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EDITORIAL COMMENTARY

Cold sensor, hot topic: TRPM8 plays a role in monocyte function and differentiation

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1 | EDITORIAL COMMENTARY

Understanding the innate immune system and how aberrant activation or impaired inhibition leads to the development of hyperinflammatory conditions, including inflammatory bowel disease, is crucial for patient management and treatment. An emerging area of interest surrounding dysregulated inflammation focuses on membrane-bound transient receptor potential (TRP) ion channels. These channels are permeable to calcium and other cations involved in the balance of leukocyte membrane potential and function, as well as afferent neuron signaling within the myenteric plexus of the GI tract, bladder, and skin.[1,2] A particular channel, TRPM8, is an important cell surface marker for prostate cancer and participates in the function of cold sensing neurons. Specifically, this ion-gated receptor has been shown to be activated by agonists such as menthol and eucalyptus,[1] which aid in the soothing, cooling effects of these agents. Furthermore, the TRPM8 channel has also been identified on the surface of resident tissue Mϕs and has also been linked to the protective role and release of calcitonin gene-related peptide (CGRP) by sensory neurons[1,2] (Figure 1).

The TRPM8 channel also participates in the attenuation of inflammation in the GI tract.[1,2] For example, *Trpm8*$^{-/-}$ mice are more susceptible to dextran sulfate sodium (DSS) induced colitis when compared to their wild-type (WT) counterparts.[1,2] This was recently demonstrated by Khalil et al. The group ultimately showed that *Trpm8*$^{-/-}$ mice and Mϕ-depleted WT mice administered *Trpm8*$^{-/-}$ Mϕs exhibited severe colitis histopathology scores and increased mortality rates that correlated with increased TNFα and attenuated IL-10 release.[2] The opposite effect was demonstrated in WT mice and *Trpm8*$^{-/-}$ mice administered WT Mϕs.[2] The group also showed that injection of exogenous IL-10 to *Trpm8*$^{-/-}$ mice greatly improved colitis scores; the same effect was appreciated when WT mice were treated with menthol enemas, which appeared to attenuate calcitonin-gene related (CGRP) release.[2]

The relationship between CGRP release and TRPM8 was also explored by de Jong et. al. Interestingly, this group demonstrated that *Trpm8*$^{-/-}$ mice were not only more susceptible to DSS induced colitis, but also exhibited defective release of CGRP from nerve fibers synapsing in the colonic mucosa.[1] Furthermore, the group also noted similar colitis severity with DSS treatment in CGRP deficient mice, suggesting the role of TRPM8 was not a cell-intrinsic effect, but related to the release of CGRP from sensory neurons adjacent to Mϕs in the colon.[1] It was also noted that splenic samples collected from *Trpm8*$^{-/-}$ mice contained increased levels of IL-6 and IL-1β, which are both potent pro-inflammatory cytokines, when compared to samples collected from WT mice.[1] Conversely, bone marrow-derived dendritic cells cultured from the 2 groups did not consistently exhibit increased release of IL-6 and IL-1β.[1]

In the current issue of the *Journal of Leukocyte Biology*, Hornsby et al.[3] further explores the role of TRPM8 in human monocyte differentiation and Mϕ participation in the development of colitis in human patients. Hornsby et al.[3] show that inhibition of the TRPM8 channel with a known antagonist, *N*-(3-aminopropyl)−2-{[(3-methylphenyl) methyl]oxy}-*N*-(2-thienylmethyl)benzamide hydrochloride salt (AMTB), leads to plasma membrane depolarization of CD14^{+} monocytes and monocyte-derived Mϕs.[3] Furthermore, culturing naïve CD14^{+} monocytes with AMTB and LPS ultimately leads to prolonged survival of these cells and enhanced TNF-α release.[3] These findings suggest that the TRPM8 channel is crucial for the survival and regulation of inflammatory cytokine production by human monocytes. Conversely, when Mϕs are continuously cultured with AMTB over a 6-day period, Mϕs exhibit decreased phagocytic potential, indicating that this channel is also involved in Mϕ function.[3] These findings are explored in line with gene expression and RNA analysis. Ultimately the group determines that 253 genes and 331 genes in the AMTB challenge group are up-regulated and down-regulated when compared to genes expressed during typical Mϕ differentiation, respectively.[3] These findings further demonstrate that engagement of this channel is crucial for gene transcription that ultimately leads to differentiation of Mϕs from bone marrow-derived monocytes.

Overall, this study expands knowledge pertaining to how the TRPM8 channel functions in monocyte to Mϕ differentiation by exemplifying how antagonism of this channel leads to dysregulated inflammation in human patients. Hornsby et al.'s findings also raises interesting questions related to the role of TRPM8 during time periods crucial for monocyte differentiation once released from the bone marrow. For further context, monocyte to Mϕ differentiation follows a sequential process once released from the marrow and is dependent on inflammatory stimuli.[4,5] Specifically, CD14^{++}CD16^{-} monocytes exhibit the

Abbreviations: AMTB, *N*-(3-aminopropyl)−2-{[(3-methylphenyl) methyl]oxy}-*N*-(2-thienylmethyl)benzamide hydrochloride salt; CGRP, calcitonin-gene related peptide; DSS, dextran sulfate sodium; TRP, transient receptor potential; WT, wild-type.

