PRDM16 - a Novel Key Player in Cardiomyopathy

S. Klaassen 1), H.-H. Kramer 2), C.A. MacRae 3), A.-K. Kahlert 2,4)

1) Department of Pediatric Cardiology, Charité- University Medicine Berlin, 13125 Berlin, Germany
2) Department of Congenital Heart Disease and Pediatric Cardiology, University Hospital Schleswig-Holstein, Campus Kiel, 24105 Kiel, Germany,
3) Cardiovascular Division, Brigham and Women´s Hospital, Harvard Medical School, and Harvard Stem Cell Institute, Boston, MA 02115, USA
4) Institute of Clinical Genetics, Technische Universität Dresden, Medizinische Fakultät Carl Gustav Carus, 01307 Dresden, Germany

We recently identified a nonsense mutation in the transcriptional co-factor PRDM16 (PR domain containing 16) resulting in left ventricular non-compaction (LVNC) and dilated cardiomyopathy in human patients. To establish a personalized disease model for the latter, we faithfully recapitulated the LVNC by cardiomyocyte-specific overexpression of both mutant and wild-type (WT) PRDM16 in zebrafish. We observed an impaired cardiomyocyte proliferation with associated physiologic defects in cardiac contractility and cell-cell coupling during development in mutant but not WT PRDM16 zebrafish and these defects persisted throughout adulthood. In a next step, using a phenotype-driven screening approach in the fish, we identified a melanocortin 4 receptor (MC4R) antagonist that rescued the physiologic defects associated with mutant PRDM16 during development. In addition, this compound also attenuated the contractile- and electrical defects observed in PRDM16 mutants. Of note, MC4R antagonists could also rescue the cardiac defects seen in zebrafish models of arrhythmogenic right ventricular cardiomyopathy (ARVC) which is consistent with our observation that PRMD16 is also mutated in ARVC patients. While future studies to further elucidate the exact mechanism of mutant PRDM16-related cardiomyopathy are warranted, our current findings underline the importance of personalized disease models. Indeed, such an approach to investigate the aberrant activation of specific pathways, would greatly accelerate the exploration of disease biology and facilitate the development of innovative tailor-made therapies.