

## In This Issue

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The RANKL cytokine at 2.6 Å (See article on pages 971–979.) The TNF superfamily represents a large, loosely related, and versatile group of homotrimeric cytokines. There has been considerable interest in the structure of these proteins, and x-ray analyses are available for several of them, both in isolated form and as co-crystals with their corresponding receptors. Still, the substantial divergence in primary sequence within this family has made it difficult to predict the structure of other members with confidence. Here, Lam et al. report a high-resolution crystal structure of the RANK ligand (RANKL), a TNF relative that acts through its receptor (RANK) to promote the differentiation and bone-resorptive activity of osteoclasts and to block apoptosis by several other cell types. As with other members of this superfamily, RANKL monomers trimerize only with each other, even when they are coexpressed with other related cytokines. Likewise, the mature trimeric protein binds specifically to RANK and not to other members of the TNF receptor family. The present crystal structure goes far toward explaining these biochemical observations. While the protein folds to form a characteristic structure that has been seen in related cytokines, there are also several solvent-exposed loops with sequences not found in other family members. Based on the well defined quaternary structure of receptors of this family, Lam et al. predicted that [...]

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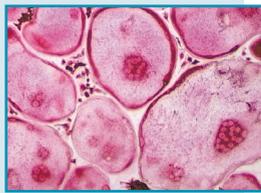
# In this issue

By John Ashkenas, Science Editor

## The RANKL cytokine at 2.6 Å

(See article on pages 971–979.)

The TNF superfamily represents a large, loosely related, and versatile group of homotrimeric cytokines. There has been considerable interest in the structure of these proteins, and x-ray analyses are available for several of them, both in isolated form and as co-crystals with their corresponding receptors. Still, the substantial divergence in primary sequence within this family has made it difficult to



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## Regulation of vascular tone by a secreted mitochondrial peptide

(See article on pages 1023–1030.)

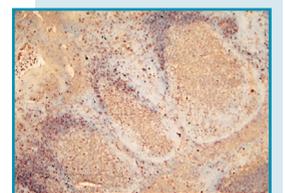
The  $F_0F_1$  ATP synthase is a large, multisubunit complex expressed in the mitochondrial inner membrane, where it uses the energy from oxidative phosphorylation to generate ATP. Surprisingly, this complex can also be found on the plasma membrane of endothelial and other cells, and the fact that it appears to be biologically active suggests that most or all of its components can be assembled at this location. Osanai and coworkers have previously argued that the peptide coupling factor 6 (CF6), an essential component of

the ATP synthase, also serves a distinct physiological role as a circulating hormone. Here, they show that CF6 localizes to the endothelial cell surface, whence it is presumably shed into circulation. Endogenous peptide is highly expressed in aortae from hypertensive rats, and the authors show that a blocking antibody to the peptide can lower blood pressure in these animals, as well as in healthy controls. Recombinant peptide, conversely, induces hypertension, apparently by suppressing the synthesis of the vasodilator prostacyclin while leaving other aspects of prostanoid metabolism intact. Agents that block this endogenous vasoconstrictor might thus provide a useful means to control hypertension.

## Censoring self-specific B cells

(See article on pages 1061–1070.)

Any one of 50 human  $V_H$  regions can be included in the final rearranged immunoglobulin chains formed in B cell precursors. Although this process is essentially random,  $V_H$  regions are not uniformly distributed among mature, IgG-secreting plasma cells, because these cells are subject to both positive and negative selection. In particular, B cells expressing the VH4-34 segment are dramatically underrepresented among plasma cells. Unlike most immunoglobulins, which acquire their antigen-specificity of a mature B cell receptor only after rearrangement and somatic mutation, those carrying the VH4-34 almost uniformly recognize a ubiquitous self-structure, an erythrocyte carbohydrate antigen. Here, Pugh-Bernard and colleagues have followed the fate of VH4-34-expressing cells in the blood, marrow, and tonsils of healthy individuals and people with systemic lupus erythematosus (SLE). They show that, whereas mature VH4-34-expressing plasma cells are rare in healthy subjects, there is no barrier to their differentiation in culture. Interestingly, individuals with SLE possess such cells, suggesting that some normal protective mechanisms that suppress self-reactive B cells are missing in this autoimmune condition. Since VH4-34-containing antibodies recognize bacterial carbohydrates in addition to the erythrocyte self-epitope, the authors suggest that VH4-34 has survived because it acts as pattern recognition receptor, as discussed in the current Perspective series on multiligand receptors. Although their expression must be limited in



duration so that they do not induce chronic autoimmunity, these antibodies may play a valuable role as a rapid host response to bacterial infections. Evidently, the ability of the immune system to censor these B cells at multiple levels is efficient enough that immature B cells expressing this sequence can be tolerated.