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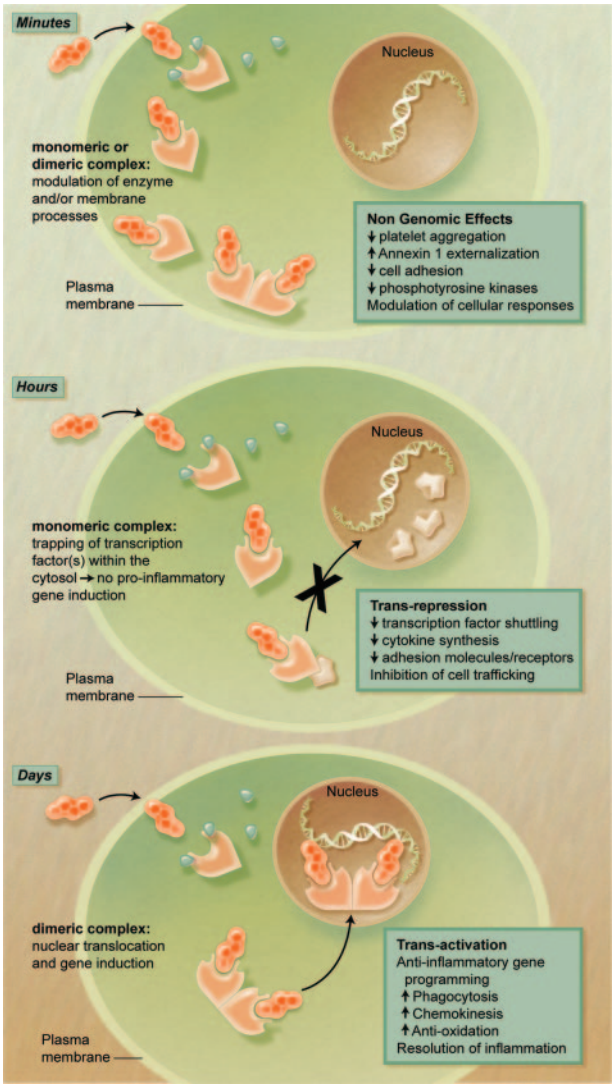
Identification of the mechanism responsible for the beneficial effects produced by glucocorticoids in clinical settings has always been a fascinating task of pharmacology. Novel data produced with human primary monocytes reveals the major mechanism of action: gene reprogramming towards marked transactivation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



Schematic representation of the multiple mechanisms of action of glucocorticoids, as stratified in relation to the length of time of application. (A) Nongenomic effects are mediated via the intracellular receptor, and are evident within minutes of glucocorticoid application. (B) Transrepression seems to be the prevalent effect produced by glucocorticoids when responses are monitored for the first few hours only (few genes are also transactivated in this timeframe [eg, annexin-1, β_2 adrenergic receptors, and protein phosphatase 2]). (C) Transactivation is the more prevalent effect of glucocorticoids when applied for longer time points (> 16 hours). The gene reprogramming induced by this treatment will have a major impact of the proresolving and homeostatic properties of these drugs, which are very often administered to patients for prolonged period of time (days). Illustration by A. Y. Chen.

present in the promoter regions of target genes to increase or decrease gene transcription.

In recent years, this model was challenged by the observation that the cytosolic monomeric glucocorticoid-GR complex could bind transcription factors, including nuclear factor-κB (NF-κB) and the complex *c-jun/c-fos* (activated protein-1 [AP-1]); interference with transcription factor activity could be obtained in several distinct manners,[2] but the endpoint would always be blockade of gene expression or transrepression. However, despite the excitement produced in the scientific community, it soon appeared that this molecular mechanism was unlikely to be the sole mode of action for this class of lifesaving drugs, since they retained anti-inflammatory effects in mice deficient for specific subunits of NF-κB.[3] In addition, the discovery that glucocorticoids can produce rapid nongenomic effects, which is evident within minutes of addition to platelets or peripheral blood mononuclear cells (PBMCs; see figure),[4,5] suggests a model where glucocorticoids can produce distinct downstream readouts in relation to the type of ligand used, its concentration/dose applied, temporal length of application, and cellular target.

In this issue of *Blood*, Ehrchen and colleagues demonstrate that the exposure of human monocytes to a low concentration of fluticasone would reprogram the cells toward an anti-inflammatory phenotype. Microarray analysis revealed that more than 100 genes were induced against approximately 40 genes that were being down-regulated; therefore, transactivation does prevail over transrepression. Gene clustering analysis indicated that transactivated genes grouped themselves in the antioxidative, migration/chemotaxis, phagocytosis, and anti-inflammatory/proresolving classes; importantly, changes in gene activity were confirmed with quantitative polymerase chain reaction (PCR) and functional assays.

Another interesting observation made by Ehrchen and colleagues is that glucocorticoids increased monocyte chemokinesis, a response effected via up-regulation of several genes involved in cell mobility; this is likely to be relevant in the context of resolution of inflammation, where monocytes—and other leukocytes—must leave the site of inflammation/infection via the lymphatic system. Another interesting observation was glucocorticoid induction of the formyl-peptide receptor, a G-protein coupled receptor activated by peptides cleaved from the annexin 1 N-terminus[6] in inflammatory exudates.

In conclusion, the glucocorticoid *real* mechanism of action has remained "elusive" for many years, and one reason for this is that *multiple* mechanisms can be operative upon glucocorticoid binding to GRs. Depending on the experimental condition applied, the glucocorticoid may elicit rapid nongenomic effects, transrepressing mechanisms, or, as now reported, delayed transactivating anti-inflammatory/homeostatic responses (see figure). This study by Ehrchen and colleagues challenges transrepression as the major glucocorticoid molecular mechanism, and restores transactivation as the more relevant mechanism, especially when considering that in clinical practice, prolonged treatment with glucocorticoids is often required. It is hoped, as the authors put it, that the current analysis of monocyte reprogramming ". . . may offer novel targets for future anti-inflammatory strategies."

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