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Humanized anti-Desmoglein-3 antibodies as tools for research on the role of the neonatal Fc receptor in pemphigus vulgaris

The autoimmune, blistering disease pemphigus vulgaris is caused by autoantibodies against the desmosomal cadherins, mainly desmoglein-3. Recently, it has been shown that blocking the neonatal Fc receptor (FcRn) can lead to a rapid decrease of pathogenic IgG and an improvement of various autoimmune diseases, including pemphigus, myasthenia gravis and autoimmune thrombocytopenia. Binding of IgG type antibodies to FcRn results in antibody recycling and increases the plasma half-life of pathogenic autoantibodies, contributing to disease phenotype. Compounds that block the binding of IgG to FcRn, such as efgartigimod, may be useful for the treatment of IgG-mediated autoimmune diseases.

To study the pathogenic action of anti-desmoglein antibodies *in vitro*, mouse monoclonal anti-desmoglein-3 antibodies, especially AK23, have been developed that mimic the pathogenic effect of patient sera (PV IgG) in cultured keratinocytes. However, mouse IgG poorly binds to human FcRn. Therefore, to study the potential function of FcRn in pemphigus in human keratinocytes, we have here used chimeric AK23 anti-desmoglein-3 antibodies that contain human Fc domains. We show that these antibodies induce changes in desmoglein-3 localization and result in acantholysis in a monolayer dissociation assay in hTert keratinocytes. Surprisingly, the effects on keratinocyte adhesion can be inhibited by blocking IgG binding to FcRn by efgartigimod. These data suggest that in keratinocytes, FcRn may play a further role in the pathogenesis of pemphigus, beyond its known contribution to IgG recycling.