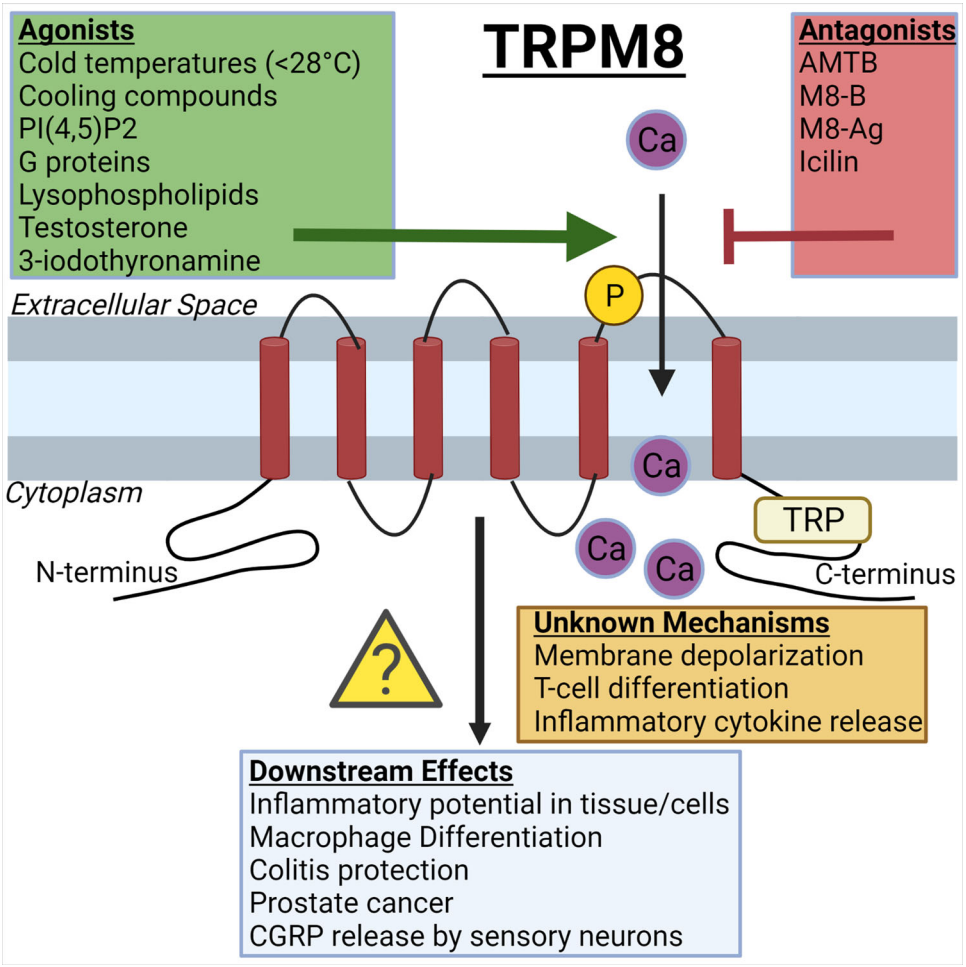

FIGURE 1 **Agonists and antagonists of the TRPM8 channel.** Shown are the known and proposed mechanisms that drive monocyte to Mϕ differentiation in relation to colitis

highest phagocytic potential with higher peroxidase and IL-10 levels with lower TNF-α release.[5] $CD14^{++}CD16^{+}$ monocytes are inflammatory regulators and can release higher levels of TNF-α and IL-1β and bind via CCR2/CCL2 interactions.[5] Finally, $CD14^{+}CD16^{++}$ are nonclassical monocytes that bind via CX3CR1/CCL3 mechanisms.[5] These blood monocytes further differentiate into tissue monocyte populations and Mϕs when released into the gastrointestinal tract, a process dubbed "the monocyte waterfall."[4] Desalegn et al.[4] demonstrated differing surface marker expression (CCR2, LY6C, MHCII, and CXCR3) and an intermediate monocyte population when comparing inflamed versus noninflamed GI tracts in a murine model.[4] When considering these mechanisms, it becomes important to understand how the engagement of the TRPM8 channel may affect the "monocyte waterfall" and subsequent Mϕ differentiation to drive dysregulated inflammation at different time points. The question of protein expression and lack of TRPM8 RNA detection may answer this question, as gene expression and epigenetic changes programmed within the bone marrow occurs during myelopoiesis. Specifically, exploration of how and when these expression patterns change once monocytes are released from the marrow and exposed to different cytokine milieu poses an interesting question.

Other promising areas for future study include exactly how depolarization of the membrane occurs, whether it be inhibition of endosomal channels leading to calcium accumulation in the cell cytoplasm, or if other cation channels are activated as a compensatory mechanism.[3] Finally, potential roles for T cell differentiation and inflammatory cytokine release are also uncovered during this study with respect to activation and inhibition of the TRPM8 channel. Further assessment of how this channel functions during the development of the adaptive immune response and how this channel informs cross talk between adaptive and innate immunity (and trained innate immunity) is promising. Expanding on these findings can also help us better understand immunologic disruptions that occur during inflammatory colitis and other states of dysregulated inflammation.

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