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Stabilization of Keratinocyte Monolayer Integrity in the Presence of Anti-Desmoglein-3 Antibodies through FcRn Blockade with Efgartigimod: Novel Treatment Paradigm for Pemphigus?

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Abstract: Pemphigus vulgaris, a blistering skin and/or mucosa disease, is caused by autoantibodies against the desmosomal cadherins, mainly Dsg-3. Binding of IgG type antibodies to the neonatal Fc receptor (FcRn) results in antibody recycling and increases the plasma half-life of all IgGs, including pathogenic autoantibodies, contributing to disease phenotype. Recently, it has been shown that blocking FcRn can lead to a rapid decrease of pathogenic IgG and an improvement of various autoimmune diseases, including pemphigus, myasthenia gravis, and immune thrombocytopenia. Efgartigimod is an engineered Fc fragment that inhibits FcRn activity and 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-Dsg-3 antibodies, especially AK23, have been developed that mimic the pathogenic effect of patient sera in cultured keratinocytes. However, mouse IgG binds poorly to human FcRn. Therefore, to study the potential function of FcRn in pemphigus in human keratinocytes, we have here used chimeric AK23 anti-Dsg-3 antibodies that contain human Fc domains.

We show that these antibodies induce changes in Dsg-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 with 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.

Keywords: Pemphigus vulgaris; desmoglein 3; neonatal Fc receptor; efgartigimod