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Therapeutic potential of Rb phosphorylation in atherosclerosis

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Coronary artery and ischemic heart disease comprise an escalating national and global health challenge. Current therapy consists of pharmacologic optimization as well as limited revascularization, reconstructive, or replacement options that suffer from issues of durability, restenosis, and atherosclerotic progression. Vascular smooth muscle cells (SMCs) retain extensive plasticity at all stages of development and are capable of major phenotypic alterations in response to growth factors/inhibitors, mechanical influences, cell–cell and cell–matrix interactions, and various inflammatory mediators. While essential for vascular repair and cell survival, this phenotypic switching also makes SMCs susceptible to atherogenic stimuli and the acquisition of adverse characteristics that contribute to the progression of vascular disease.[1] There has been great effort and progress in recent years to elucidate the genetic mechanisms that control phenotypic expression that is specific or selective to these negative processes with the hopes of identifying therapeutic targets on which to intervene.

In a recent study published in *Cell Cycle*, Lange and colleagues have exploited the significant resistance of the internal mammary artery SMC layer to intimal hyperplasia to home in on the cell cycle mechanistic events that confer this territory-specific protection against restenosis and atherosclerosis.[2] More specifically, their work focuses on the residue-specific phosphorylation profile of the retinoblastoma tumor suppressor protein (Rb), which differs significantly between the internal mammary and coronary artery and may be a consequence of differences in the content of cyclin-dependent kinase 2 (CDK2).

Rb is part of a gene family which collectively suppresses genes that regulate programs governing cell cycle progression, apoptosis, and differentiation and exert much of their growth-suppressive control during the G_1 phase of the cell division cycle. They are themselves regulated by cyclin D-dependent kinases, which phosphorylate and thereby inactivate Rb's growth-suppressive functions.[3] In their recent study, Lange and colleagues have been able to demonstrate that SMCs from the coronary and the internal mammary arteries differ significantly in their content of CDK2 protein and specific phospho-Rb species, and that SMCs exhibit significantly lower proliferative capacity when the CDK2 content is reduced to the level in the internal mammary SMCs. These results indicate that the phosphorylation of Rb in SMCs is controlled, at least in part, by CDK2. In an elegant proof of concept, siRNA duplexes used to knockdown CDK2 resulted in coronary artery SMCs with reduced content of CDK2 and subsequently less of specific phosphorylated Rb variants (e.g., S807) that are less responsive to mitogenic stimuli and, in effect, function like the internal mammary SMC phenotype, which is relatively resistant to cell proliferation and cell migration. These findings provide new and important information regarding the factors and mechanisms that convert SMCs to a phenotype that promotes plaque stabilization versus plaque destabilization, arterial restenosis, and atherosclerosis. Additionally, Lange and colleagues have identified several exiting new targets to potentially manipulate the phenotypic state of arterial SMCs for therapeutic purposes.

As the related epidemics of obesity and physical inactivity continue to spread, and as the global life expectancy lengthens, the incidence of cardiovascular disease-related morbidity and mortality will undoubtedly increase. In a morbid synergy with large vessel stenosis, microvascular dysfunction has also been shown to be an important independent predictor of ventricular remodeling, heart failure, and death.[4] This has spurred the search for an innovative microrevascularization strategies that can serve as a primary therapy and/or as a supplemental, adjunctive therapy to traditional coronary revascularization methods.[5,6] Advances in identifying and developing novel agents and delivery systems to combat ischemic heart disease are being made rapidly, and the work by Lange and colleagues has opened up another fertile avenue of research and many potential therapeutic targets.[7]

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