Cell Calcium 84 (2019) 102082

Contents lists available at ScienceDirect

Cell Calcium

journal homepage: www.elsevier.com/locate/ceca

TRPing the homeostatic alarm — Melanoma cells are selectively vulnerable to TRPML1 deletion

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A B S T R A C T

To thrive in otherwise inhospitable conditions, cancer cells utilize endolysosomes to impose homeostatic control over cellular metabolism and growth. In a recent study, Kasitinon et al. demonstrate a requirement for the endolysosomal channel, TRPML1, in proliferation and survival of melanoma cells. This study adds to a growing list of cancers that exhibit selective vulnerability to the loss of TRPML1.

Melanomas are potentially lethal cancers that arise from the transformation of epidermal melanocytes. A new line of inquiry into the pathophysiology of this disease stem from reports of overabundant lysosomes in melanoma. Indeed, the lineage-specific transcription factor and melanoma driver, microphthalmia-associated transcription factor (MITF), promotes both endolysosomal biogenesis and Wnt-dependent cancer cell proliferation [1,2]. Furthermore, upregulation of a late-endosomal GTPase, Rab7, is necessary for lysosomal degradation and the attendant liberation of tumor-promoting nutrients [3]. A recent study has added to the repertoire of actionable lysosomal targets in melanoma [4]. By conducting a screen designed to identify channels and transporters that sustain tumorigenesis, Kasitinon et al. report that *MCOLN1*, which encodes an endolysosomal cation channel called TRPML1, promotes melanoma [4]. *MCOLN1* expression was significantly higher in melanoma cells compared to normal melanocytes, and knockdown or deletion of this gene selectively diminished the proliferation and survival of cancer cells, but not normal melanocytes [4]. These data raise the possibility that targeting TRPML1 could deter the growth of melanoma without affecting healthy melanocytes.

TRPML1 directs the fusion of endolysosomes with each other and the plasma membrane, and thereby, promotes signaling via several kinase cascades including mTORC1 and RAS–ERK [5,6]. Given the involvement of these signaling modalities in cancers, two independent groups previously interrogated the requirement for TRPML1 in cancer. These studies found that TRPML1-dependent mTORC1 and RAS–ERK signaling aggravate triple negative breast cancer and oncogenic *HRAS*-driven cancers, respectively [5,6]. While ostensibly agreeing with previous studies, Kasitinon et al.'s analyses yielded many surprises. Most notably, deletion of *MCOLN1* in melanoma *increased* both MEK–ERK and mTORC1 signaling [4]. The authors attribute the potentiation of ERK to endosomal relocation and reduced lysosomal degradation of growth factor receptors [4]. Although diminished receptor degradation agreed with previous findings [7], enhancement of downstream signaling was unexpected. TRPML blockade in non-cancer cells arrests endosomal trafficking subsequent to ESCRT-mediated receptor sorting [7]. Thus, internalized receptors in *MCOLN1* deficient cells would not have been expected to potentiate downstream signaling. The unique mutational landscape of melanoma may underlie this discrepancy. For instance, concomitant mutations in genes encoding ESCRT proteins — previously reported in cancer [8] — could permit the perdurance of signaling-competent receptors on endosomal surfaces leading to ERK hyperactivation in the absence of TRPML1.

Placing ERK upstream of mTORC1, Kasitinon et al. found that MEK inhibition attenuated mTORC1 in *MCOLN1* deficient melanoma cells [4]. Additionally, mTORC1 inhibition rescued growth and survival of cells lacking TRPML1 [4]. As would be expected from regulation of mTORC1, TRPML1 antagonizes protein synthesis, and prevents proteotoxic stress [4]. Thus, inhibition of protein synthesis partially restored cell survival in TRPML1-deficient cells. These data lend themselves to the speculation that cancer cells with upregulated TRPML1 might have a survival advantage owing to their capacity to withstand proteotoxic stress. *MCOLN1* deletion also diminished lysosomal degradation of macropinosome content [4]. Interestingly, inhibition of MEK or mTORC1 partially restored the uptake and degradation of macropinosomes [4]. Since mTORC1 negatively regulates endolysosomal biogenesis [9], it is possible that the restoration of macropinocytosis reflects engagement of compensatory pathways.

