GRC2.Fc promotes convergent macrophage reprogramming for tissue repair and inflammation resolution

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Abstract

Conventional cytokine-based macrophage polarization yields stochastic heterogeneity that limits therapeutic predictability. We report GRC2.Fc, an engineered bifunctional biologic comprising tandem heparan sulfate-binding domains fused to human IgG1 Fc, which achieves convergent macrophage reprogramming through cis co-engagement of syndecan proteoglycans and FcγRI (CD64). Single-cell profiling of human monocyte-derived macrophages demonstrates 97% transcriptional and 81% metabolic convergence into a reparative state — far exceeding IL-4's maximum of 32.7% — with coordinated induction of *ATF3*, *ATF4*, *PPARγ*, and *NOR1* alongside simultaneous activation of glycolysis and oxidative phosphorylation and paracrine secretion of metabolic intermediates. In cardiotoxin-induced muscle injury, GRC2.Fc enriched $ARG1^{+}$ macrophages, expanded satellite cells, and promoted neovascularization. In leptin-deficient *ob/ob* mice, GRC2.Fc achieved complete wound closure by day 12, over two weeks faster than hIgG1 controls. In a bleomycin-induced acute lung inflammation model, delayed intravenous GRC2.Fc significantly reduced pathology scores and preserved alveolar architecture. These findings establish rational dual-receptor co-engagement as a new design principle for convergent macrophage reprogramming across injury, metabolic disease, and inflammatory conditions.