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Genomic Variation in the Lipid Anchor Biosynthesis Protein PIGC as a Cardiovascular Risk Factor

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Atherosclerosis is a hardening and narrowing of the arteries, which are blood vessels that transport blood from the heart throughout the body. Arteries are lined with a thin layer of cells called the endothelium. This endothelium keeps the inside of arteries smooth to ensure an even flow of blood. Atherosclerosis begins with damage to the endothelium, and can be caused by high blood pressure, smoking, high cholesterol or chronic bacterial infections. This damage can lead to the formation of plaque build-up, thereby putting blood flow at risk, which in turn may cause heart attacks, strokes, and peripheral vascular disease. A further hallmark of atherosclerosis is a chronic inflammation of the arterial wall, which is caused by the body's own immune system.

Our research focuses on the role of immune cells called monocytes, which circulate in the blood stream that may contribute to the development of atherosclerosis. Normally, monocytes recognize lipopolysaccharides (LPS), which are present in their outer membrane of (gram-negative) bacteria. Monocytes express specific receptors on their surface that bind LPS; binding of LPS leads then to the activation of monocytes and inflammation. However, in some instances, some receptors are as well shed from monocytes, which may contribute to a systemic inflammation and the onset of atherosclerosis. We found that some people have increased levels of these soluble receptors even in the absence of infection; this finding correlates with inflammatory disease activity and risk of atherosclerosis development.

The mechanism of receptor release from monocytes is not known, neither do we know why these soluble receptors are pro-atherogenic. In a previous study we found that increased levels of soluble receptors correlate with genetic variations (single nucleotide polymorphisms, also known as SNPs). Interestingly, the most recent data suggest that certain SNPs are also associated with obesity and body fat distribution, which is as well associated with heart disease.

We are interested in the identification of these genetic variations, how they translate into an altered function of immune cells, and how this correlates with an increased activation of monocytes in the absence of bacterial infection. Our overall goal is to develop novel assays to stratify patients by targeted therapeutic attenuation of innate immune activation and thereby to improve patient survival.