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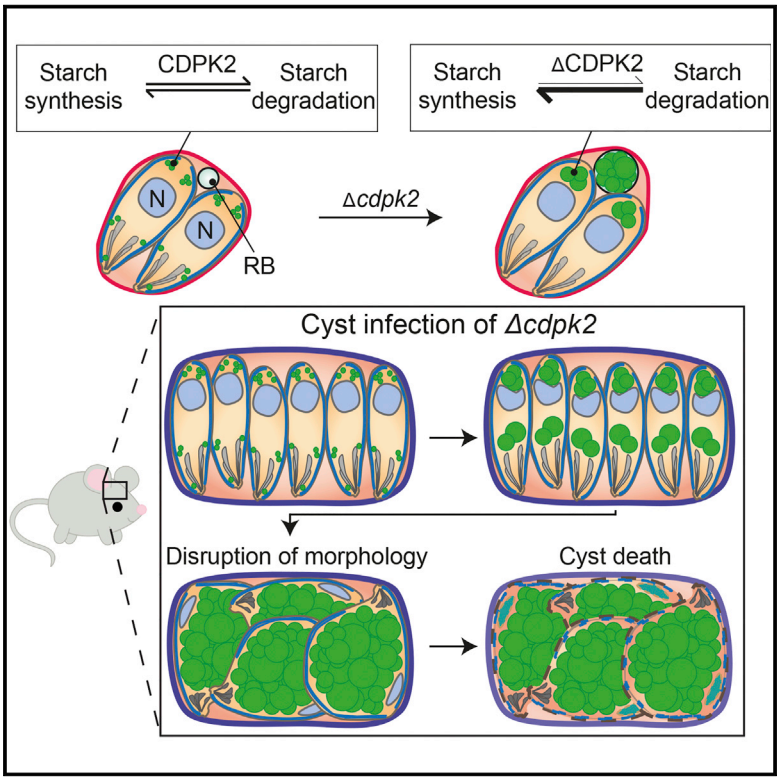
Regulation of Starch Stores by a Ca^{2+}-Dependent Protein Kinase Is Essential for Viable Cyst Development in *Toxoplasma gondii*

Graphical Abstract



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In Brief

Encysted lifecycle stages of *Toxoplasma gondii* produce and store starch. Uboldi et al. show that the kinase CDPK2 is targeted to starch stores and regulates starch turnover in a Ca^{2+}-dependent manner. CDPK2 deficiency leads to unchecked starch accumulation and death of parasite tissue cysts.

Highlights

- The *Toxoplasma* kinase CDPK2 has functional Ca^{2+}- and carbohydrate-binding domains
- CDPK2 deficiency causes unchecked accumulation of starch in *Toxoplasma* parasites
- Phosphorylation of several starch-metabolic enzymes relies on CDPK2 activity
- Loss of CDPK2 results in starch hyperaccumulation and death of chronic-stage parasites

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Regulation of Starch Stores by a Ca^{2+}-Dependent Protein Kinase Is Essential for Viable Cyst Development in *Toxoplasma gondii*

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SUMMARY

Transmissible stages of *Toxoplasma gondii* store energy in the form of the carbohydrate amylopectin. Here, we show that the Ca^{2+}-dependent protein kinase CDPK2 is a critical regulator of amylopectin metabolism. Increased synthesis and loss of degradation of amylopectin in CDPK2 deficient parasites results in the hyperaccumulation of this sugar polymer. A carbohydrate-binding module 20 (CBM20) targets CDPK2 to amylopectin stores, while the EF-hands regulate CDPK2 kinase activity in response to Ca^{2+} to modulate amylopectin levels. We identify enzymes involved in amylopectin turnover whose phosphorylation is dependent on CDPK2 activity. Strikingly, accumulation of massive amylopectin granules in CDPK2-deficient bradyzoite stages leads to gross morphological defects and complete ablation of cyst formation in a mouse model. Together these data show that Ca^{2+} signaling regulates carbohydrate metabolism in *Toxoplasma* and that the post-translational control of this pathway is required for normal cyst development.

INTRODUCTION

Toxoplasma gondii is an obligate intracellular protozoan parasite of warm-blooded animals, including humans. Toxoplasmosis results from the ingestion of sporulated oocysts present in soil, water, or vegetables contaminated with cat feces, or by ingesting raw or undercooked meat harboring tissue cysts. Both stages can differentiate into rapidly dividing tachyzoite stages that are usually controlled by a protective immune response. However, in immunocompromised individuals severe systemic disease can occur, while in the developing fetus *Toxoplasma* infection can cause spontaneous miscarriage, blindness, or congenital neurological defects, including epilepsy, mental retardation, and hydrocephaly (Hill et al., 2005; Torgerson and Mastroiacovo, 2013).

Under immune pressure, a proportion of tachyzoites differentiate back into the relatively quiescent, slow-growing bradyzoites, which form latent cysts in muscle and CNS tissue that can persist for the lifetime of the infected host. Most chronic infections are asymptomatic, but bradyzoites can differentiate back to tachyzoites in CNS tissue of immunosuppressed individuals, leading to serious neurological disease and death if not treated. In addition, cyst formation in the retina is a significant cause of blindness (Glasner et al., 1992).

Toxoplasma tachyzoites can utilize both glucose and glutamine scavenged from the host cell to drive energy production (MacRae et al., 2012; Oppenheim et al., 2014; Blume et al., 2009), and following host cell egress, tachyzoites accumulate γ-aminobutyric acid, which may provide extracellular tachyzoites with a short-term energy reserve to fuel motility and invasion (MacRae et al., 2012). *Toxoplasma* tachyzoites also produce the storage polysaccharide amylopectin, which contains a backbone of α(1-4)-linked glucose residues modified with α(1-6)-linked branch points (Guérardel et al., 2005). Tachyzoites generally express very low levels of amylopectin unless stressed, but in contrast, bradyzoites and oocysts accumulate high levels of amylopectin granules in the cytoplasm (Coppin et al., 2003; Guérardel et al., 2005; Ferguson et al., 1974; Ferguson and Hutchison 1987). It has been postulated that amylopectin granules may be a long-term energy reserve during transmission to maintain parasite viability in low-nutrient niches and/or to drive rapid differentiation when they encounter favorable conditions. However, essentially nothing is known about how amylopectin accumulation and utilization is regulated in different *Toxoplasma* life cycle stages.

Ca^{2+}-dependent protein kinases (CDPKs) are key mediators of Ca^{2+} signaling in apicomplexan parasites (Billker et al., 2009). They share a domain structure consisting of a variable N-terminal region, a kinase domain, and a calmodulin (CaM)-like domain containing Ca^{2+}-binding EF-hands. During Ca^{2+} signaling events,

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