

Infant with tacrolimus induced hypertrophy after heart transplantation – increased expression of CRTC-1, but not CRTC-2 and -3.

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Introduction: The role of calcineurin (CN) in the development of cardiac hypertrophy is controversial. In humans CN expression is increased in hypertrophied non-failing hearts, while tacrolimus induced hypertrophy (TIH) can occur in humans after solid organ transplantation and immune-suppression with CN antagonists. Lately, the CREB-regulated transcriptional co-factor (CRTC), was described the heart. It is closely tied to the cAMP-responsive element-binding protein (CREB) which is activated by CN. We hypothesized that the CN antagonist tacrolimus influences the expression of CRTC in TIH.

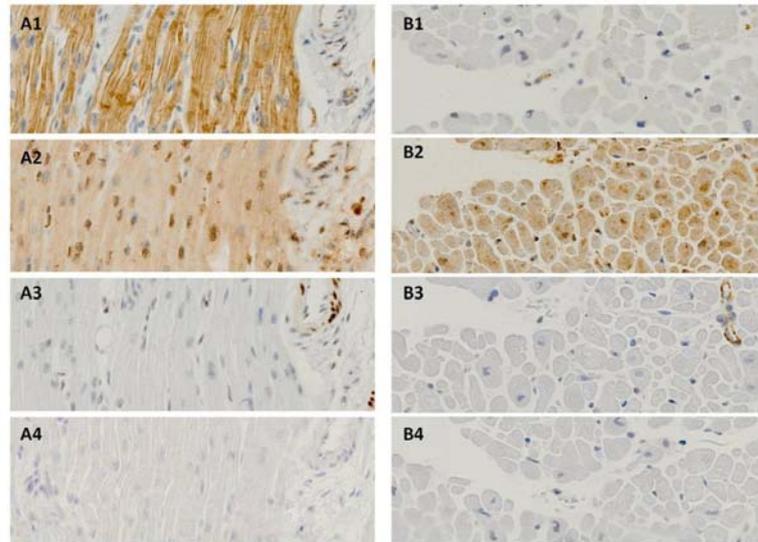


Figure 2: A: EMBs at d 5, B: EMBs at 8 Weeks post HTX. 1-3: CRTC 1-3, 4: control.

Case Report and methods: A now 20 months old male infant underwent heart transplantation (HTX) due to dilatative cardiomyopathy at the age of 10 months. Immunosuppression consisted of anti-IL-2 antibody, methylprednisone, mycophenolatemofetil and tacrolimus (TAC). Initial target TAC through levels (TL) were 13-15 [micro]g/l. Endomyocardial biopsies (EMB) were obtained after 5 days, no rejection was detected (ISHLT 0R). Due to high metabolic turnover, stable tacrolimus TL of 13[micro]g/l were reached only with high doses of TAC (0,5 mg/kg/d). Marked hypertrophy occurred after 4 weeks. Steroids were tapered and ended after 12 weeks, hypertrophy persisted. EMBs were obtained again, histology revealed diffuse hypertrophy, no signs of rejection (ISHLT 0R), establishing the diagnosis of TIH. TAC TL were adjusted to 6 [micro]g/l with tacrolimus 0,06 mg/kg/d. Cardiac hypertrophy decreased remarkably and function improved. EMBs before and after onset of TIH were subjected to CRTC immunohistochemistry with CRTC antibodies [figure 2].

Results: In non-hypertrophied samples at d 5 after HTX, CRTC-1 and -2 are found in the cytosol of most cardiomyocytes (Fig. 2 A1 and A2). For CRTC-1 some, and CRTC-2 most nuclei are stained. In the TIH samples, only CRTC-2 is found (Fig. 2 B2). CRTC-3 is unchanged and only found in vascular endothelial cells (Fig. 2 A3, B3).

Conclusion: TIH occurred due to initially high doses of TAC within a few weeks after HTX and resolved upon reduction of TAC. Immunohistochemistry revealed decreased CRTC-1 expression in TIH samples. CRTC-2 expression decreases slightly with TIH development. The change in CRTC-1 and -2 expressions are a hint that the CN dependent CREB/ CRTC pathway is involved in the development of TIH.