

MEETING ABSTRACT

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# Molecular engineering of the TRPC3 pore structure identifies $\text{Ca}^{2+}$ permeation through TRPC3 channels as a key determinant of cardiac calcineurin/NFAT signaling

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## Background

TRPC channels have been identified as key players in cardiac remodeling and as crucial upstream components of NFAT signaling. The linkage between non-selective TRPC conductances and calcineurin/NFAT signaling may involve either direct TRC-mediated  $\text{Ca}^{2+}$  entry or indirect mechanisms involving crosstalk with other cardiac  $\text{Ca}^{2+}$  transport systems.

## Methods

The pore structure of TRPC3 was analyzed by site-directed mutagenesis guided by a molecular modeling approach combined with patch-clamp measurements in the HEK293 expression system. TRPC3-mediated  $\text{Ca}^{2+}$  entry as well as NFAT translocation was investigated by fluorescence microscopy using Fura-2 and expression of a GFP-NFAT fusion protein in HEK293 as well as in HL1 cells.

## Results

Elimination of  $\text{Ca}^{2+}$  permeation through TRPC3 abrogated its ability to trigger NFAT translocation in both HEK293 cells and in HL-1 atrial myocytes. Wild-type TRPC3 was found capable of initiating NFAT translocation in atrial myocytes by a small, homogenous elevation of cytoplasmic  $\text{Ca}^{2+}$  that was independent of voltage-gated  $\text{Ca}_v1.2$  channels. By contrast, a  $\text{Ca}^{2+}$  impermeant TRPC3 mutant strongly promoted endothelin-induced  $\text{Ca}^{2+}$  signals in HL1 cells via enhanced activity of  $\text{Ca}_v1.2$  channels without concomitant NFAT translocation.

## Conclusions

Our results demonstrate two strictly separated  $\text{Ca}^{2+}$  signaling functions of cardiac TRPC3 channels as well as a tight and efficient link between TRPC3-mediated  $\text{Ca}^{2+}$  permeation and calcineurin/NFAT signaling.

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