Functional interaction between TRP4 and CFTR in mouse aorta endothelial cells

ABSTRACT

It is concluded that TRP4 is necessary for CFTR activation in endothelium, possibly by providing a scaffold for the formation of functional CFTR channels.

INTRODUCTION

Background The cystic fibrosis transmembrane conductance regulator (CFTR) is well described as a low-conductance, cyclic nucleotide-regulated Cl- channel in epithelial cells. Only recently, CFTR has also been detected in vascular endothelium. Endothelial cells (EC) form an anticoagulative barrier but also control many other functions, such as regulation of the vascular tone by secretion of vasoactive compounds such as bradykinin, and autocoids, such as nitric oxide and prostacyclin]. These functions are modulated by a diversity of ion channels among which Cl channels [. Endothelial Cl- channels, the volume-regulated anion channel, VRAC, and Ca2+ activated Cl- channels, CaCC, have been shown to modulate EC electrogenesis, are possible mechano-sensors, serve as permeation pathways for amino acids and organic osmolytes and may be involved in regulation of the driving force for Ca2+ entry [for a review, see]. This list of Cl channels has been extended with CFTR, which is functional in human umbilical vein endothelium and in human lung microvascular endothelial cells, but not in bovine pulmonary artery endothelial cells. As we show in this work, it is also functional in mouse aorta endothelial cells. MAEC express different types of putative ion channel transcripts which are encoded by genes of the trp family, trp1, 2, 3, 4, and 6. TRP4 forms part of a store operated Ca2+ entry channel which is involved in the control of NO-dependent relaxation of the mouse aorta. In addition, TRP4 has been shown to interact via a VTTRL motif in its C-terminal region with the first PDZ domain of the regulatory factor of the Na+- H+exchanger NHERF, which also interacts with PLCβ. The two PDZ domain protein NHERF associates also with the actin cytoskeleton via members of the ezrin/radixin/moesin family. It is also well established that the C terminus of CFTR constitutes a PDZ-interacting domain (QDTRL for the last five C-terminal amino acids) that is required for CFTR polarization to the apical plasma membrane and interaction with the PDZ domain-containing protein NHERF. Thus, both TRP4 and CFTR may bind to similar PDZ-domain proteins. We have studied the functional expression of CFTR in both trp4 wild type and in trp4 deficient MAEC cells. We show here that CFTR is present in both cell types, but is not functional in trp4 deficient endothelial cells. These data may hint to a more general function of trp4 as regulator of other ion channels and to a novel regulatory mechanism for CFTR.

CONCLUSION

Conclusions This is the first report describing a functional interaction between a member of the TRP family and CFTR. It is therefore tempting to speculate that TRPs might be either regulators of CFTR or targets of CFTR regulating proteins.