fucose to rescue GDP-fucose biosynthesis, restoring fucosylation. In the absence of fucose, the $FX^{-/-}$ mice display a profound neutrophilia. Part of this neutrophilia can be explained by loss of selectin ligands (Sialyl Lewis x contains fucose), but proliferation of myeloid progenitor cells suggests that myelopoiesis is being stimulated. Zhou and coworkers have now examined the proliferation of myeloid lineages in $FX^{-/-}$ mice and attributed it to loss of fucose-dependent Notch activation in myeloid progenitors. The authors present compelling data that suggests a role for Notch activation in suppression of myeloid differentiation, a somewhat controversial area. Another recent publication highlighted the importance of *O*-fucose at a specific site on Notch1 in T-cell development.[4] Ge and Stanley generated a mouse in which endogenous Notch1 was replaced with a mutant lacking the *O*-fucosylation site in the ligand-binding domain (within EGF repeat 12). Homozygotes developed fairly normally but had a reduced number of T cells, suggesting that *O*-fucosylation of Notch1 at EGF repeat 12 is important for T-cell development.

These results raise a number of interesting questions. All 4 receptors should be unfucosylated in $FX^{-/-}$ mice, but it is not known which Notch receptor is responsible for suppression of myeloproliferation. As mentioned, modification of *O*-fucose by Fringe modulates Notch activity. In the absence of Fringe, *O*-fucose remains a monosaccharide, but in the presence of Fringe it is elongated to a tetrasaccharide. The relevant structures of the *O*-fucose glycans that are lost in $FX^{-/-}$ mice are unknown. Because *O*-fucosylation of EGF repeat 12 in Notch1 plays such an important role in T-cell development, it would be interesting to know if loss of this specific fucose also suppresses myelogenesis. The future of Notch and hematopoiesis certainly looks sweet.

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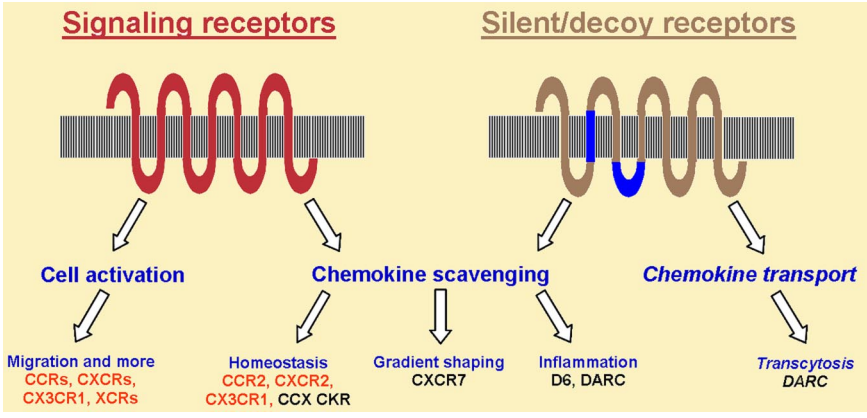
CHEMOKINES

Comment on Cardona et al, page 256

Housekeeping by chemokine scavenging

Alberto Mantovani and Massimo Locati ISTITUTO CLINICO HUMANITAS IRCCS; UNIVERSITY OF MILAN INSTITUTE OF GENERAL PATHOLOGY

A report in this issue of *Blood* reveals novel, unexpected regulatory mechanisms of the chemokine universe.



Chemokine scavenging in the function of signaling and silent chemokine receptors. Regions of silent receptors with an altered sequence that is likely responsible for lack of signaling (D in the second transmembrane domain; the DRY motif in the second intracellular loop; see Mantovani et al[2]) are in blue. Activities not supported by genetic evidence are in italics.

Chemokines are a complex superfamily of molecules that guide trafficking and positioning of hematopoietic and nonhematopoietic cells. In this issue of *Blood*, Cardona and colleagues show that mice genetically deficient in representative members of chemokine receptor classes have high levels of cognate ligands in blood and in inflamed tissues. Altered levels of promiscuous ligands perturb the system by affecting other receptors. This and previous scattered reports[1] suggest that signaling chemokine receptors internalize and scavenge cognate ligands, thus acting as rheostats and tuners of the system. These findings have broad implications for pathophysiology, interpretation of receptor-gene targeting experiments, and assessment of pharmacological inhibitors.

The chemokine system is a complex universe consisting of 42 genes encoding ligands and 20 signaling receptors, both having splice and processing variants; it also includes "silent" receptors that have alterations in sequence motifs essential for signaling (eg, the so-called DRY motif in the second intracellular loop), distinct spectra of ligands recognized, and peculiar tissue distribution, and can act as professional decoys and scavengers[2,3] (see figure). D6 binds most inflammatory CC chemokines, that is, those produced in response to inflammatory, immunological, or microbiological stimuli (eg, CCL2/MCP-1). CCX CKR binds homeostatic CC chemokines, which guide trafficking of lymphocytes to lymph nodes (eg, CCL19/ELC and CCL21/SLC). The Duffy Antigen Receptor for Chemokines (DARC; also known as Duffy antigen) binds inflammatory CC and CXC chemokines, and in addition to ligand degradation, it may also act as a facilitator of chemokine transfer across cellular barriers. Strong genetic data indicate that D6, CCX CKR, and to some extent, DARC are decoys and scavengers for chemokines that tune leukocyte trafficking under inflammatory (D6) and homeostatic (CCX CKR) conditions,[2-4] and recent evidence indicates that CXCR7, the second receptor for CXCL12/SDF1, also sharpens chemokine concentration and focuses the migration of zebrafish primordial germ cells by means of ligand scavenging.[5] Thus, professional decoy receptors play an essential tuning role in the chemokine system; this paradigm could also extend beyond the chemokine system, as some evidence that the C5a receptor

