Inflammatory Diseases
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Blocking FcαR1 (CD89)/IgA interaction using CD89 specific antibodies is a potential therapeutic target to resolve tissue damage in chronic inflammation and autoimmunity

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Introduction: Immunoglobulin A (IgA) is considered to be a non-inflammatory regulator at mucosal areas. However, previous work of our group showed that IgA is also involved in disease pathology, because it provides a potent stimulus to activate neutrophils after crosslinking of surface CD89, resulting in chronic inflammation and collateral tissue damage. Moreover, IgA (auto)antibodies and neutrophils are key players in various diseases, including blistering skin diseases (linear IgA bullous disease and dermatitis herpetiformis), rheumatoid arthritis and inflammatory bowel disease. Therefore, we investigated if therapeutic targeting of neutrophils by anti-CD89 monoclonal antibodies (mAb) will decrease inflammation and resolve disease. In this research, the biological activity of newly developed anti-CD89 mAbs and their potential therapeutic capacity were investigated.
Methods: Human neutrophils were isolated from heparinized healthy donor blood. The ability of anti-CD89 mAbs to bind human neutrophils was investigated by flow cytometry. Furthermore, the capacity of these anti-CD89 mAbs to inhibit IgA-mediated phagocytosis, neutrophil extracellular trap (NET) release and migration was studied. To this end, neutrophils were pre-incubated with/without anti-CD89 mAbs after which they were stimulated with IgA-coated beads. The amount of phagocytosed beads, NET release and migrated neutrophils were subsequently analyzed. In parallel, chemoattractant leukotriene B4 and lactoferrin (as a measure for degranulation) release were determined. Finally, the therapeutic potential of our prototypic anti-CD89 mAb clone 10E7 was in vivo tested in anti-mouse collagen XVII human IgA-treated transgenic CD89 mice, a preclinical model for autoimmune linear IgA bullous disease (LABD).
Results: Our results show that all generated anti-CD89 mAbs can bind surface CD89 and block IgA binding to neutrophils. Furthermore, these anti-CD89 mAbs have the capacity to inhibit IgA-mediated phagocytosis, NET release and migration of human neutrophils. Moreover, human IgA-mediated leukotriene B4 and lactoferrin release are decreased from anti-CD89 mAbs-treated neutrophils. Finally, anti-CD89 antibody clone 10E7 reduced anti-mouse collagen XVII human IgA-induced neutrophil influx (and subsequently tissue damage) in our in vivo LABD model.
Conclusion: Our data clearly indicate that the anti-CD89 mAbs are able to inhibit IgA-induced neutrophil activation. Moreover, our lead anti-CD89 mAb clone 10E7 reduced anti-autoantigen IgA-induced neutrophil influx in our pre-clinical in vivo LABD model showing its therapeutic potential.