


# Ca<sup>2+</sup> Signalling is a Conserved Game of Contact

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Contact  
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## Abstract

Apicoplasts are critical for the growth of medically important parasites. It is now reported that they form contacts with the endoplasmic reticulum (ER) via two pore channels thus enabling Ca<sup>2+</sup> trafficking. This highlights the dynamic physical association between organelles as a critical motif in Ca<sup>2+</sup> signaling.

## Text

The separation of the cell into discrete domains is critical to the spatio-temporal precision of signal transduction. The archetype of this principle is the signaling of Ca<sup>2+</sup>: the cell's most abundant second messenger. The Ca<sup>2+</sup> homeostasis relies upon steep gradients maintained by stringent spatial separation, which is harnessed to deliver a rapid, cell-wide response (Bagur & Hajnóczky, 2017). Contact sites mediating physical and functional links between organelles are therefore paramount to the regulation of Ca<sup>2+</sup> dynamics.

The largest intracellular Ca<sup>2+</sup> store, the endoplasmic reticulum (ER), is tethered to the mitochondria, which responds sensitively to changes in Ca<sup>2+</sup> concentration in order to fine-tune metabolic responses and pleiotropic signaling events.

The physical and functional bond between ER and mitochondria epitomizes the key role played by contiguity in the correct execution of inputs whilst minimizing signal dispersion (Reane et al., 2020). The importance of molecular mechanisms that regulate formation and function of these inter-organelle junctions make Ca<sup>2+</sup> signaling a game of contacts.

In this elegant and informative manuscript (Li et al., 2021), Moreno and co-workers show that such a frame of signaling is conserved in *Toxoplasma Gondii* (Tg). Alongside other medically important parasites such as *Plasmodium* and *Eimeria*, *Toxoplasma* are apicomplexans and possess secondary plastids known as apicoplasts, four-membrane-bounded organelles, which are ancestrally related to chloroplasts with key roles in lipid biosynthesis and iron metabolism (Van Dooren & Striepen, 2013).

The work reports that the apicoplasts (McFadden, 2014) hold trafficking capacity for Ca<sup>2+</sup>, made possible by the formation of contacts with the ER. Whilst previous papers have reported the formation of ER contacts with double membrane-bound chloroplasts (Andersson et al., 2007) – which are indeed acknowledged as contributors to Ca<sup>2+</sup> signaling and storage

(Navazio et al., 2020) – this is the first one to report the existence of contacts between ER and apicoplasts.

The authors provide compelling evidence on the accumulation and redistribution of Ca<sup>2+</sup> occurring in the apicoplasts and on the key role played by the Two-Pore Channels (TPC) (Patel, 2015) – referred to as TgTPC – which drives this critical inter-organelle route of communication.

TPC is a ubiquitous family of cation channels capable of regulating numerous Ca<sup>2+</sup>-dependent events. Hitherto, TPCs had been characterized in multi-cellular organisms but never in the unicellular ones; a gain in knowledge that will further propel the general attention on these tantalizing conduits of cell signaling.

In mammals, TPCs (isoforms 1 and 2) operate in response to the Ca<sup>2+</sup> mobilizing messenger NAADP but they can also be activated by phosphoinositide PI(3,5)P<sub>2</sub> originated from the endosomes.

A recent breakthrough (Gerndt et al., 2020) has unveiled how the isoform 2 of the TPC is selective for Ca<sup>2+</sup> when first bound to NAADP and then becomes selective for Na<sup>2+</sup> when bound by PI(3,5)P<sub>2</sub>. These findings have therefore enriched the field of pharmacology, bearing transformative and far-reaching prospective in the design of synthetic cell signaling regulators.

The TgTPC presented in this manuscript is proposed to hold a key role in the functional coupling between ER and

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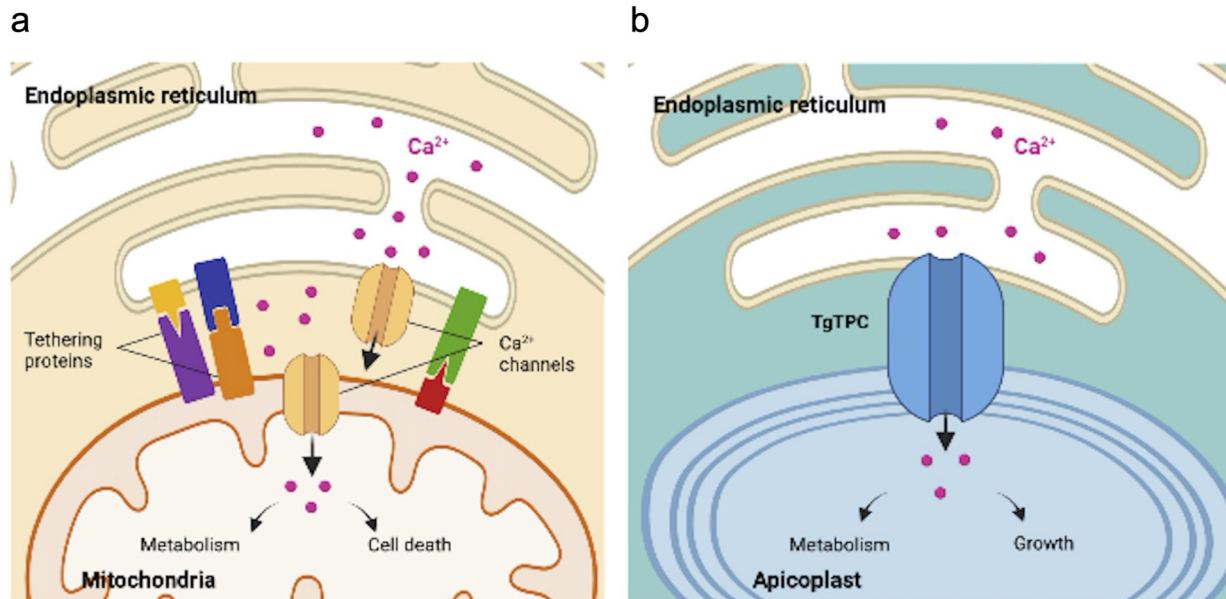
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**Figure 1.** Inter-organelle contact sites across phyla.

the apicoplasts, mediating transmission of  $\text{Ca}^{2+}$  indicative of sequential and successful endosymbiosis.

Though a role as uniporter for TgTPC between ER and apicoplasts is speculated, it is the tethering one to be flagged as the most plausible one. TgTPC therefore mediates both physical and functional coupling between ER and apicoplasts, thus proving pivotal for the growth of the *Toxoplasma Gondii*.

In this way a channel that forges a contact shows how the geometrical regulation of inter-organelles communication is conserved across species and a logical new focus of interest in biological discovery (Figure 1).

### Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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