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IMMUNOBIOLOGY

Comment on Orr et al, page 1061

Pairing SOCS with CD33

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SOCS molecules function in a negative-feedback loop to dampen inflammatory responses. Their role in regulating CD33 expression may have important implications for normal host defense responses and in the use of CD33-targeted therapy of myeloid leukemia.

The family of suppressor of cytokine signaling (SOCS) proteins has been implicated in the control of immune responses by reducing cytokine-mediated effects, thus acting in an inhibitory fashion. In a study by Orr and colleagues in this issue of *Blood*, it is shown that SOCS may have another role that is actually proinflammatory. The study showed that intracellular SOCS3 binds to phosphorylated CD33, competing with SHP-1/2 for binding to the CD33 immunoreceptor tyrosine–based inhibitory motif (ITIM) and leads to proteosomal degradation of complexed SOCS and CD33. Thus, both SOCS and CD33 are down-regulated, removing an inhibitory pathway of inflammation. This may be an important regulatory pathway in host defense responses. CD33 is a cell-surface glycoprotein specifically expressed on myeloid cells, including granulocytes, monocytes, and myeloid leukemia cells. Monoclonal antibodies (mAbs) against CD33 have been used in the diagnosis and therapy of acute myeloid leukemia (AML) for many years, well before the physiologic role of CD33 was known. CD33, a member of the ever-expanding sialic acid–binding immunoglobulin-related lectin (Siglec) family, is engaged in sialic acid–dependent cell interactions and adhesion of myeloid cells. The cytoplasmic tail of CD33 contains 2 ITIMs and therefore may serve as an inhibitory receptor. Engagement of CD33 induces apoptosis and inhibition of proliferation in AML cells. The immediate mediators of this effect include the tyrosine kinase Syk and SHP-1/2. mAb therapy directed to CD33 has shown some efficacy in the treatment of AML. The immunotoxin gemtuzimab ozogamycin (GO), composed of a humanized anti-CD33 mAb and calichiamycin, is a US Food and Drug Administration (FDA)–approved drug. Clinical trials with an unmodified anti-CD33 mAb are also in progress. The findings by Orr and colleagues suggest that SOCS3 expression in AML cells could affect the efficacy of anti-CD33 mAb by forming complexes with CD33 and subsequently leading to its degradation. Ligation of CD33 leads to its phosphorylation, thus providing the docking site for SOCS and the subsequent degradation of CD33. Perhaps the variable response of AML cells to the effects of GO and other anti-CD33 mAbs could be due in part to differential levels or modulation of SOCS3. These findings point to new research directions, including determining the differential expression of SOCS3 in AML cells, blocking SOCS3 binding to CD33, and perhaps inhibiting the proteosomal degradation of SOCS/CD33 as a means to maintain CD33 surface expression. Thus, SOCS3 binding to CD33 in normal myeloid cells may augment inflammatory responses in host defense reactions. However, in malignant cells SOCS might possibly be getting in the way of the desired inhibitory effect of CD33 ligation by natural or man-made ligands and contributing to growth and resistance to therapy. This is speculative and requires further study.

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PHAGOCYTES

Comment on Ehrchen et al, page 1265

Glucocorticoids in innate immunity: more transactivation than transrepression!

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Identification of the mechanism responsible for the beneficial effects produced by glucocorticoids in clinical settings has always been a fascinating task of pharmacology. Novel data produced with human primary monocytes reveals the major mechanism of action: gene reprogramming towards marked transactivation of multiple anti-inflammatory genes.

The seminal observation by Philip Hench et al that adrenal cortex extracts possessed potent antiarthritic properties in humans[1] has produced one of the major breakthroughs in biology and clinical practice. The identification of cortisol, and the ensuing development of several synthetic derivatives, has indeed provided the clinician with strong weapons for treatment of diseases spanning from asthma to arthritis to inflammatory bowel disease. But how do glucocorticoids work? Upon addition to cells, the lipophilic glucocorticoid will rapidly cross plasma membranes to interact with specific cytoplasmic glucocorticoid receptors (GRs). The GR is kept in an inert status by binding to intracellular chaperones (heat shock proteins); however, interaction with the ligand causes dissociation, activation, and dimerization. The homodimer complex (2 glucocorticoid molecules and 2 GR molecules) will travel to the nucleus, where it will bind to specific positive or negative glucocorticoid-response elements[2] that are