Dokumenttyp: journal article

Autor(en) des Beitrags: Jaschke, B; Milz, S; Vogeser, M; Michaelis, C; Vorpahl, M; Schömig, A; Kastrati, A; Wessely, R

Titel des Beitrags: Local cyclin-dependent kinase inhibition by flavopiridol inhibits coronary artery smooth muscle cell proliferation and migration: Implications for the applicability on drug-eluting stents to prevent neointima formation following vascular injury.

Abstract: In-stent restenosis is a hyperproliferative disease which can be successfully treated by drug-eluting stents releasing compounds that exhibit cell-cycle inhibitory properties to inhibit coronary smooth muscle cell (CASMC) proliferation and migration, resembling the key pathomechanisms of in-stent restenosis. Cyclin-dependent kinases (CDK) are key regulators of the eukaryotic cell cycle. CDK activity may be blocked by novel compounds such as flavopiridol. Therefore, CDK inhibitors are attractive drugs to be used for the local prevention of in-stent restenosis. In this study, we demonstrate that flavopiridol leads to potent inhibition of CASMC proliferation and migration. Molecular effects on cell-cycle regulatory mechanisms and distribution were evaluated by post-transcriptional assessment of distinct cyclins and cyclin-dependent kinase inhibitor (CKI) levels and flow cytometry. Cellular necrosis and apoptosis was assessed in CASMC and coronary endothelial cells. Flavopiridol induced a potent antiproliferative effect by cell-cycle inhibition in G1 and G2/M and led to increased protein levels of CKIs p21cip1 and p27kip1 as well as p53 in CASMC. Hyperphosphorylation of retinoblastoma protein was abrogated.
and mitogen-mediated smooth muscle cell migration significantly reduced. No accelerated cytotoxicity or increased apoptosis was detectable. Flavopiridol-coated stents, implanted in rat carotid arteries, led to significant decrease of neointima formation. As proof of principle, our results demonstrate that stents eluting CDK inhibitors such as flavopiridol effectively inhibit neointima formation. Therefore, this new class of therapeutics may be suitable for further clinical investigations on drug-eluting stents to prevent in-stent restenosis.