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Failing heart in patients suffering Duchenne muscular dystrophy: A disease animated by compromised genome of stem cells

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Duchenne muscular dystrophy (DMD) is a genetic condition characterized by the lack of functional dystrophin. Majority of the DMD patients develops heart muscle fibrosis and cardiomyopathy, leading to heart failure. Although several molecular mechanisms leading to the DMD cardiomyocyte death were described during the recent decades, the link between dystrophin deficiency and delayed onset of cardiomyopathy is still unclear. Recent evidence suggests involvement of progenitor population failure: Thus we focused on studying DMD stem cells. In order to dissect the mechanism of cardiac progenitor cells (CPCs) depletion in humans, we used DMD patient specific induced pluripotent stem cell model and human embryonic stem cells with dystrophin mutation introduced by CRISPR/Cas technology (DMD hPSC for both models). We observed that absence of dystrophin in DMD hPSC leads to dysregulation of nitric oxide synthase (NOS), resulting in excessive release of reactive oxygen species (ROS). ROS are in turn associated with increased DNA damage and elevated mutant frequency in DMD hPSCs. The inhibition of NOS or ROS scavenging, results in DNA damage reduction. Finally we observed dramatic increase in CPCs population in young adult (2-3 months) mdx mice hearts, followed by steep decrease in mature animals, which is in contrast to stable CPCs population in WT mouse hearts. CPCs depletion in mdx animal hearts is associated with elevated nuclear DNA damage. Based on these results, we suggest that elevated proliferation of CPCs together with NOS induced-ROS mediated-genomic instability leads to CPCs depletion, and subsequently to limited regenerative capacity of the heart muscle.

Biography

Vladimir Rotrekl has completed his PhD from Masaryk University in Czech Republic and Max Planck Institute in Cologne (DE) and Postdoctoral studies from Health Science Center at San Antonio, University of Texas, USA. He is an Assistant Professor and Scientific Board Member at the Department of Biology, Masaryk University and Group Leader of Stem Cell and Disease Modeling group at the International Research Center (ICRC) at St. Anne's University Hospital in Brno, Czech Republic. He has published more than 20 papers in reputed journals.

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