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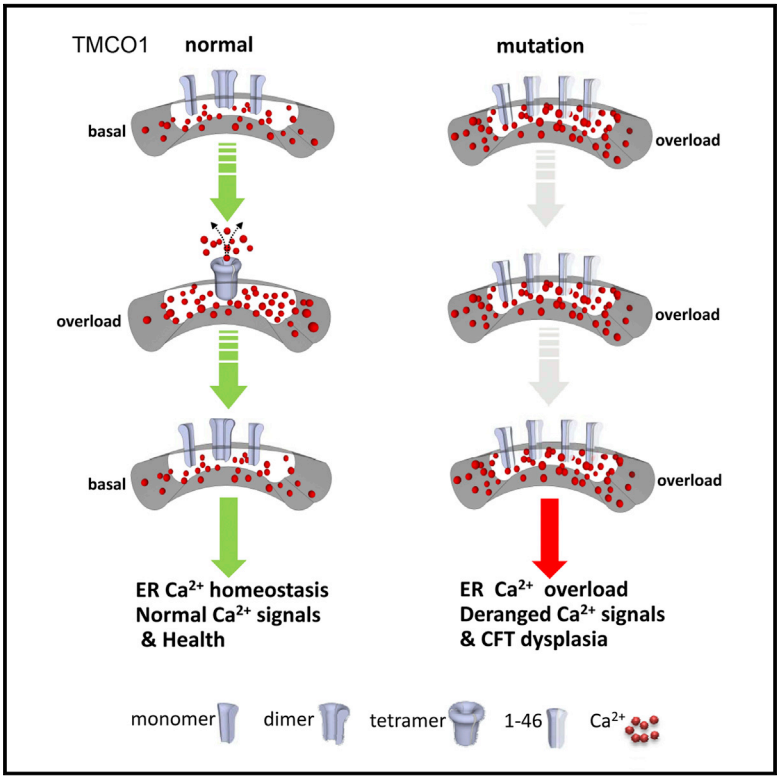
TMCO1 Is an ER Ca^{2+} Load-Activated Ca^{2+} Channel

Graphical Abstract



Highlights

- *TMCO1* gene encodes an evolutionarily conserved ER transmembrane-spanning protein
- Loss of TMCO1 causes overloading of ER Ca^{2+} store and mishandling of Ca^{2+} signaling
- TMCO1 assembles into a Ca^{2+} selective channel in response to ER Ca^{2+} overloading
- Ca^{2+} channel function of TMCO1 is disrupted by CFT dysplasia spectrum mutations

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In Brief

TMCO1 is an ER membrane channel that detects overfilling of calcium stores and restores calcium homeostasis, a function that is disrupted in human CFT dysplasia.

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TMCO1 Is an ER Ca^{2+} Load-Activated Ca^{2+} Channel

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SUMMARY

Maintaining homeostasis of Ca^{2+} stores in the endoplasmic reticulum (ER) is crucial for proper Ca^{2+} signaling and key cellular functions. The Ca^{2+}-release-activated Ca^{2+} (CRAC) channel is responsible for Ca^{2+} influx and refilling after store depletion, but how cells cope with excess Ca^{2+} when ER stores are overloaded is unclear. We show that TMCO1 is an ER transmembrane protein that actively prevents Ca^{2+} stores from overfilling, acting as what we term a "Ca^{2+} load-activated Ca^{2+} channel" or "CLAC" channel. TMCO1 undergoes reversible homotetramerization in response to ER Ca^{2+} overloading and disassembly upon Ca^{2+} depletion and forms a Ca^{2+}-selective ion channel on giant liposomes. TMCO1 knockout mice reproduce the main clinical features of human cerebrofaciothoracic (CFT) dysplasia spectrum, a developmental disorder linked to TMCO1 dysfunction, and exhibit severe mishandling of ER Ca^{2+} in cells. Our findings indicate that TMCO1 provides a protective mechanism to prevent overfilling of ER stores with Ca^{2+} ions.

INTRODUCTION

Calcium ion (Ca^{2+}) is a highly versatile intracellular signal that controls many different cellular functions such as contraction, secretion, memory formation, gene transcription, cell growth, and cell death (Berridge, 1993; Clapham, 2007). The endoplasmic reticulum (ER) is the main intracellular Ca^{2+} store. Ca^{2+} concentration in the ER ($[Ca^{2+}]_{ER}$) must be maintained in a steady state for proper Ca^{2+} signaling (Berridge et al., 2003; Clapham, 2007), and disarrangement of ER Ca^{2+} homeostasis has been implicated in many severe diseases (Bezprozvanny and Mattson, 2008; Sammels et al., 2010; Tu et al., 2006). Stimulation of cells with a variety of physiological stimuli leads to an inositol-1,4,5-trisphosphate (IP_3)-mediated Ca^{2+} release from ER and a depletion of Ca^{2+} stores (Berridge et al., 2003). Cells evolve a mechanism termed store-operated Ca^{2+} entry (SOCE) or capacitative Ca^{2+} entry (CCE) to refill the cell and ER Ca^{2+} stores (Cahalan, 2009; Lewis, 2007; Putney, 2009). It is known that Ca^{2+}-release-activated Ca^{2+} (CRAC) channels are responsible for the SOCE activity and Ca^{2+} store refilling after store depletion (Brandman et al., 2007; Feske et al., 2006; Liou et al., 2005; Luik et al., 2008; Park et al., 2009; Prakriya et al., 2006; Roos et al., 2005; Vig et al., 2006; Zhang et al., 2005). However, it remains unclear if there is a mechanism for ER to extrude the excess Ca^{2+} when the store gets overloaded.

Transmembrane and coiled-coil domains 1 (TMCO1)-defect syndrome is characterized by distinctive craniofacial dysmorphism, skeletal anomalies, mental retardation, ataxia, and many other clinical symptoms. A frameshift mutation in the *TMCO1* gene has been identified as the pathogenic cause for this autosomal-recessive syndrome in the isolated Old Order Amish of northeastern Ohio (Xin et al., 2010). The *TMCO1* gene encodes a protein predicted to be 188 amino acids, and its c.139_140delAG mutation is predicted to result in severe protein truncation (p.Ser47X) leading to a loss of protein function. Non-Amish cases with a nonsense mutation in the *TMCO1* gene (that results in a p.Arg87X truncation) have recently been reported (Alanay et al., 2014; Caglayan et al., 2013). TMCO1-defect syndrome, initially thought to represent a distinct disorder, belongs to the genetically heterogeneous cerebrofaciothoracic (CFT) dysplasia spectrum (Alanay et al., 2014).

The TMCO1 is a highly conserved protein among species (from slime-mold to human), implicating an evolutionarily conserved physiological function for TMCO1. However, the physiological function of TMCO1 is not known, nor the pathogenic mechanism of CFT dysplasia spectrum. Here, we provide biochemical and imaging, molecular and cellular,