Rheumatoid Factor and Anti–Modified Protein Antibody Reactivities Converge on IgG Epitopes

In this issue, Mergaert et al (p. 984) describe the repertoire of epitopes bound by anti–modified protein antibodies (AMPAs) and demonstrate that this repertoire includes modified IgG epitopes. The newly discovered IgG epitopes are bound by AMPAs in addition to rheumatoid factors (RFs). The findings expand on and partially merge the known reactivities of RFs and AMPAs and position IgG as a common antigen that connects the otherwise divergent reactivities of RFs and AMPAs.

In their study, the investigators evaluated IgG binding to all possible linear epitopes on the constant region of IgG heavy chain. They found that seropositive RA sera showed high IgG binding to multiple citrulline- and homocitrulline-containing IgG-derived peptides, and they characterized the variability among epitopes as well as variability in IgG binding among subjects and monoclonal AMPAs. When the researchers examined sera from patients with non-RA disease, however, they found consistent IgG binding to only 1 linear IgG epitope: a hinge region epitope bound in anti-SSA+ Sjögren’s syndrome. The team discovered that the monoclonal AMPAs bound citrulline- and homocitrulline-containing IgG peptides and modified IgG Fc. In their discussion, the authors suggest that AMPAs with limited multireactivity may develop first, and are then followed by anti–modified IgG antibodies and later RF, possibly via epitope spreading.

Figure 1. The reactivities of RFs and AMPAs converge on IgG epitopes. The Venn diagram illustrates RF and AMPA reactivities.

Antiphospholipid Antibodies Increase Cell Decidualization, Senescence, and Inflammation

The presence of antiphospholipid antibodies (aPLs) is one of the single biggest maternal risk factors for recurrent miscarriage. Because appropriately controlled decidualization and function of endometrial stromal cells (EnSCs) are key for successful implantation, placentation, and the establishment of a healthy pregnancy, scientists wonder whether these processes may be impaired in obstetric antiphospholipid syndrome (APS). In this issue, Tong et al (p. 1001) report findings that shed new light on the pathogenesis of pregnancy complications in women with aPLs.

For their experiments, the investigators used the aPL IIC5, describing it in their article as a well-characterized mouse IgG1 anti-human β2-glycoprotein I monoclonal antibody. They found that aPLs increased decidualization and senescence and induced inflammation in human EnSC cells, findings that they were able to replicate in primary human EnSCs. The researchers described the aPL-induced response in primary human EnSCs as reminiscent of an inflammatory senescence-associated secretory phenotype.

The team then turned to a mouse model of decidualization and APS to validate their in vitro findings and demonstrated that aPLs increased decidualization and induction of uterine inflammation and senescence. The researchers next sought to determine which receptor on human EnSCs was activated by aPLs to mediate the process; they found that aPL-induced up-regulation of EnSC decidualization and inflammation occurred, in part, through Toll-like receptor 4 and, in part, through p38 MAPK, a signaling pathway reported to be increased in trophoblasts exposed to aPLs. In contrast, the decidualization and senescence responses were reactive oxygen species-dependent.

Finally, the team investigated whether the standard therapeutics for women with obstetric APS, low molecular weight heparin (LMWH), could protect against the effect of aPLs on EnSC function. They found that LMWH reduced the ability of aPLs to increase EnSC decidualization and inflammation. The authors conclude that their findings underscore the benefit of heparin in the prevention of pregnancy loss in this high-risk population.
Necroptosis Contributes to Myofiber Death in Idiopathic Inflammatory Myopathies

Idiopathic inflammatory myopathies (IIMs) include several distinct entities: dermatomyositis (DM), amyopathic DM (ADM), and immune-mediated necrotizing myopathy (IMNM). Not only do DM and IMNM show different clinical manifestations and pathologic features, but animal studies indicate that DM and IMNM have differing pathogeneses. While muscle damage is a prominent feature of all IIMs, the underlying mechanism behind this damage has not been fully clarified. Some researchers have suggested, however, that necroptosis (programmed necrosis that has been associated with many types of diseases affecting the tissue) may be behind the damage. Initiators of necroptosis include death receptors, pathogen-recognition receptors, and the nucleic-acid–sensing protein ZBP1.

