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Taking personalized medicine to heart

Tailoring treatment to the individual patient has revolutionized cancer therapy, but personalized medicine has yet to make much headway in the treatment of cardiovascular disease. With emerging insight into disease mechanisms and new treatment options, the time is now ripe for the cardiovascular field to adopt a more personalized approach to therapy.

Research on cardiovascular genetics has had some spectacular successes in uncovering new therapeutic targets—for example, the finding that people with inactivating mutations in the gene encoding the trafficking protein PCSK9 are at a much lower risk for heart attacks led to the development of antibody therapy targeting this protein. However, when it comes to personalizing treatment for cardiovascular disease on the basis of an individual patient's genetic makeup or biomarker data, there are currently only a handful of options where such an approach has proven to be clinically useful.

Prominent examples of cardiovascular drugs for which patient response is affected by gene polymorphisms include warfarin and clopidogrel, used to prevent blood clotting. For warfarin, the correct dose for a patient is determined in part from assessment of polymorphisms in the genes encoding the molecular target of the drug, VKORC1, and an enzyme that inactivates the drug, CYP2C9. In the case of clopidogrel, a variant in the gene encoding an enzyme needed for its bioactivation, CYP2C19, influences the drug's efficacy. Genetic variation also affects the response to drugs used to modify lipid levels and thereby reduce atherosclerosis and the risk of myocardial infarction. For instance, a genetic polymorphism affecting the transporter SLCO1B1 is a risk factor for myopathy, a serious side effect of statins. Another example is the drug dalcetrapib, designed to raise the level of high-density lipoproteins through inhibition of cholesteryl ester transfer protein (CETP). Although dalcetrapib and other CETP inhibitors have had a disappointing track record in clinical trials, retrospective analysis indicates that dalcetrapib may be more beneficial in individuals with a specific polymorphism in the gene encoding adenylate cyclase 9, and a clinical trial is underway to test this hypothesis more stringently.

As a blood-based biomarker, the level of C-reactive protein (CRP), which reflects an individual's inflammatory status, is emerging as an important parameter for predicting the efficacy of treatments used to prevent myocardial infarction. Statins were originally designed to lower the level of low-density lipoproteins, but they also have anti-inflammatory effects, which may explain part of their benefit. In support of this idea, statins have shown efficacy in patients with a normal level of low-density lipoprotein but a high level of CRP. Taking this concept one step further, a recent clinical trial with an antibody blocking the inflammatory cytokine IL-1β showed that a more targeted anti-inflammatory agent can prevent cardiac events in individuals with high blood CRP levels. The efficacy of the antibody, canakinumab, correlated with its ability to reduce blood CRP levels, suggesting that only patients with high CRP levels are likely to benefit from this treatment.

The success of canakinumab might also open the door to a different type of strategy for patient stratification based on a recently discovered connection between inflammation and blood cell aging. As people age, mutations occur in hematopoietic stem cells, leading to the accumulation of mutant blood cells. This condition, called clonal hematopoiesis, is a risk factor for both leukemia and heart disease. Recent research indicates that the increase in cardiovascular risk may be due to elevated inflammatory activity of the mutant blood cells, including increased production of IL-1β. Indeed, heightened inflammation arising from clonal hematopoiesis may in part explain why age is such a strong risk factor for heart disease. According to this line of thinking, patients with high levels of clonal hematopoiesis—as detected by mutational profiling of blood cells—may be more likely to benefit from treatment with anti-inflammatory agents.

Another emerging area of research with the potential to lead to personalized treatment is the influence of the gut microbiome on the cardiovascular system. For example, specific types of bacteria in the gut use particular dietary constituents to generate compounds that can promote atherosclerosis or thrombosis. Profiling an individual's microbiome could conceivably guide treatment choice, particularly if microbiome-targeted treatments can be developed.

The development of new blood biomarkers—beyond lipoprotein and CRP levels—may also shake up the status quo and uncover new avenues for personalizing therapy. Notably, recent evidence suggests that high levels of ceramides—a type of lipid—in blood may be associated with an increased risk for cardiac events. This finding could spur efforts to test whether treatments designed to lower ceramide levels would benefit such individuals.

Drug development for cardiovascular disease is extremely challenging—clinical trials typically require large numbers of patients followed over long periods of time, and the tolerance for adverse side effects is very low. These obstacles have slowed down the pace of new drug development, as other areas of biomedicine have seemed more tractable. However, the recent emergence of new insights into how cardiovascular disease develops and the identification of new therapeutic targets may help to reinvigorate the field, providing a wider variety of treatment options that can be tailored to the individual patient.