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Elucidating the Role of a Lysyl Oxidase Polymorphism in Risk for Coronary Atery Disease

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Elucidating the Role of a Lysyl Oxidase Polymorphism in Risk for Coronary Artery Disease

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Cardiovascular disease (CVD) is the leading cause of mortality in the United States and is heritable. Identifying human genetic differences associated with CVD such as coronary artery disease (CAD) has the potential to identify genes and pathways with direct relevance to disease. Functional studies can then be used to discover the mechanisms through which these genes affect the heart and vasculature. Recent studies have robustly associated a naturally occurring human genetic polymorphism (R158Q) in the gene lysyl oxidase (*LOX*) with increased risk of CAD. LOX is synthesized intracellularly and then released into the ECM where it is cleaved into a pro-peptide and an enzymatic peptide. The polymorphism in *LOX* alters the coding sequence of the pro-peptide region of the gene, leading us to question whether the increase in atherosclerosis is due to altered enzymatic activity of the protein or from altered function of the pro-peptide itself. To study this, we cloned murine *Lox* cDNA into the pCMV6-Myc-His vector and used site-directed mutagenesis to insert the mutation of interest at site 152, which is the analogous position in murine *Lox* corresponding to amino acid 158 in human *LOX*. We then subcloned the pro-peptide regions of both wild-type and 152Q *Lox*. Next, we were able to transfect PP-*Lox* into cultured cells and purify each protein from the media. We are assessing whether the PP-Lox polymorphism affects cell growth in a BrdU proliferation assay. To determine if the PP-Lox polymorphism altered enzymatic activity, we are performing an activity assay with the purified full length wild-type and 152Q Lox proteins. We hypothesize that intracellular signaling in proliferation pathways will be altered in the 152Q PP-Lox when compared to the wild-type while the enzymatic activity will be unchanged. By studying the genetic basis of CAD our findings have the potential to reveal novel biology and new therapeutic targets.