Pharmacogenetics of the Human Prostacyclin Receptor: “hIP, SNIp COX and Vioxx”.

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Thirty years have passed since Sir John Vane and colleagues first described a substance, prostanoid X (later called prostacyclin), from microsomal fractions, that relaxed arteries. The critical role of prostacyclin in cardiovascular pathophysiology was unappreciated, as redundancy with other vasoactive substances such as NO was thought to compensate for any deficiencies. Only recently has prostacyclin signaling been fully appreciated, first revealed by enhanced atherothrombosis from prostacyclin receptor knockout mice. This was further supported by the recent withdrawal of Vioxx, a selective COX-2 inhibitor which reduces prostacyclin production (in addition to other eicosanoids), due to increased heart attacks and strokes. We sought to directly address the hypothesis that defective prostacyclin signaling directly leads to increased adverse cardiovascular events in human subjects, through discovery and characterization of dysfunctional human prostacyclin receptor genetic variants (“human knockouts”) and assessing them both biochemically and clinically. In collaboration with 12 other centers nationally and internationally we have thus far sequenced the coding region of the prostacyclin receptor (class A-rhodopsin like G-protein coupled receptor) in 1,798 patients and volunteers and have uncovered 34 distinct genetic variants. I will describe the characterization of one of these mutations (R212C) which structurally changes the critical third intracellular loop, leading to defective signaling, accelerated coronary artery disease and increased cardiovascular events (1, 2). We continue to discover and characterize additional genetic variants from further resequencing. The coming decade is likely to yield many more exciting advances in prostanoid studies, in addition to prostacyclin targeted therapies for the management of cardiovascular disease. These studies were kindly supported by NIH-NHLBI (HL074190) and an American Heart Association Established Investigator Award.
