Activated Platelet Targeted Fibrinolysis (p 1083)

Wang et al develop a low dose, low risk thrombolytic fusion protein for busting blood clots.

Thrombolytic drugs such as tissue plasminogen activator are used to breakdown blood clots in the event of a heart attack or stroke, but because these drugs act systemically, they carry a high risk of causing excessive bleeding. If such drugs could be targeted specifically to blood clots, it would both increase their potency and decrease their associated bleeding risk. Wang and colleagues therefore created a new fusion protein between a plasminogen activator and an antibody that specifically targets clot-initiating activated platelets. They found that the fusion protein inhibited platelet aggregation in culture, and maintained blood flow velocity more effectively than an equivalent dose of commercial untargeted plasminogen activator when given to mice that were induced to develop thrombi. A high dose of the commercial drug gave results similar to the fusion protein, but it dramatically increased bleeding times following tail transections. Based on the ability to the fusion protein to breakdown clots at a lower dose, without drastically increasing bleeding risk, Wang and colleagues suggest that such antibody targeted clot-busting strategies might be used not only as thrombolytic agents but also as a preventative treatment in patients at high risk of thrombosis.

O-GlcNAcylation and Vascular Calcification (p 1094)

Heath et al find a causative link between O-GlcNAcylation and vascular calcification in diabetes.

Vascular calcification is a common complication of diabetes and is associated with an increased risk of life-threatening cardiovascular events. Determining how calcification occurs and how to prevent it are therefore major goals of current diabetes research. Previous work has shown that proteins in the calcified blood vessels of patients with diabetes exhibit high levels of a post-translational modification called O-GlcNAcylation, in which N-acetylg glucosamine moieties are linked to serine or threonine residues. But whether and how O-GlcNAcylation might cause calcification was unknown. Heath and colleagues, therefore, experimentally induced O-GlcNAcylation in mouse vascular smooth muscle cells (VSMCs) and found that both were subject to increased calcification. Furthermore, they found that O-GlcNAcylated directly modified AKT, a protein kinase known to promote VSMC calcification. Mutational analysis revealed that the O-GlcNAcylated occurred on threonine 430 and 479 of AKT, which in turn promoted phosphorylation of serine 473; thereby enhancing AKT activity and activating the downstream calcification pathway. Blocking O-GlcNAcylation of AKT may therefore be a novel strategy for preventing vessel calcification in diabetes, say the authors.

CPVT CaM Mutants and RyR2 Channels (p 1114)

Hwang et al investigate how different calmodulin mutants affect ryanodine receptor 2 calcium channels.

Calmodulin (CaM) is a calcium-binding protein that regulates several cell functions, including calcium sensing and calcium release from intracellular stores. Mutations in the CaM gene have been linked to cardiac arrhythmia, although different mutations cause different types of irregularity. For example, two specific CaM mutants, associated with stress-induced polymorphic ventricular tachycardia, are referred to as CPVT-CaMs, while another three associated with long QT syndrome are referred to as LQTS-CaMs. In the heart, wild type CaM binds to and inhibits the sarcoplasmic reticulum calcium channel ryanodine receptor 2 (RyR2), reducing the frequency of calcium release. Hwang and colleagues have now discovered that CPVT-CaMs bind with higher efficiency to RyR2 and that they increase rather than reduce the frequency of calcium release. LQTS-CaMs on the other hand tend not to affect RyR2 function, suggesting an alternative mechanism of arrhythmogenesis. CPVT-CaMs dysregulated RyR2 even in the presence of an 8-fold excess of wild type protein. This potency of the mutant proteins explains their dominant phenotypic effects. Altogether the results explain the distinct types of arrhythmia caused by the different CaM mutations, which in turn may help in the development of appropriate treatment strategies for carriers of the mutations.
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