

## ADAMTS Revenge on Eve?



Despite major progress in diagnosis and treatment of rheumatoid arthritis (RA), this systemic autoimmune disorder is still a challenge for predicting the course of disease, therapeutic response, and outcome on the individual level. This is no surprise: the pathogenesis of RA is extremely complex, involving genetic predisposition, gender bias, dysregulation of immunologic tolerance, and environmental factors, to name a few factors. Finally, an infiltrating army of various immune-competent cells induces production and release of proinflammatory cytokines as well as proteinases, inevitably causing destruction of cartilage and bone. On the other hand, our skills and opportunities to stop this process have significantly improved through introduction of biologic disease-modifying antirheumatic drugs. However, it again became evident that RA is not uniform, and new efforts have been made to identify markers for stratification of disease, also allowing prediction of response. As an example, encouraging data have come from clinical trials using rituximab, where seropositive patients (positive for rheumatoid factor and/or antibodies against citrullinated antigens) were characterized as the subgroup responding better to therapy<sup>1,2,3</sup>. Recently, a stronger reduction in disease activity under tumor necrosis factor (TNF) blockers was observed in seronegative patients with RA in a multicenter study in the UK<sup>4</sup>, and this unexpected finding was also confirmed in Italian and German cohorts. Since biomarkers to predict response are available not only from the autoantibody profile (as part of the immunome), but may also be encoded in the genes (the genome) or provided by the composition of mRNA expression (the transcriptome), proteins, and metabolites (proteome and metabolome), the field for future research is wide open. For example, transcription profiling on monocytes revealed that increased expression of CD11c at baseline is associated with response to adalimumab monotherapy in patients with RA<sup>5</sup>. In this issue of *The Journal* Tsuzaka, *et al* identify mRNA expression levels of ADAMTS-5 as a novel predictive marker for response to a TNF-blocking agent<sup>6</sup>.

ADAMTS (derived from “a disintegrin and metalloproteinase with thrombospondin motifs”) belong to a group of secreted enzymes widely expressed in connective tissues including cartilage. These complex proteases consist of a protease domain and an ancillary domain for specific binding of substrate<sup>7</sup>. Since several ADAMTS express proteoglycanase activity and participate in the proteolysis of large aggregating proteoglycans within the cartilage, an important role has been suggested in the pathogenesis of osteoarthritis (OA) and RA, where aggrecan loss represents a major feature<sup>8</sup>.

Interestingly, ADAMTS are also involved in other human pathologies without a gender predisposition such as in a subtype of Ehlers-Danlos syndrome, where failure to process procollagen I in the dermis of the skin is related to ADAMTS-2 mutations<sup>9,10</sup>. Further, failure to cut ultra-large “von Willebrand factor” into an optimal size for normal coagulation is related to an inherited form of thrombotic thrombocytopenic purpura (TTP) caused by ADAMTS-13 mutations, whereas acquired TTP is caused by ADAMTS-13 autoantibodies<sup>11,12</sup>.

Coming back to the field of arthritis, loss of articular cartilage caused by extracellular matrix breakdown is a hallmark in the pathogenesis of animal as well as human diseases. ADAMTS-4 and -5 in particular have been implicated in the degradation of aggrecan due to their expression profile in the cartilage, at both the mRNA and protein levels. Tsuzaka, *et al* provide evidence that low mRNA expression levels of ADAMTS-5 in peripheral blood mononuclear cells (PBMC) are predictive of good clinical response to the TNF blocker infliximab in the treatment of patients with RA<sup>6</sup>. Interestingly, baseline levels of ADAMTS-5 were significantly lower in good responders compared to patients with moderate or non-response after 38 weeks of infliximab treatment<sup>6</sup>. The high positive predictive value of about 90% and a negative predictive value of about 60% for good response makes ADAMTS-5 a potential candidate for a new predictive marker at least for

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*See ADAMTS5 is a biomarker for prediction of response to infliximab in RA, page 1454*

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this treatment modality in patients with RA. Further, patients with low expression of ADAMTS-5 at baseline not only showed a stronger reduction in Disease Activity Score-28, but also a better improvement in their functional capacity as determined by the Health Assessment Questionnaire. Notably, the study compared 2 different size groups, where low expression levels of ADAMTS-5 were observed in only 10 out of 73 patients (13%). Thus, these results have to be confirmed in subsequent studies in larger cohorts of patients. Further, the study did not investigate whether ADAMTS-5 expression levels also correlate with the radiological outcome, which would be of major interest.

