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TRPV1: Turning up the heat on intestinal tumorigenesis

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TRP channels are associated with the development and progression of cancer but their precise molecular roles in these processes are unclear. Recently, we showed that the transient receptor potential cation channel, subfamily V, member 1 (TRPV1) ion channel is part of a negative feedback loop downstream of epidermal growth factor receptor signaling that suppresses intestinal tumorigenesis.

The hallmarks of cancer include sustained proliferative signaling, evasion of growth suppressors, acquired resistance to cell death, and the acquisition of invasive and metastatic properties. It has also been established in recent years that the 'tumor microenvironment', which consists of stromal cells and their associated extracellular matrix, hematopoietic cells, and neurons, among others, is essential for the malignant transformation of epithelial cells.[1] Recent evidence suggests that members of the transient receptor potential (TRP) family of ion channels contribute to many of the aforementioned cellular and molecular events. The mammalian TRP channel family consists of at least 28 members, divided into 6 subfamilies based on amino acid sequence homology: canonical (TRPC; 7 members), vanilloid (TRPV; 6 members), melastatin (TRPM; 8 members), ankyrin (TRPA; 1 member), polycystin (TRPP; 3 members), and mucolipin (TRPML; 3 members). All TRP channels are permeable to cations, with the permeability ratio of calcium relative to sodium (P_{Ca}/P_{Na}) typically ranging between 0.3 and 10 (exceptions are the TRPV5 and TRPV6 channels with P_{Ca}/P_{Na} of ~100). Thus, TRP channel activation generally results in an increased concentration of cytosolic free Ca^{2+} leading to various Ca^{2+}-mediated, cell type-specific, and context-dependent responses. However, the molecular mechanisms of TRP channel activation in the context of cancer and their downstream consequences are largely unknown.[2,3] TRP channels are expressed by excitable cells (neurons) and non-excitable cells (e.g., epithelial, hematopoietic, and stromal cells). Studies on the cellular effects of TRP channel activation in the context of tumor cell transformation have mostly focused on the protumorigenic effects of downstream Ca^{2+}-dependent effector pathways. We recently proposed a non-redundant role for the TRPV1 ion channel in the regulation of epidermal growth factor receptor (EGFR) signaling in the intestinal epithelium through Ca^{2+}/calpain-mediated phosphatase activity, which acts to prevent tumorigenesis.[4]

TRPV1 is considered the founding member of the TRPV channel subfamily, with its prototypical agonists being exogenous stimuli such as capsaicin (the pungent component of chili pepper), heat (>43°C), and acidity (pH < 6.0), in addition to various endogenous agonists such as anandamide and certain lipoxygenase products. Furthermore, TRPV1 gating is regulated by various endogenous modulators, including bradykinin, protease-activated receptor 2 (PAR2) agonists, adenosine triphosphate (ATP), and receptor tyrosine kinase activity. The polymodal (i.e., chemicophysical) sensory properties of TRPV1 and its ubiquitous expression in multiple cell types underline the multifaceted contribution of TRPV1 signaling to tissue homeostasis[5] and tumorigenesis.[6] In order to understand the role of the TRPV1 channel in intestinal neoplasia development, it is necessary to define its full expression profile in the gut. The distal gastrointestinal tract is densely innervated by extrinsic, primary afferent $TRPV1^+$ sensory neurons.[7] This has led to a broad interest in the role of neurogenic inflammation, mediated by a variety of pre-stored neuropeptides that are released upon TRPV1 triggering. In the context of colorectal cancer, Vinuesa et al.[8] suggested an immunoregulatory role for TRPV1 in the gut that affects the activity of inflammatory cells in the intestinal mucosa, thus changing the tumor microenvironment. The authors reported that $TRPV1^+$ sensory neurons release neuropeptides such as vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating peptide (PACAP),[8] 2 known modulators of immune cell functions.[9] In addition, $Trpv1^{-/-}$ mice showed enhanced release of the cytokines