In this issue, Peng et al. (p. 1048) report the results of the first attempt to investigate the dysregulation of necroptosis in IIMs. Their data demonstrate that overactivated necroptosis contributes to muscle damage in IIM (both DM and IMNM). The team analyzed muscle biopsy samples from 26 patients with confirmed IIM and identified elevated expression of receptor-interacting protein 3 and mixed-lineage kinase domain–like proteins. The researchers also found elevated expression of high mobility group box chromosomal protein 1, a protein released extracellularly during necrotic cell death in the muscle tissue of patients with IIM. Taken together, their results indicate that the muscle tissues of IIM patients not only had significant features of myofiber necrosis but also had high levels of expression of key molecules that participate in the necroptosis machinery.

The investigators then performed in vitro cell culture experiments in which they used tumor necrosis factor to induce necroptosis in C2C12 myoblasts in the presence of the pan-caspase inhibitor Z-VAD. They found that when they inhibited necroptosis, they were able to prevent necroptosis-induced cell death of C2C12 cells. The authors suggest that necroptosis inhibitors could represent a new therapeutic target in the treatment of IIMs.

Journal Club

A monthly feature designed to facilitate discussion on research methods in rheumatology.

Nintedanib in Patients with Autoimmune Disease–Related Progressive Fibrosing ILDs: Subgroup Analysis of the INBUILD Trial

Matteson et al, Arthritis Rheumatol 2022;74:1039–1047

Interstitial lung disease (ILD) is a common manifestation of systemic autoimmune diseases. Progression of ILD is associated with a poor prognosis. Nintedanib is a tyrosine kinase inhibitor that has been shown to slow the decline in forced vital capacity (FVC) in patients with idiopathic pulmonary fibrosis (IPF), other fibrosing ILDs with a progressive phenotype, and fibrosing ILD associated with systemic sclerosis (SSc). The INBUILD trial investigated the efficacy and safety of nintedanib compared to placebo in 663 patients with progressive fibrosing ILDs other than IPF. To be eligible to enter the INBUILD trial, patients needed to have >10% extent of fibrosing ILD on a high-resolution computed tomography (HRCT) scan and to have shown progression of their ILD, based on a worsening of FVC, symptoms, or fibrotic abnormalities on HRCT, within the previous 2 years, despite management deemed appropriate in clinical practice.

This study presents data from the 170 patients with autoimmune disease–related ILDs who participated in the INBUILD trial. Results are presented for this subgroup on the annual rate of decline in FVC in ml/year over 52 weeks (i.e., the primary end point in the overall trial population and in patients with a usual interstitial pneumonia–like fibrotic pattern on HRCT), as well as on the proportions of patients with acute exacerbation of ILD or death, an absolute decline in FVC percent predicted of ≥10% or death, and death over the whole trial (i.e., after a mean exposure to trial medication of ~16 months). For the annual rate of decline in FVC, a P value for interaction was calculated as an indicator of the potential heterogeneity in the effect of nintedanib versus placebo across subgroups based on diagnosis (rheumatoid arthritis, SSc, mixed connective tissue disease, other autoimmune diseases). The safety and tolerability of nintedanib was assessed by examining the proportions of patients with adverse events and with adverse events leading to discontinuation of the trial drug, irrespective of causality.

Questions

1. How easy would it be to use the inclusion criteria from this trial to identify patients with progressive ILD in clinical practice?
2. What do these results tell us about the effects of nintedanib in patients with autoimmune disease–related ILDs in general and in those with specific diseases?
3. How compelling are the findings on end points that were underpowered, such as the risk of acute exacerbations and death?
4. What evidence is there to support the use of other drugs in patients with ILD associated with autoimmune diseases other than SSc?