TPC1 in plants

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TPC1 in plants is localized in the vacuolar membrane. Its activity is strictly regulated by several factors emphasizing its complex structure and function. The physiological role of TPC1 is under debate. The TPC1 hyperactive version *fou2* (carrying D454N mutation) is characterized by an overproduction of jasmonate acid (JA), however the *tpc1-2* knockout mutant has no pronounced phenotype. The intriguing concept of Ca^{2+}-induced Ca^{2+} release was assigned to *Vicia faba* TPC1 in 1994 by Ward and Schroeder, however it has still not been confirmed for the model plant *Arabidopsis thaliana.*

Keywords: TPC1 ; fou2 ; TPC1 function in plants ; Calcium Induced Calcium Release Theory

1. TPC (two-pore channel)

TPC1 is a non-selective, cation channel belonging to the superfamily of voltage-gated ion channels. TPC1 consists of 12 transmembrane domains (S1–S12) subdivided into two shaker-like segments connected via a cytoplasmic linker region carrying two EF-hand motifs. Each shaker-like segment consists of six transmembrane domains (S1–S6) including the voltage-sensing S4 domain and the ion-conducting pore domain between S5 and S6 [1].

TPCs probably originate from a gene-duplication event of single-domain NaV channels and in contrast to TRPML channels, are widely found in terrestrial (e.g., *Arabidopsis thaliana*) and marine plants (e.g., *Klebsormidium nitens*) [1][2]. All plants harbor at least one TPC gene, already present in the genome of charophytic algae that appeared on earth around 793 million years ago [1][3][4]. TPC1 activity was first shown by Hedrich and Neher in barley mesophyll vacuoles [5]. Upon activation, plant TPC1 provides an ion-conducting pathway for various cations, mainly K^+ and Na^+ [6]. Plant TPC1 (or SV, slow vacuolar channel as it was originally named) is modulated by several factors, underpinning its complex regulation. Beside voltage, TPC1 is regulated by calmodulin [7] , 14-3-3 proteins [8], kinases and phosphatases [9][10], pH [6] [11], redox state [12], and Mg^{2+} and Ca^{2+} [5][13]. In addition, natural polyamines (e.g., spermidine [14][15]) and heavy metals [16] have been reported to inhibit ion passage through open TPC1 channels in red beet and radish.

2. TPC1 function

Since loss of TPC1 function does not drastically impair plant growth [17], its physiological role is a matter of debate. However, roots of seedlings exposed to salt treatment show reduced growth in the TPC1 knockout *tpc1-2* mutant compared to WT plants [18]. In contrast, TPC1 overexpression increases salt tolerance [18]. Interestingly, salt-triggered propagating Ca^{2+} signals in the root were attenuated in *tpc1-2* mutants, but increased in TPC1 overexpression lines [18]. Furthermore, it was shown that systemic Ca^{2+} signals, generated upon wounding, were gone upon loss of TPC1 function. This observation pointed to a role of TPC1 in systemic Ca^{2+} signaling [19]. *The Arabidopsis thaliana* TPC1 *fou2* variant (fatty acid oxygenation upregulated 2) point mutation D454N leads to an increased production of the stress hormone jasmonate, even *under non-stre*ssed conditions. The *fou2* plants exhibit a strong growth retardation phenotype [20][21], probably originating from the increased vacuolar K^+ release due to TPC1 hyperactivity [21]. It is important to note that a TPC1-independent pathway of jasmonate signaling has also been postulated [22]. Since TPC1 participates likely indirectly in the generation/modulation of the Ca^{2+} wave, it seems to be reasonable to suggest a supreme trigger, regulating Ca^{2+} and K^+ fluxes [22]. Vacuolar membrane depolarization may be one of the missing early triggers for jasmonate production. Furthermore, TPC1 is a prerequisite for vacuole membrane excitability [23], thus triggering of vacuolar membrane depolarization in local spots may be an elaborate way to encode more complicated information in long- and short-distance signaling pathways in plants.

3. Calcium Induced Calcium Release theory

The concept of Ca^{2+}-induced Ca^{2+} release (CICR), initially proposed by Fabiato et al. (1985) in the animal field, was adapted by Ward and Schroeder (1994) to plant research [24][25][26]. Based on patch-clamp measurements, they postulated cytosolic Ca^{2+} signals generated by TPC1 in *Vicia faba* guard cell vacuoles. However, the ionic composition used in this study was far away from the physiological concentration for Ca^{2+} and K^+. By applying non-physiological ionic conditions, TPC1 channel-mediated Ca^{2+} currents were also recorded in other species, but only in the opposite direction, from cytosol to vacuole [27][28][29]. Furthermore, an inhibitory effect of vacuolar Ca^{2+} was postulated [30], likely attributable to the highly conserved vacuolar Ca^{2+}-binding motifs of TPC1 [1][31]. To solve the above long-lasting debate, structural models for the different species will be helpful. Of note, the gain-of-function *Arabidopsis thaliana* TPC1 channel variant (*fou2*) shows increased vacuolar Ca^{2+} and slightly lower resting cytosolic Ca^{2+} levels compared to WT, which would be difficult to reconcile with TPC1 releasing Ca^{2+} under physiological conditions [11][22]. In sum, the contribution of plant TPC1 to global as well as local Ca^{2+} signals remains debated and needs to be further evaluated. A similar complex debate exists in the field of mammalian TPC research, where the role of TPCs in endo-lysosomal Ca^{2+} release remains likewise controversially discussed [32][33][34][35][36][37][38].

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