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interleukin-6 (IL-6) and IL-11, in addition to increased activity of the protumorigenic signal transducer and activator of transcription 3 (STAT3) and nuclear factor kappaB (NF-κB) signaling pathways in colonic lysates. Together, these data suggested that TRPV1 regulates neurogenic inflammation, which alters the intestinal microenvironment (i.e., neuroimmune–epithelial crosstalk), resulting in a reduced release of proinflammatory cytokines with a concomitant decreased risk of STAT3 and/or NF-κB-driven epithelial tumorigenesis.[8] However, the proproliferative effects of proinflammatory neuropeptides, such as substance P or calcitonin gene-related peptide (CGRP) that commonly co-localize with $TRPV1^+$ afferents in the gut, remain unclear. The underlying molecular mechanisms (e.g., the activity of proliferative versus antiapoptotic signaling pathways) in intestinal epithelial cells in the context of TRPV1-mediated neurogenic inflammation should therefore be studied in more detail.

In addition to this neurogenic component, intrinsic TRPV1 expression in intestinal epithelial cells is likely to directly affect growth factor receptor signaling and tumor formation. We recently demonstrated the functional expression of TRPV1 in intestinal epithelial cells.[4] We also found that TRPV1 can be activated downstream of EGFR in epithelial cells.[4] EGFR is a prototypical receptor tyrosine kinase, as well as a phospholipase C (PLC)-coupled receptor. Thus, EGFR activation leads to autophosphorylation of its intracellular tail, followed by PLC-mediated hydrolysis of the membrane lipid phosphatidylinositol-4,5-bisphosphate (PIP_2). Since PIP_2 has been postulated as a tonic inhibitor of TRPV1 gating, EGFR activation thereby results in potentiation of TRPV1 channel activity.[10] Indeed, our experimental data suggested functional coupling between the EGFR and TRPV1, via PLC-mediated PIP_2 hydrolysis, in intestinal epithelial cells. Finally, we demonstrated that upon activation in epithelial cells TRPV1 exerts a negative regulatory effect on EGFR activity that requires Ca^{2+}/calpain and protein tyrosine phosphatase, non-receptor type 1 (PTPN1, which encodes the PTP1B protein) activity.[4] This model represents a novel way of regulating receptor tyrosine kinase activity through the potentiation of a TRP channel and its associated Ca^{2+} influx, followed by downstream PTP activity, which then feeds back to the same receptor. This negative feedback loop is likely to act promptly (i.e., within seconds), significantly faster than either

