inside blood

Starting out right: Kozak sequences and clots

Understanding genetic risk factors for thrombotic disorders presents a challenge: exactly how does a given polymorphism lead to thrombosis risk? A straightforward answer presents itself when polymorphisms affect coding sequences, for example factor V_{Leiden} and resistance to activated protein C. Other polymorphisms have less obvious effects. The prothrombin gene's 20210A>G polymorphism affects only the 3′ untranslated region, leading to more efficient processing of prothrombin mRNA and higher prothrombin levels, but the relationship between this observation and subsequent thrombosis remains speculative.

Now González-Conejero and colleagues (page 2081) provide evidence that links a 5′ untranslated polymorphism in the translation initiation sequence (Kozak consensus site) of the annexin V gene (−1C>T) to reduction in myocardial infarction (MI) risk in a Mediterranean population. The −1T allele was present in 23% of controls but only 13% of young MI survivors. Annexin V cDNA constructs containing the −1T allele were translated in vitro 1.4 times as efficiently as constructs with the −1C allele. Circulating levels of annexin V were almost twice as high in subjects carrying the T allele as levels in those homozygous for C. The authors propose that the higher circulating annexin V may protect against thrombosis by binding to prothrombotic, negatively charged phospholipids exposed on platelet surfaces during activation, as demonstrated by others.

This is not the first analysis of Kozak sequence polymorphism in a coagulation gene related to thrombosis risk. Frank and colleagues (Blood. 2001;97:875-879) studied a Kozak polymorphism in the glycoprotein Ibα gene, for which the C allele is thought to increase translation, and to increase GPIbα receptor levels on platelets. Significant changes in risk were not established in a cohort of young women with stroke or MI.

Candidate gene polymorphisms are now easy to come by. González-Conejero et al have set a high standard by coupling epidemiology with demonstration of plausible biology and an underlying molecular mechanism. The significance of this polymorphism in other populations remains to be established, and studies on the putative protective effect of circulating annexin V are now needed to test this interesting hypothesis.

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The mechanism of action of high-dose IgG in idiopathic thrombocytopenic purpura

The treatment of thrombocytopenic purpura (ITP) by high-dose IgG or much lower doses of anti-D have become mainstays of therapy. Yet the use of these 2 effective interventions followed empiric clinical observations that were serendipidous rather than scientifically based. For example, in their landmark study, Imbach and coworkers demonstrated the effectiveness of high doses of IgG in ITP (Imbach et al, The Lancet. 1981;1:1228-1230). One hypothesized mechanism was that the administered IgG could remove thrombocytopenia-causing immune complexes composed of viral particles (Imbach et al, Blut. 1983;46:117-124). The dose dependent effect of IgG on the platelet count was dramatic and initially reinforced this postulated mechanism of action. The observations by Fehr and associates clarified what has become the accepted mechanism of action of IgG in ITP (Fehr et al, N Engl J Med. 1982;306:1254-1258). These investigators found that the rise in the platelet count paralleled the inhibition of Fc-dependent RE function.

Today, 20 years later, it is not too late to try to better understand a successful treatment. At best, progressively strategic modifications of an effective therapy could result. At worst, enhanced clinician comfort could be gained by knowing what was done and why it worked.

In this issue, Hansen and Balthasar (page 2087) use a rat model of immune thrombocytopenia to study the mechanism of action of high-dose IgG. A few initial caveats: any in vivo experiment crossing 3 species has profound complexities. More importantly, the pathogenic, platelet-clearing antibody was not at steady state (more about that later). The results are compelling. Like the human situation, the high-dose IgG raised the platelet count in a dose-dependent fashion. But unlike the human situation, the investigators were able to measure the pathologic antibody and found its clearance was increased by the administered IgG.

These observations extend our understanding of the efficacy of high-dose IgG. But questions remain: Would the same effect occur if the pathologic antibody was produced at steady state (human disease) rather than a single injection? If altered pathogenic antibody clearance helps explain the effectiveness of high-dose IgG in ITP, does this mechanism have relevance to anti-D in ITP? Questions are answered. More questions remain.

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