

Acetylation of TBX5 by KAT2B and KAT2A regulates heart and limb development

Congenital Heart Defects (CHD) affect around 1 in 150 newborns and represent the most common form of congenital abnormality. The heart is the first organ to form and multiple different types of abnormality can arise during the course of development: from small holes in the walls of the cardiac chambers, to more complex defects which can eventually lead to an early death. Human genetic studies have shown that most of the faulty genes responsible for CHDs are transcription factors that regulate and control a wide range of events taking place during heart development, such as atrial and ventricular septation or great vessel formation.

Early work from our lab led to the identification of mutations in TBX5, a T-box transcription factor, as the cause of Holt-Oram syndrome, a rare genetic condition that affects the development of the heart and upper limb. Further studies have confirmed TBX5 as a master regulator of cardiac development; however, how TBX5 activity is regulated during cardiogenesis remains largely unknown.

In this study, we report that histone acetyltransferases KAT2A and KAT2B regulate TBX5 transcriptional activity. Using interactional and transcriptional assays, we show that both KAT2A and KAT2B physically interact with TBX5 *in vitro* and acetylate it at Lys339. Acetylation augments its transcriptional activity and is required for its nuclear export. To examine the *in vivo* role of *kat2a* and *kat2b* we performed gene knock-down experiments in zebrafish at early stages of development and examined the phenotypic consequences. Morpholino-mediated knockdown of *kat2a* or *kat2b* produced both heart and fin phenotypes similar to that observed in TBX5 mutants, which includes pericardial oedema, incomplete heart looping, lack of blood flow into the heart and absence of functional fins. The phenotypes found in MO-injected embryos were also observed when we introduced mutations in the *kat2a* or *kat2b* genes using the CRISPR-Cas system.

This work provides the basis for further experiments to understand the role of TBX5 and its modulator proteins during heart development