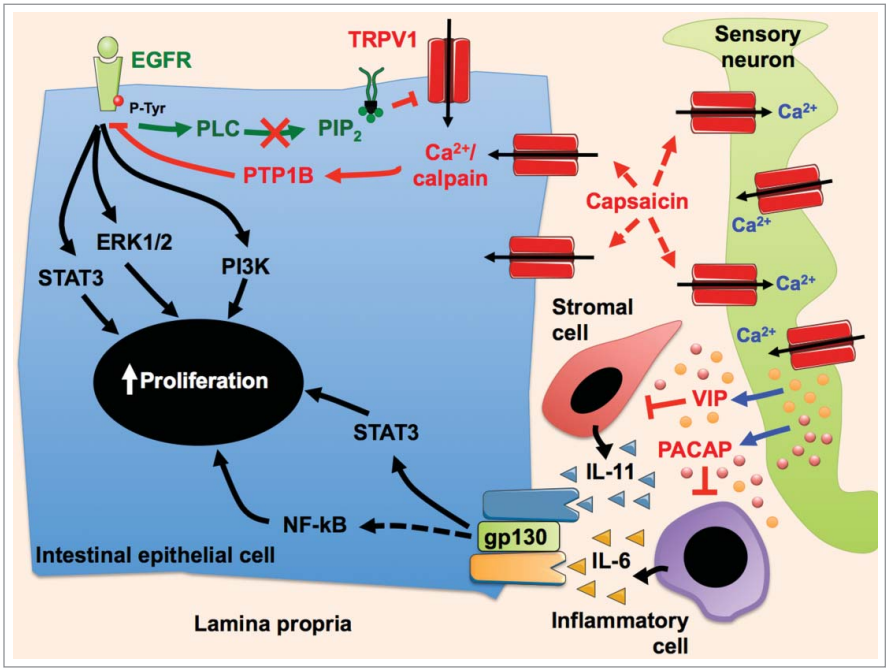

Figure 1. TRPV1-mediated regulation of proliferation and tumorigenesis. TRPV1 may play a role in the regulation of intestinal tumorigenesis on multiple levels. First, cell-intrinsic activation of TRPV1 in intestinal epithelial cells is potentiated by EGFR signaling. This results in activation of PLCG1 and hydrolysis of the membrane lipid PIP_2, followed by Ca^{2+} influx due to opening of the TRPV1 ion channel. Concomitantly, a negative feedback loop is initiated through Ca^{2+}/calpain and PTP1B, which then reverses EGFR phosphorylation thereby suppressing its oncogenic and proproliferative downstream effector pathways. The latter include STAT3, ERK1/2, and PI3K pathways, among others. Second, TRPV1 signaling in sensory neurons that innervate the gut results in the release of immunoregulatory neuropeptides, e.g., VIP and PACAP. These suppress release of the proinflammatory and proproliferative cytokines IL-6 and IL-11 by inflammatory and stromal cells, respectively, which are associated with the triggering of oncogenic pathways such as STAT3 and NF-κB in intestinal epithelial cells. The dotted line between the gp130 co-receptor and NF-κB shows that a direct correlation between these pathways is not clear. Both epithelial and neuronal TRPV1 signaling could potentially be modulated by the dietary or pharmacological administration of TRPV1 agonists (e.g., capsaicin) to 'hijack' its tumor-suppressive effects in the intestinal tissue microenvironment. EGFR, epidermal growth factor receptor; ERK1/2, extracellular signal-regulated kinase 1/2; IL, interleukin; NF-κB, nuclear factor kappa B; PACAP, pituitary adenylate cyclase-activating peptide; PI3K, phosphatidylinositol 3-kinase; PIP_2, phosphatidylinositol-4,5-bisphosphate; PLCG1, phospholipase C, gamma 1; PTP1B, protein tyrosine phosphatase, non-receptor type 1; STAT3, signal transducer and activator of transcription 3; TRPV1, transient receptor potential cation channel, subfamily V, member 1; VIP, vasoactive peptide.

proteasomal or lysosomal degradation of the EGFR or de novo transcriptional induction of negative EGFR regulators. Hence, we propose that this TRPV1-dependent negative feedback is able to quickly and dynamically fine-tune EGFR-mediated proliferative responses. Conversely, the absence of TRPV1 signaling results in hyperactivation of EGFR-mediated growth factor pathways, an increased basal rate of proliferation, and an enhanced risk of sporadic neoplasia development in the intestinal epithelium in genetically susceptible hosts (e.g., $Apc^{min/+}$ mice).

The expression of TRPV1 in both sensory neurons and epithelial cells in the gut complicates the interpretation of its role in tumor development and progression. However, both findings confirm a tumor suppressor role for TRPV1 in intestinal neoplasia development, albeit through different mechanisms, as summarized in **Fig. 1**. These data suggest a therapeutic potential of TRPV1 agonists in colorectal cancer prevention, as we presented in a murine model,[4] which may be addressed in future clinical studies. Finally, this overview does not account for potential cellular effects of TRPV1 signaling in hematopoietic or stromal cells, which could further affect the intestinal tumor microenvironment. Thus, despite these recent advances, the pleiotropic cellular effects of TRPV1 in gut tumorigenesis are only now emerging and future studies may shed more light on this topic.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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