. However, as TNF-α is not specifically secreted by these cells, it is not possible from these studies to accurately assess which cell types are the origin of the proinflammatory cytokines, nor is it possible to assess if specific cell populations of the myeloid lineage (either the populations of macrophages or neutrophils or a combination) are expanded in RA.

Masuda, *et al* show evidence that the concentration of soluble products (sFcγRIII) originating from activated cells of the myeloid lineage are increased in patients with RA compared to controls, making it possible to study the specific involvement of these cells in the pathogenicity of the disease[1]. They took advantage of the unique expression profile of the 2 FcγRIII receptors: FcγRIIIb is solely expressed on neutrophils, and FcγRIIIa is expressed on NK cells and macrophages/monocytes. Moreover, these FcγRIII receptors are released from the membrane upon cell activation, suggesting that the presence of sFcγRIII can serve as a marker for the size or activation state of the respective cell populations[7].

Given the extended homology between sFcγRIIIa and sFcγRIIIb, it is difficult to discriminate these 2 soluble proteins. It is, however, possible to discriminate between their allelic forms. FcγRIIIb has 2 allotypes, NA1-FcγRIIIb and NA2-FcγRIIIb[8], whereas the gene encoding FcγRIIIa bears 2 polymorphisms, resulting in different amino acids at position 158 (Phe or Val) and at position *–48H* or *–48R*[9]. It is possible to discriminate between the 2 forms because monoclonal antibodies (Mab) such as CLBgranII specifically bind NA1-FcγRIIIb, and the Mab GRM-1 specifically binds NA2-FcγRIIIb and all allotypes of FcγRIIIa.

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Masuda, *et al* observed that total soluble FcγRIII is increased in serum of patients with RA. This is a relatively easy experiment that can be replicated in most populations all over the world. However, Masuda, *et al* also took advantage of the unique composition of the Japanese population with respect to the NA1 genotype distribution. NA1/NA1 homozygous individuals in the Caucasian population are relatively rare (about 10% of the population), but are quite common in Japan. Thus, this genetically unique population made it possible to select only NA1/NA1 donors. Using an antibody that recognized only the NA2 variant of FcγRIIIb and all variants of FcγRIIIa (the GRM-1 antibody), the authors were able to specifically measure also sFcγRIIIa in NA1/NA1 homozygous individuals. This allowed the authors to conclude that sFcγRIIIa is increased in patients with RA. Given the origin of the sFcγRIIIa, the conclusion is that the monocyte/macrophage and/or NK cell line is expanded and/or activated in RA patients. Further studies, aimed at also measuring sFcγRIIIb, could shed light on the possible contribution of neutrophils to the pathogenesis of RA.

Since the study reveals the involvement of macrophages and/or NK cells in RA, assessing the activation status of these cells in the synovium of RA patients could be an interesting approach to unravelling the relative contribution of the 2 different populations to the increase in sFcγRIIIa titers in the plasma of these patients, and could also give an indication whether this increase is due to activation rather than expansion of these cell populations. Although the authors could not exclude the possibility that NK cells are the source of increased sFcγRIIIa, previous studies in animal models do not offer any supporting data to this possibility. Moreover, the authors show no specific expansion of this cell population in RA patients compared to controls.

Another soluble marker of accumulated tissue macrophages is CD163. Interestingly, in sera from patients with RA compared to sera from controls, elevated concentrations of sCD163 are found[10]. For this marker additional data are available, such as a high expression on the macrophages within the RA synovium. In summary, the combination of the data on the increased levels of sFcγRIIIa and sCD163 point to an increased total body macrophage mass and/or an increased activation of macrophages.

In this context, it is noteworthy that the issue of different subpopulations of macrophages has not been studied. Recently, it has become clear that different subpopulations of macrophages can be identified. Classically, interferon-γ-activated macrophages are recognized that promote the secretion of proinflammatory cytokines and the production of effector molecules like TNF-α and reactive oxygen/nitrogen intermediates that might contribute to tissue damage. Coming from the successes of anti-TNF therapies, it seems logical to hypothesize that this population is expanded. However, alternatively activated macrophages have been described as well. These subsets secrete interleukin 10 as the signature cytokine and have been suggested to exert specific functions associated with tissue homeostasis and tissue remodeling[11,12]. Alternatively activated macrophages have also been shown to induce T cell hyporesponsiveness and to express specific proteases and enzymes that mediate destruction of cartilage, such as metalloproteases and arginases[13,14]. In particular, macrophages modulated by type 2 cytokines promote fibrogenesis from fibroblasts[15], which is a hallmark of RA as well. Given these different data sets, it is equally possible that either one of the subpopulations is expanded in different disease states in RA, but it is unknown what the distribution of the different subsets of macrophages is in RA and which subsets are expanded.

Masuda, *et al* found that sFcγRIIIa levels correlated with variables reflecting the extent of joint inflammation (C-reactive protein, erythrocyte sedimentation rate, and Lansbury index). These data are compatible with the idea that inflammation is caused by macrophages, but do not allow conclusion whether these soluble products can be used for monitoring the number or activation state of the tissue macrophage. Longitudinal studies will be necessary to assess the information coming from these markers.

In conclusion, the data on serum markers such as those from Masuda, *et al* contribute to our understanding of what is going on in RA. Further studies are eagerly awaited in which a combination of plasma markers from different subsets of macrophages is followed in well characterized patients over time. Only then can conclusions be made about which subset of monocytes or macrophages is expanded or activated. Such studies may open the possibility for specific immune monitoring or intervention in our patients.

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