As mentioned, ADAMTS-5 as a member of the aggrecanases is involved in cartilage degradation in arthritis. Interesting insights came also from animal models, where ADAMTS-4 and -5 knockout mice expressed no major phenotypical abnormalities, but showed a significant reduction in the severity of surgically induced OA in the ADAMTS-5 in contrast to the ADAMTS-4 knockout groups<sup>13,14,15</sup>. These data were supported by a similar observation in a model of inflammatory arthritis, where ADAMTS-5 but not ADAMTS-4 knockout mice were protected against aggrecan loss<sup>15</sup>. In this context, it was also shown that aggrecanase activity was inducible in the articular cartilage explants from wild-type and ADAMTS-4 knockout mice but not from ADAMTS-5 knockouts. As reported in other studies, mice with a deletion of the ADAMTS-5 catalytic module were resistant to induced arthritis<sup>14,15</sup>. It was also shown that the expression of ADAMTS genes is influenced by growth factors as well as different cytokines. In this context, ADAMTS-4 but not ADAMTS-5 was upregulated upon the influence of transforming growth factor- $\beta$  in articular cartilage at the mRNA level<sup>16</sup>. Expression of ADAMTS-4 transcripts was inducible by proinflammatory cytokines such as interleukin 1 (IL-1) or TNF, whereas constitutive expression of ADAMTS-5 was not increased<sup>17,18</sup>. Further, exposure to TNF- or IL-1-blocking agents reduced only the activity of ADAMTS-4 but not ADAMTS-5<sup>19</sup>. These results are in good agreement with the current observation of Tsuzaka, *et al*<sup>6</sup>. Indeed, failure of TNF blockers to inhibit ADAMTS-5 expression may suggest that patients with a high expression of ADAMTS-5 are more resistant to infliximab, for example. However, to further support such a pathogenic link, it would be of interest to correlate the expression of ADAMTS-5 between peripheral compartments (PBMC) and targeted tissue (synovium). The immunoblotting results of the present study provide evidence that ADAMTS-5 is indeed expressed in PBMC at the protein level. However, the function of ADAMTS-5 in PBMC is unclear, thus further investigations are required to clarify the significance of this observation.

Recently, it was also shown that ADAMTS-4 cleaves COMP (cartilage oligomeric matrix protein) as well as fibromodulin and decorin, indicating that the proteolytic

spectrum of this subgroup of proteinases is not restricted to the cleavage of proteoglycans<sup>7,20</sup>. Apart from ADAMTS-4 and -5, other ADAMTS such as ADAMTS-7 and ADAMTS-12 might also play a role in the pathogenesis of arthritic disorders<sup>8</sup>. Expression of ADAMTS-7 and ADAMTS-12 was shown to be upregulated in COMP-producing musculoskeletal tissues, especially in the cartilage and synovium of patients with RA, where both proteinases can interact and degrade COMP<sup>21</sup>.

Thus several ADAMTS are likely to be involved in the initiation and progression of arthritic diseases in humans. Especially in RA and OA, where female offspring of Eve are clearly predisposed to a more frequent and severe disease manifestation, an overexpression and subsequently increased activity of ADAMTS is likely to be involved in the destructive process in the affected joints. The data from animal as well as human studies suggest that ADAMTS-5 represents a major aggrecanase within the cartilage and therefore might play a special role in the pathogenesis of arthritic disorders. The work by Tsuzaka, *et al* provides additional evidence that the expression of ADAMTS-5 might not only be linked to the pathogenesis of disease, but may also represent a useful marker for predicting therapeutic response and thus a potential tool for stratification of patients with RA.

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