If it’s Tuesday, this must be a Belgian chemokine

In 1969, a forgettable Hollywood movie parodied the information overload that tourists experience when they visit several countries in the shortest time possible. Thirty years later, scientists who are interested in chemokines also find their heads spinning in response to a seemingly endless and rapid parade of newly discovered chemokines and receptors. In this issue, Struyf and colleagues (page 2197) introduce us to the newest member of this family of proteins, which they call Regakine-1 in honor of the Rega Institute of Leuven, Belgium, where the discovery occurred.

Chemokines are best known for their ability to attract specific leukocyte subsets, and like with any chemotactic factor, directionality is dictated by establishing a chemokine concentration gradient. Thus it is one of the particularly galling puzzles of chemokine biology that a small number of these proteins circulate at high concentrations in plasma. Regakine-1 is one of these. Struyf and colleagues purified it from bovine serum, and like another circulating chemokine, HCC-1 (CCL14), Regakine-1 is present at 100-300 ng/mL in bovine serum. It is a weak chemoattractant for neutrophils and T lymphocytes, but given its high ambient concentration, its role as a primary attractant for these cells seems unlikely.

Instead, Struyf and colleagues show that it enhances chemotactic responses to suboptimal doses of more potent chemokines and other attractants. It may be that Regakine-1 circulates in order to enhance migratory responses of blood-borne leukocytes. Why nature would choose this route rather than simply enhancing the inherent efficacy of chemokine receptor signal transduction is a mystery (if, in fact, this is Regakine-1’s function). Solving the conundrum posed by Regakine-1’s high plasma concentration will be a fascinating problem and is likely to reveal unexpected opportunities for influencing leukocyte migration in health and disease. Meanwhile, like gawkers on a whirlwind tour, we must do our best to keep up with the changing scenery.

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Point mutations in the FLT3 gene in AML

Approximately 20% of acute myeloid leukemia (AML) patients have been found to have constitutive activation of the FLT3-receptor tyrosine kinase due to internal tandem duplications of the juxtamembrane domain (FLT3-ITD). Yamamoto and colleagues (page 2434) now report that Asp835 in the kinase domain of FLT3 is mutated in an additional 7% of AML patients (30 of 429). Asp835 mutations were also found in 1 of 29 myelodysplastic syndrome patients and 1 of 36 acute lymphocytic leukemia patients, while none were detected in a broad range of other hematologic malignancies. Taken together, these results indicate that FLT3 is the single most commonly mutated gene in AML. As is the case for FLT3-ITD, Asp835 mutations spontaneously activate tyrosine kinase activity and induce factor-independent proliferation of hematopoietic cell lines. Although the role of FLT3 mutations in the transformation of myeloid cells is not yet known, it is highly likely that they provide a strong mitogenic and antiapoptotic signal. Thus these mutations may act synergistically with mutations blocking differentiation to induce AML. Interestingly, unlike FLT3-ITD mutations, the Asp835 mutations were not associated with higher white blood cell counts or poorer survival.

The Asp835 residue is located in a region predicted to function as an “activation loop.” When the receptor is inactive, this loop folds into the active site of the kinase, blocking access. The loop folds out after receptor activation and phosphorylation of a nearby tyrosine residue. Based on detailed studies of the insulin receptor, mutations in this highly conserved asparagine residue probably cause the activation loop to adopt the active configuration in the absence of ligand. The mechanism of activation of FLT3 by the more common juxtamembrane tandem duplications is probably different, perhaps inducing spontaneous dimerization and/or rotation of the receptors.

This study is important for several reasons. First, it shows that FLT3 can be activated by mutation of the same asparagine residue already known to activate c-KIT in mastocytosis and gastrointestinal sarcomas. Second, it significantly extends the number of patients with AML that harbor mutations in FLT3. Small-molecule tyrosine kinase inhibitors active against FLT3 are under development and could prove to have significant clinical activity. Finally, it suggests that we may still be seeing only the tip of the iceberg. A careful search for activation of other tyrosine kinases in other types of hematologic malignancies is warranted.

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A time to live, a time to die

T cells contained in marrow or mobilized peripheral blood apheresis products used for hematopoietic stem cell transplantation have both beneficial and detrimental effects in allogeneic recipients. Donor T cells that recognize recipient alloantigens prevent rejection and recurrent malignancy but also cause graft-versus-host disease (GVHD). Donor T cells that do not recognize recipient alloantigens contribute to immune reconstitution after the transplantation. The “surgical” approach of removing all T cells in the graft prevents GVHD but also prevents the beneficial effects of these cells. Drobyski and colleagues (page 2506) have
identified a way to retain some of the benefits of donor T cells while preventing GVHD.

Previous studies have shown that GVHD can easily be prevented when donor T cells are transfected to express the \textit{H} \textit{simplex} virus enzyme thymidine kinase. Proliferating cells that express this enzyme are susceptible to ganciclovir, an antiviral drug. When ganciclovir is given at the right time after transplantation, TK$^+$ donor T cells that proliferate rapidly in response to recipient alloantigens are induced to commit suicide, while some of the more slowly proliferating cells that do not recognize recipient alloantigens are spared. Drobyski and colleagues now show for the first time that, by delaying the administration of ganciclovir until 8-12 days after the transplantation, donor T cells that recognize recipient alloantigens have enough time to prevent rejection but not enough time to cause severe GVHD. These results offer proof of principle that strategies can be developed for controlling the detrimental effects of donor T cells while retaining some of their benefits. Precise balance in the conditioning regimen, number of T cells, and timing of ganciclovir administration was needed for success with this approach, emphasizing the formidable complexity likely to be encountered when attempts are made to translate these results in hematopoietic stem cell transplantation for humans.

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**G-CSF: early benefits but late risks?**

Many oncologists are considering granulocyte colony-stimulating factor (G-CSF) a drug of mainly benefits with only few and minor side effects for patients with neutropenia following treatment with myelosuppressive chemotherapy. In a retrospective study, Volpi and colleagues (page 2514) describe significant long-term cellular immune impairment of T cells in patients treated after HLA haplotype-mismatched hematopoietic stem-cell transplantations with G-CSF to reduce the period of neutropenia and improve engraftment after transplantation. The benefits shortly after transplantation appeared to be minor, whereas the long-term immune dysregulation may be significant, as illustrated by the reduced capacity of T cells to cope with fungal infec-

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G-CSF: early benefits but late risks?

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