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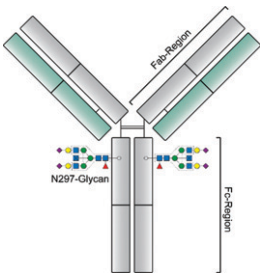
Glycoengineering the Complement Cascade

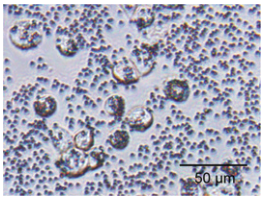


In humans, the most abundant IgG isotype Abs have a single glycan in their Fc region that is critical for mediating function, including C1q binding. In this Top Read, van Osch et al. (p. 1545) study how galactosylation at this site impacts induction of the classical complement cascade. Glycoengineering did not affect the ability of IgG1 to bind its Ag, but galactosylation enhanced IgG1 hexamer formation. In turn, hexamer formation enhanced C1q and downstream complement deposition and activation, increasing cell-dependent cytotoxicity. These data suggest that tools available to optimize the therapeutic potential of Abs may expand to include glycoengineering.

Glycosylation and SARS-CoV-2

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been shown to alter many aspects of the immune response. In this Top Read, Alves et al. (p. 1591) characterized changes in glycosylation associated with SARS-CoV-2 infection and observed that peripheral T cells from COVID-19 patients had a pattern of less complex *N*-glycosylation. Further analysis indicated that an increased level of serum IL-2 in COVID-19 patients was a driver for changes in T cell glycosylation, especially in asymptomatic patients. They observed that the virus sensor C-type lectin dendritic cell–specific ICAM-3–grabbing nonintegrin (DC-SIGN) was elevated on monocytes from SARS-CoV-2–infected patients and correlated directly with poor outcomes. These results highlight the potential use of glycosylation as a biomarker for SARS-CoV-2 infection and may offer insights into potential novel therapies.

Making Alveolar Macrophages



Alveolar macrophages (AMs) are critical for innate immune responses in the lung, but most alveolar cell lines used for in vitro studies differ from primary AMs collected from bronchoalveolar lavage fluid (BALF), both phenotypically and functionally. In this Top Read, Luo et al. (p. 1683) described an in vitro culture system for generating AM-like cells. They expanded murine bone marrow cells in vitro in the presence of GM-CSF and TGF-β for 9 d and added the PPARγ agonist rosiglitazone (GTR) for 7 d. AM-like cells displayed phenotypic and morphologic features resembling primary AMs, as well as a gene signature and functional attributes similar to primary AMs. This culture system supported the expansion of AM-like cells from fetal liver cells and BALF-AMs. Importantly, the cultured AM-like cells could be modified genetically using CRISPR-Cas9. These findings suggest that the novel culture system is a viable strategy for expanding AM-like cells and can be used for both basic and clinical studies.

Thrombin Cleavage of C5

In this Top Read, Nilsson et al. (p. 1641) demonstrate that thrombin is unable to cleave the native form of C5. Anticoagulation of whole blood is necessary to study complement activation, and previous experimental systems used a thrombin inhibitor, interfering with thrombin-induced cleavage of C5. The authors developed a four amino acid inhibitor (Gly-Pro-Arg-Pro [GPRP]) of fibrin polymerization, which allows for effective anticoagulation downstream of thrombin. Complement activation with GPRP was similar to previous systems. However, in the GPRP system, thrombin did not cleave native C5. Acidification of plasma resulted in a C5 conformational change that allowed thrombin-mediated cleavage. These data suggest that thrombin cleavage of C5 requires a conformational change and may be restricted to certain pathophysiological conditions.

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