JCI The Journal of Clinical Investigation

In This Issue

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J Clin Invest. 2001;108(7):941-941. https://doi.org/10.1172/JCI119935.

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By John Ashkenas, Science Editor

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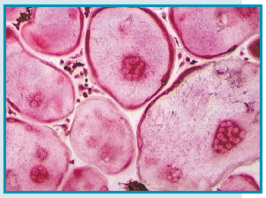

Regulation of vascular tone by a secreted mitochondrial peptide

(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.