Regulation of Vascular Smooth Muscle Cell Growth
Targeting the Final Common Pathway

Angela M. Taylor, Coleen A. McNamara

The study by Zhang et al.\(^1\) in this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology* describes the role of Grb2 in vascular neointimal formation and provides further evidence underscoring the rationale of targeting the final common pathway. The authors focus mainly on inhibiting downstream results of ras activation including activation of the Raf-MEK-ERK MAPK cascade, PI3 kinase-PDK1-Akt cascade, ral cascade, JNK, and p38 MAPKs all of which culminate in affecting gene expression, cytoskeletal regulation, metabolism, and cell cycle progression (Figure). In order to accomplish this, they focus on the protein Grb2, which facilitates ras activation in response to activation of several upstream receptors. Clearly Grb2 is important to normal development in that the knockout mice do not survive embryogenesis due to defective endoderm and inability to develop epiblast. The authors demonstrate that Grb2 is, indeed, important to SMC proliferation and neointimal development following injury. Through use of morpholino antisense oligodeoxynucleotides (ODNs) directed against Grb2, it is clearly shown that reducing Grb2 levels results in decreased SMC growth in culture. They further demonstrate that Grb+/− animals develop less neointima in response to injury. They nicely show that this likely occurs through decreased activation of p38, ERK and JNK, thus creating a break in the series of events involved in the final pathway leading to cellular proliferation. Grb2, therefore, represents a possibly useful target for in vivo oligonucleotide or pharmacologic therapy as it appears to have multiple effects on downstream participants in the final common pathway of events.

Manipulation of the expression and function of these final common pathway proteins does indeed lead to reduction in neointimal formation after injury. Inhibition of membrane adherence of the small G protein p21\(^{ras}\) with a farnesyl transferase inhibitor inhibited activation of MAPK, thus decreasing neointimal size in injured porcine coronary arteries.\(^2\) Growth factor receptor tyrosine kinases have also been shown to be useful targets as inhibitors prevent the initial phosphorylation event necessary for recruiting downstream participants in the final pathway to accomplish this, they focus on the protein Grb2, which facilitates ras activation in response to activation of several upstream receptors. Clearly Grb2 is important to normal development in that the knockout mice do not survive embryogenesis due to defective endoderm and inability to develop epiblast. The authors demonstrate that Grb2 is, indeed, important to SMC proliferation and neointimal development following injury. Through use of morpholino antisense oligodeoxynucleotides (ODNs) directed against Grb2, it is clearly shown that reducing Grb2 levels results in decreased SMC growth in culture. They further demonstrate that Grb+/− animals develop less neointima in response to injury. They nicely show that this likely occurs through decreased activation of p38, ERK and JNK, thus creating a break in the series of events involved in the final pathway leading to cellular proliferation. Grb2, therefore, represents a possibly useful target for in vivo oligonucleotide or pharmacologic therapy as it appears to have multiple effects on downstream participants in the final common pathway of events.

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has been shown to inhibit down regulation of p27kip1 and formation in humans includes pharmacologic agents and been successfully brought to the clinical arena. Yet few of these strategies have given us many potential targets for limiting neointimal formation.43

intimal size in vivo have been attained targeting these aspects of neointimal formation.43–49 Thus, advances in understanding the molecular mechanisms involved in neointimal formation have given us many potential targets for limiting neointimal formation in humans. Yet few of these strategies have been successfully brought to the clinical arena.

The current armamentarium for targeting the neointimal formation in humans includes pharmacologic agents and brachytherapy. Pharmacologic agents have been studied in relation to various components of the pathway. Rapamycin has been shown to inhibit down regulation of p27kip1 and block enzymatic activation of cyclin-dependent kinases and phosphorylation of the retinoblastoma gene product thus inhibiting proliferation.50–53 Paclitaxel stabilizes microtubules and indirectly upregulates p21waf1.54,55 Rapamycin- and paclitaxel-coated stents have been used successfully as directly delivered pharmacologic therapy in humans, effectively decreasing neointimal formation after stent placement.56–59 However, pharmacologic stents have failed to obliterate restenosis as initially suggested and require longer periods of anticoagulation.60,61 Brachytherapy employs beta and gamma radiation to create breaks in double stranded DNA halting cell division and successfully decreasing rates of restenosis.62–64 Edge stenosis and late total occlusion have complicated its use.65,66 Although these therapies have greatly impacted restenosis, they have clinically problematic limitations and do not address the issues of vein graft occlusion and transplant arteriopathy. Local delivery of oligonucleotides that bind the cell cycle regulatory factor E2F has successfully prevented vein graft failure in peripheral and coronary vein graft bypasses in human trials representing a unique class of therapy that may prove useful in multiple cardiovascular disease processes.67,68

It is, therefore, of extreme importance that we continue, as these authors have, to search for new mechanisms that regulate neointimal proliferation, new targets that may limit this process, and new mechanisms of therapy. Both our wealth and lack of knowledge present us with the difficult task of somehow translating this knowledge into clinically relevant and useful strategies while we still strive to further elucidate the final common pathway.

References


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