C5L2 plays a similar role in the complement system has been provided.[6]

Ligand internalization and degradation is part of the natural life cycle of signaling chemokine receptors.[7] The new data from Cardona and colleagues clearly indicate that this pathway of disposal is physiologically relevant to the determination of chemokine levels in biological fluids and at least one inflamed tissue, the brain. The increased chemokine levels observed in mice deficient in a given receptor (CCR2) were shown to perturb the function of an unrelated receptor (CCR1). The explanation of this surprising result rests in the promiscuity and redundancy of the system. CCR2 ligands include CCL7/MCP-3, CCL8/MCP-2, and CCL13/MCP-4, which also bind CCR1; increased levels of these ligands are expected to down-regulate CCR1, as reported here. Thus, ligand internalization and degradation play key roles in tuning the system (see figure), and blocking some receptors may raise waves of perturbation in distant, unrelated receptors.

These and previous results have profound implications, ranging from pathophysiology to therapeutic intervention. This extensive set of data confirms and extends the concept that chemokine scavenging, be it performed by professionals or by conventional receptors[1,2,8] (see figure), is key to chemokine homeostasis in a complex system. The ligand scavenger function of chemokine decoy receptors is increased by exposure to increasing concentrations of the ligand,[9] making them more efficient in this function when compared with signaling receptors, which are rapidly down-regulated by ligand engagement.[7] The relative contribution of these 2 classes of receptors in keeping chemokine levels in check in vivo will have to be defined. The finding that blocking one receptor raises waves of perturbation of the system beyond the specific target, as shown here for CCR2 and CCR1, cautions against simplistic interpretations of data in gene-targeted mice. Moreover, it has implications for the pharmacology of chemokine receptors antagonists. With clinical approval of the CCR5 antagonist maraviroc, chemokine pharmacology has come of age.[10] But are allosteric inhibitors, which do not interfere with chemokine scavenging, desirable? Do waves of perturbations have a role in the activity of antagonists? Housekeeping by scavenging raises more issues than one would have expected.

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NEOPLASIA

Comment on Qiang et al, page 374

Wnt signaling: bone's defense against myeloma

Claire M. Edwards VANDERBILT CENTER FOR BONE BIOLOGY

In this issue of *Blood*, Qiang and colleagues show that increasing Wnt signaling within the myeloma bone microenvironment inhibits myeloma bone disease and consequently reduces tumor burden.

For many years, the osteoclast was thought to be the main culprit in the development of the destructive osteolytic bone disease that is a characteristic feature of multiple myeloma. Only more recently were suppression of osteoblastogenesis and bone formation found to contribute to the systemic bone loss and osteolytic bone lesions associated with myeloma bone disease. Current therapies targeting the osteoclast are effective at preventing further bone destruction, but cannot replace bone that has already been lost. Therefore, targeting bone formation in multiple myeloma is an attractive therapeutic approach.

Compelling evidence for the critical role Wnt signaling plays in promoting osteoblast differentiation and bone formation, and the discovery of Dickkopf1 as a mediator of the reduction in osteoblastic bone formation in multiple myeloma, both identify the Wnt signaling pathway as a potential therapeutic target in multiple myeloma.[1-3] Qiang and colleagues took 2 complementary approaches to exploring this new avenue: overexpression of Wnt3A in myeloma cells, and systemic Wnt3A treatment. Both approaches use the severe combined immunodeficient (SCID) hu myeloma model, in which human myeloma cell growth is restricted to human bone implanted into immunodeficient mice. Under normal circumstances, the SCID-hu myeloma model is associated with tumor growth and osteolysis of the human bone fragment. However, increasing Wnt signaling with Wnt3A resulted in a reduction in tumor burden, an increase in bone mineral density, and a decrease in the osteoclast:osteoblast ratio. These data support an earlier study by Edwards et al in which systemic activation of Wnt signaling with lithium chloride was shown to prevent myeloma bone disease and indirectly reduce tumor burden in bone in the 5TGM1 murine model of myeloma.[4]

The direct effect of Wnt signaling on myeloma cells remains controversial. Qiang and colleagues demonstrate that although Wnt3A activates Wnt signaling in myeloma cells, this is not associated with an increase in proliferation, either in vitro or in vivo. This eliminates the possibility of direct proliferative effects through Wnt signaling in myeloma cells in this model. Although bone formation is not directly assessed, evidence is provided to support a direct effect of Wnt3A in increasing Wnt signaling in cells of the osteoblast lineage. Taken together, the results presented by