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COMMENTARY

TRIM2: a double-edged sword preventing apoptosis

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TRIM2 belongs to the TRIM-NHL class of ubiquitin E3-ligases and inhibits apoptosis by a dual function. Liao *et al.* reported in the recent issue that under glutamine deprivation, TRIM2 transcription is activated by ATF4 to increase the uptake of long fatty acids into mitochondria. Here, TRIM2 acts as a direct activator of CPT1 independent of its E3 ubiquitin ligase activity and prevents apoptosis otherwise triggered by starvation. On the contrary, TRIM E3-ubiquitin ligase has been described to ubiquitinate and thus target proapoptotic BIM for its degradation in the proteasome. Thus, TRIM2 inhibits apoptosis classically via its ligase activity but also independent of this stimulating energy metabolism.

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Almost 80 TRIM (tripartite motif-containing) protein family members have been identified in humans, based on their common domain architecture. Most TRIM proteins (also known as RBCC proteins) are defined as E3 ubiquitin ligases as they contain a classic RING-finger domain at their N terminus, which typically confers ligase activity. The RING finger is followed by a BBOX, a zinc-finger domain, and a BBC domain, forming a coiled-coil region (Fig. 1). Following the coiled-coil domain, the C terminus of TRIM proteins comprises assemblies of variable domains with diverse functions. Many of these domains are involved in protein binding and thus, substrate recognition. TRIM RING-finger proteins are involved in carcinogenesis, defense against viral infection, the regulation of autophagy and apoptosis, and the etiopathology of some human hereditary diseases [1]. One of the classic TRIM proteins with a leading RING-, B-box, and CC-domain is TRIM2. Here, the N terminus is followed by a filamin-type immunoglobulin domain (IG_FLMN) and six NHL domains (named after NCL-1, HT2A, and Lin-41). The NHL domains form a six-bladed beta propeller-like structure in TolB and other proteins. These latter domains have been described as protein-binding modules, although the NHL repeat is also known to form a more global RNA-binding platform [2]. In the mouse, TRIM2 ubiquitinates Nfl and the NHL domains were described as mandatory for Nfl binding [3]. In humans, TRIM2 has been reported to be involved in the manifestation

Abbreviations
ATF4, activating transcription factor 4; ATP, adenosine triphosphate; BBC, B-box C-terminal; B-box, following the A-box; BIM, Bcl-2-interacting mediator of cell death; CC, coiled coil; CPT1, carnitine *O*-palmitoyltransferase 1; IG_FLMN, filamin-type immunoglobulin domain; NADH2, reduced nicotinamide adenine dinucleotide; Nfl, neurofilament light polypeptide; RBCC, N-terminal RING finger/B-box/coiled coil; RING, really interesting new gene (originally called A-box); TCA, tricarboxylic acid cycle; TolB, translocation protein B; TRIM2, tripartite motif-containing protein 2.

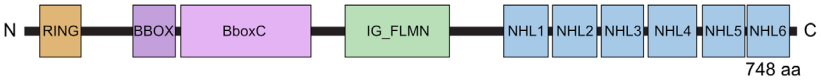

Fig. 1. Architecture TRIM-2 protein. TRIM2 belongs to the TRIM-NHL class of ubiquitin E3-ligases and consists of the catalytically RING domain, the E3-ubiquitin ligase active site followed by a coiled-coil region (BboxC, C-terminal to BBOX), a Filamin-like domain and six NHL domain forming a six-bladed propeller structure.

of axonal neuropathology [4,5]. It interacts with BIM and may control apoptotic signals by targeting BIM proteins for degradation by the proteasome. We found that TRIM2 plays a role in the determination and differentiation of neural progenitors in Xenopus. Knockdown of TRIM2 led to a reduction in brain size caused by increased apoptosis [6]. However, recent publications indicate that *bona fide* TRIM proteins do not necessarily function as E3 ubiquitin ligases but may form a binding platform for the corresponding proteins and thus regulate their function [7].

By comparing the transcriptomes of adenocarcinoma cells under glutamine deprivation to ATF4 knockdown cells, Liao *et al.* [8] identified *TRIM2* as a target gene of ATF4. The authors revealed that TRIM2 is a positive regulator of carnitine O-palmitoyltransferase 1 (CPT1A). Surprisingly, the regulation appeared to be independent of the E3 ligase activity of TRIM2. CPT1A localizes to the outer membrane of mitochondria and facilitates the first and rate-limiting step of long-chain fatty acid transport into the organelle. Mitochondria are of central importance to maintaining cellular metabolism; they are not only essential for the generation of the energy-rich compound ATP from diet-derived nutrients but also for integrating many metabolites into anabolic pathways. In this respect, CPT1A supports β-oxidation for the breakdown of long-chain fatty acids, indirectly supplying the tricarboxylic acid cycle (TCA) with acetyl-CoA, allowing the cell to regenerate its ATP pool. The authors describe the effect of TRIM2 in response to glutamine deprivation in cancer cells. Under this condition, the transcription factor ATF4 drives the expression of TRIM2, potentially helping the cells adapt to the energy needs under cellular stress. In contrast to other acyl transferases, CPT1A contains a regulatory domain at its N-terminal, which is important for binding a key inhibitory molecule, malonyl-CoA. Therefore, it would be interesting to know whether TRIM2 and malonyl-CoA compete for binding, which would

