UKE Paper of the Month June 2014

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Dichloroacetate prevents restenosis in preclinical animal models of vessel injury

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ABSTRACT:

Despite the introduction of antiproliferative drug-eluting stents, coronary heart disease remains the leading cause of death in the United States. In-stent restenosis and bypass graft failure are characterized by excessive smooth muscle cell (SMC) proliferation, and concomitant myointima formation with luminal obliteration. Here we show that during the development of myointimal hyperplasia in human arteries, SMCs show hyperpolarization of their mitochondrial membrane potential (ΔΨm) and acquire a temporary state with a high proliferative rate and resistance to apoptosis. Pyruvate dehydrogenase kinase isoform 2 (PDK2) was identified as a key regulatory protein, and its activation proved necessary for relevant myointima formation. Pharmacologic PDK2 blockade with dichloroacetate or lentiviral PDK2 knockdown prevented ΔΨm hyperpo-larization, facilitated apoptosis and reduced myointima formation in injured human mammary and coronary arteries, rat aortas, rabbit iliac arteries and swine (pig) coronary arteries. In contrast to several commonly used antiproliferative drugs, dichloroacetate did not prevent vessel re-endothelialization. Targeting myointi-mal ΔΨm and alleviating apoptosis resistance is a novel strategy for the prevention of proliferative vascular diseases.

STATEMENT:

Myointimal hyperplasia has been described in several diseases such as coronary artery disease, carotid artery and peripheral artery diseases, as well as bypass graft failure. Our paper shows for the first time the involvement of the mitochondrial membrane potential in the development of myointimal hyperplasia in a new humanized animal model (developed by our group) and 4 other well-established animal models of myointimal hyperplasia as well as human in vitro cell culture. An important regulator of smooth muscle cell mitochondrial membrane potential is pyruvate dehydrogenase kinase isoform 2 (PDK2). Using dichloroacetate (DCA), a pharmacologic PDK2 blocker, and lentiviral PDK2 knockdown, we demonstrate that hyperpolarization of mitochondrial membrane potential and subsequent resistance to apoptosis, which eventually leads to myointimal formation, is dependent on PDK2. Thus, our study provides preclinical support for a potentially new therapeutic target for myointimal hyperplasia in the hope of preventing restenosis or bypass graft failure. Our publication is a great example of collaborative efforts involving basic scientists, translational scientists and clinicians to address a major clinical problem by going back to the research bench, exploring new pathways, and developing a novel therapeutic strategy, which could soon enter clinical trials.

BACKGROUND:

This study was mainly performed at the Transplant and Stem Cell Immunobiology Lab (TSI-Lab) headed by Sonja Schrepfer supported by the Heisenbergprogram of the DFG.In total, 15 UKE scientists from 5 UKE departments worked together in this translational project. This work is also part of the Doctoral thesis of med. stud. Dong Wang, who participated in the first cycle of the UKE-Graduiertenkolleg "Individualized Cardiovascular Medicine" 2012/2013 of the Cardiovascular Research Center. Dong Wang is also supported by the UKE Mentoring Program, which provided the contact to the basic science field. Noteworthy, this publication demonstrates the first translational and multidisciplinary collaboration of the DZHK (University Hamburg) and includes basic scientists, translational scientists and clinicians from the UKE. International collaborators are from Stanford, Stockholm, Lübeck, Erlangen, and Salamanca. The TSI-lab has among others a strong interest in cardiovascular biology focusing onpathways related to the development of myointimal hyperplasia and re-stenosis. Source of funding: The work was supported by the DFG, the UHZ Förderverein, the ISHLT, the Hermann und Lilly Schilling Stiftung, and the NIH.