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Filamin A regulates shuttling of Core-Binding-Factor-beta during cardiac stress

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The zebrafish model is a valuable tool for studying and identifying novel genetic causes as well as the molecular pathways that underlie the pathogenesis of human cardiovascular diseases, such as cardiomyopathies.

In the present work, it was shown that filamin A is ubiquitously expressed in zebrafish embryos with the highest expression in the brain and in the cardiac and skeletal muscle. In order to investigate the function of the FLNA-ortholog in vivo, it was inactivated in zebrafish embryos using morpholino injections and characterized at several developmental stages in regards to its cardiac and skeletal function. Knockdown of FLNA in zebrafish results in a cardiac phenotype resembling human dilated cardiomyopathy with severely reduced ventricular contractility and dilated heart chambers. Moreover, lack of FLNA during early embryogenesis leads to a severe disorder of skeletal muscles hindering the typical escape reaction of zebrafish embryos.

Publications in recent years have shown that the filamin network is associated with the transcription factor core-binding factor β (CBFβ). In this study, the interaction between FLNA and CBFβ was analyzed specifically in-vivo using the zebrafish model. Detailed experiments revealed that in the absence of FLNA, CBFβ is able to move from the cytoplasm, where it predominantly resides, into the nucleus. Here it has the ability to form a heterodimer with CBFα and regulate transcriptional activity.

In conclusion, it could be shown using a reverse genetics strategy in zebrafish that filamin A, as well as its interaction with CBFβ, play an essential role in preserving cardiac and skeletal function. The findings in this study can contribute in the future to a better understanding of genetically induced cardiomyopathy and thereby enable development of new drugs for this disease.