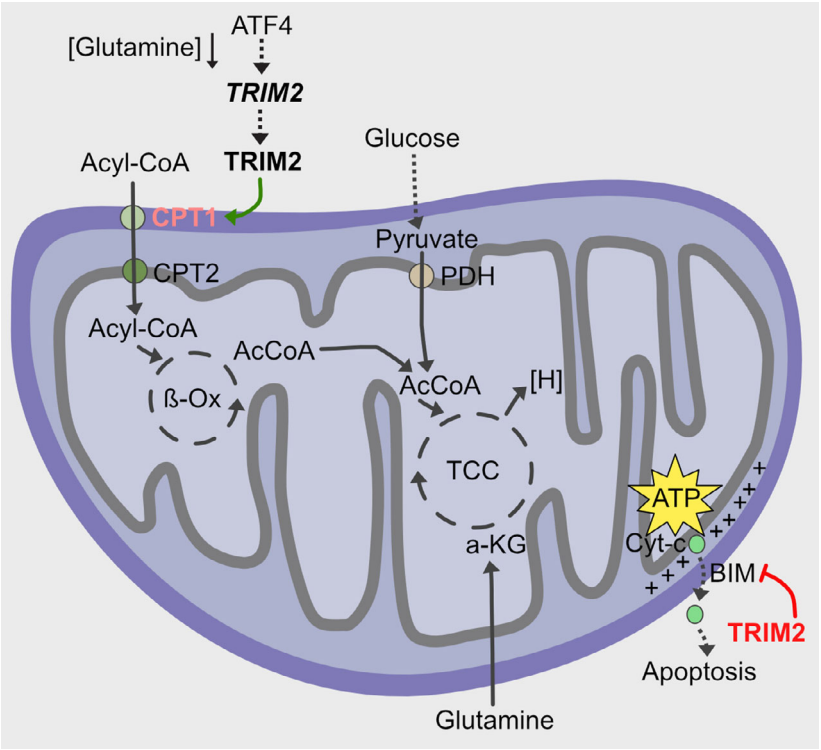

Fig. 2. TRIM2 inhibits apoptosis by a dual function. Under glutamine deprivation, *TRIM2* transcription is activated by ATF4 to increase the uptake of long fatty acids into mitochondria. Here, TRIM2 acts as a direct activator of CPT1 independent of its E3 ubiquitin ligase activity and prevents apoptosis otherwise triggered by starvation. On the contrary, TRIM E3-ubiquitin ligase has been described to ubiquitinate and thus target proapoptotic BIM for its degradation in the proteasome. Thus, TRIM2 inhibits apoptosis classically via its ligase activity but also independent of this being a stimulating energy metabolism.

maintain the transferase in an active state even when malonyl-CoA is present. In addition, Liao *et al.* observed that TRIM2 knockdown in cancer cells enhanced apoptosis, which was reversed by the overexpression of CPT1A. The lack of the positive regulator TRIM2 could be compensated by more active CPT1A proteins. Glutamine is needed to replenish the alpha-ketoglutarate pool of the TCA cycle when intermediates are employed for anabolic reactions. Without sufficient glutamine, the TCA cycle may run empty, leading to an insufficient supply of reducing equivalents, like NADH2, for the efficient generation of a proton gradient and ATP by the respiratory chain. As a result, mitochondrial physiology is severely affected as neither the proton-driven import of mitochondrial proteins is further maintained nor the efficient production of ATP. Together, this may lead to the breakdown of mitochondria and the release of cytochrome C, which would induce apoptosis via the intrinsic pathway. Thus, cancer cells may depend on the function of TRIM2 under glutamine deprivation or similar stress conditions, which may otherwise lead to a fatal collapse of their energy status. To address the question more directly, the authors injected TRIM2 knockdown cells as well as cells transfected with CPT1A into BALB/c Nude mice and analyzed the resulting tumors 36 days after injection. As a result, the suppression of TRIM2 expression significantly inhibited the growth of the xenograft tumor. It is interesting to note that TRIM2 targets BIM for protein degradation [9]. Since BIM is a major factor driving the intrinsic apoptotic pathway, the loss of TRIM2 may stabilize BIM, which may also support apoptosis. Together, TRIM2 possesses oncogenic potential, since it helps a cancer cell to survive. As the authors suggest, TRIM2 represents a druggable target for the treatment of defined cancer types in its dual role as a BIM inhibitor and as a positive regulator of CPT1A (Fig. 2).

Conflict of interest

The author declares no conflict of interest.

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