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The good company of T-type calcium channels

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Commentary on : ‘T-type calcium channelosome’, a review by N. Weiss and

G.W. Zamponi

(no abstract)

‘You’ll never walk alone’ is the title of a popular song that now sounds well for ion channels. In recent years, the word ‘channelosome’ has been coined to better capture the way in which some ion channels intimately involve protein partners to properly drive their functional

signaling. In their 'T-type calcium channelosome' review, Weiss & Zamponi [10] provide for the first time a channelosome view of T-type Cav3 voltage-gated calcium channels (Cav) by gathering and merging a wealth of recent evidence showing that these channels are functionally determined by a wide range of protein-dependent modulations. As a rational definition, the 'channelosome' may be presented as the collection of all the proteins involved in intrinsic channel support and anchoring, as well as the proteins involved in post-translational modulations, e.g. phosphorylation. In the Cav channel family this corresponds perfectly to the L-types (Cav1) and neuronal P/Q-, N- and R-types (Cav2) channels, whose native activities depends on a tight association of the $\alpha 1$ pore subunit with the auxiliary β and $\alpha 2/\delta$ subunits, and possibly also the γ subunit [2]. Some studies have now consistently expanded our knowledge of the Cav1 and Cav2 channelosomes by employing proteomics approaches [9] [1] [4]. Apart from the Cav channel landscape, there are many ion channels that depend critically on their channelosome structure to be functionally active. One recently described situation in the 4-domain channel family relates to sodium-leak channel NALCN, which must be co-expressed with three subunits UNC-79, UNC-80 and FAM155/NLF1 [8] to exhibit channel activity.

The great interest of the Weiss & Zamponi review [10] is to scheme the appearance of the T-type Cav3 channelosome as illustrated in Figure 1, although to date very few proteomics studies have been reported for these channels. The lack of available selective- or specifically-designed tools, such as Cav3 antibodies or epitope-tagged Cav3 channels, has hampered investigations of the Cav3 channelosome. We can expect these approaches to be developed soon for any of the Cav3.1, Cav3.2 or Cav3.3 channels, enabling better resolution of the 'primary' Cav3 channelosome. A more complex level of the channelosome is linked to the so-called '*regulators*'. In this review, it appears that Cav3 channels are subject to a variety of protein-dependent modulations that can significantly tune their functional activity. Up to eighteen such regulators are described here, including syntaxin1A, $\beta 2\gamma 2$ G-protein, calmodulin, USP5, STAC1 ... So far, it is not clear whether any of these regulations are exclusive for one of the three Cav3 channel isoforms (Cav3.1, Cav3.2 or Cav3.3), although the published data nicely compiled here show there are selective features for some of these modulations, with Cav3.2 channels being by far the most prone to modulation. Some findings remain

puzzling, such as how Cav3 channels might autoregulate themselves, possibly through self-assembly, to promote an auto-inhibitory phenotype [6,7]. In addition, Cav3 channels can also interact with other ion channels, including calcium-activated potassium channels (e.g. KCa1.1 and KCa3.1), based on a Cav3-KCa colocalization that delimit a calcium microdomain responsible for functional modulation of KCa channels. This modulation ultimately regulates the resting membrane potential and cellular excitability.

When considering this ‘regulatory’ channelosome (modulosome) of Cav3 channels, little is known about the post-translational regulation of the Cav3 proteins. But the first steps are taken, with reports on how glycosylation, ubiquitination or phosphorylation of the Cav3 proteins impact their activity. Deciphering further these direct protein-dependent regulations will open up new opportunities to develop innovative therapeutic strategies, as reported for the dynamic deubiquitinase USP5-Cav3.2 regulation in pain therapy [3]. Mass spectrometry approaches will undoubtedly allow the identification of other active regulation sites in a near future, hopefully selective for a single Cav3 isoform or for a few splice variants of a given isoform. In the meantime, studies of mutations causing diseases (channelopathies), which are currently being identified for Cav3 channels [5], may also help further decipher how some of the reported Cav3 regulations can be specifically affected in some disease conditions.

Taken together, this ‘T-type calcium channelosome’ review by Weiss & Zamponi digests decades of effort to decipher Cav3 modulations and, more importantly, points to future research needed to document both the generic” and the “isoform-selective” T-type calcium channelosomes. Clearly, the Cav3.1, Cav3.2, and Cav3.3 subunits of T-type channels “*never walk (work) alone*” in the panorama of cellular excitability.

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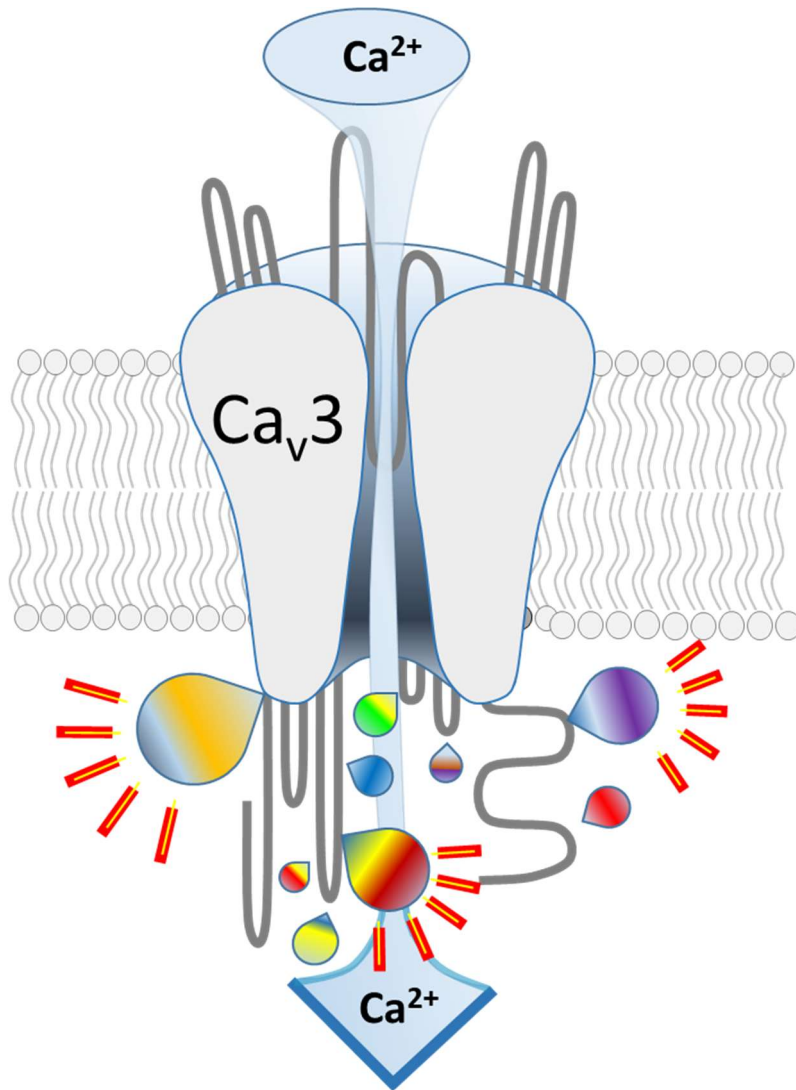


Figure 1. An illustration symbolizing the many regulators decorating Cav3 T-type calcium channels