In conjunction with previous reports, Kasitinon and colleagues'

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https://doi.org/10.1016/j.ceca.2019.102082
Received 17 September 2019; Received in revised form 18 September 2019; Accepted 20 September 2019
Available online 01 October 2019

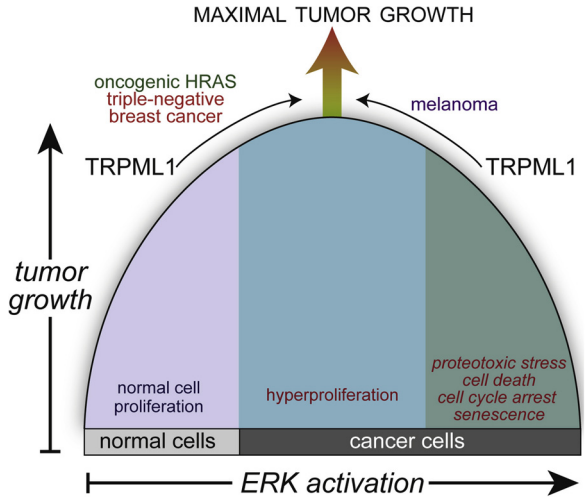

Fig. 1. TRPML1 functions as a rheostat that optimizes ERK activity in cancer cells. Cancer cells exhibit biphasic response to ERK activity. While increased ERK phosphorylation in some cancers promotes cell proliferation, ERK hyperactivation can cause the arrest of cell cycle, senescence, and even cell death. TRPML1 functions as a rheostat to maintain ERK activation within a range necessary for maximal tumor growth. Inhibition of TRPML1 in tumors with oncogenic HRAS lead to decreased ERK phosphorylation, whereas loss of TRPML1 in melanoma leads to increased ERK phosphorylation. In either situation, decreased TRPML1 correlates with diminished tumorigenesis.

findings underscore the relevance of TRPML1 to cancer [4–6]. Future studies should attempt to reconcile the divergent effects of TRPML1 on ERK phosphorylation in different cancers [4–6]. The qualitative relationship between TRPML1 and ERK signaling could vary between cell types, or emerge from the unique genomic constraints in different cancers. For instance, if *MCOLN1* were upregulated during the early stages of tumorigenesis, high channel activity could guide the accumulation of mutations that irrevocably couple MEK–ERK signaling with TRPML1. Another important consideration is that while low level activation of the MEK–ERK axis promotes neoplastic proliferation, hyperactivation of this pathway is poorly tolerated by most cells (Fig. 1). Indeed, ERK hyperactivation has been shown to trigger senescence in melanoma [10]. Thus, inherently high MAPK activation in melanoma necessitate strategies to attenuate these signals. In contrast, HRAS-driven tumors leverage pathways that augment ERK signaling [5]. Remarkably, either strategy demands an increase in *MCOLN1* expression (Fig. 1). In light of these findings, we recommend reframing our view of TRPML1 as a 'rheostat' that can either potentiate *or* dampen cancer signaling depending on the context (Fig. 1). An arguably teleological extension of this idea is that the ability of TRPML1 to modify ERK signaling in diametrically opposing ways makes *MCOLN1* upregulation an optimal strategy for cancer cells (Fig. 1). This concept informs the hopeful message that knockdown of *MCOLN1* or inhibition of TRPML1 might be an effective therapeutic strategy in a range of malignancies.

Acknowledgements

Research in the K.V. laboratory is funded by NIH grants, R01NS08130 and R21AG061646. J.J. is supported by a grant from the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the ministry of education (NRF-2016R1D1A1B03932051). We are grateful to Nicholas Karagas for suggesting the title, Dr. Ching-On Wong for scientific discussions, and Dr. Sean Morrison for comments. The authors declare that there are no conflicts of interest.

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