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Harnessing the Role of Transient Receptor Potential (TRP) Channels as Pathogen Sensors: Potential for Novel Therapeutic Interventions?

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Abstract

The role of Transient Receptor Potential (TRP) channels as pathogen sensors presents a compelling narrative in understanding cellular defense mechanisms against microbial invasion. We dwell on the intricate interplay between TRP channels and pathogen recognition, elucidating their pivotal role in initiating immune responses. TRP channels are recognized for their multifaceted responsiveness to various environmental cues, thereby emerging as key players in detecting pathogenic components. Upon stimulation by pathogenic cues, TRP channels undergo conformational changes or activation, initiating a cascade of intracellular events. This activation prompts the influx of ions, predominantly calcium, into the cell, culminating in the activation of downstream signaling pathways. These signaling cascades orchestrate a robust immune response, encompassing the activation of immune cells, the release of cytokines, and the priming of neighboring cells to fortify their defenses against the invading pathogens. Understanding the intricacies of TRP channels as pathogen sensors unveils promising avenues for therapeutic interventions. Targeting these channels holds potential for manipulating immune responses, developing strategies to bolster the host's defense against infections, and potentially mitigating immune-related disorders.

Keywords: Bacterial endotoxin; Lipopolysaccharides; Transient receptor potential; Pathogen-associated molecular patterns

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Introduction

Lipoteichoic Acids (LTA) and Lipopolysaccharides (LPS) are the two principal components of the cell walls of gram-positive and gram-negative bacteria, respectively. At the onset of an infection these bacterial substances and toxins are released as a result of their multiplication or lysis, resulting in changes in the cell environment [1]. Some TRP channels are sensitive to these specific molecules or changes. Upon detection of these pathogenic cues, the TRP channels undergo conformational changes or activation. This activation can result in the influx of ions (such as calcium or sodium) into the cell [2]. The influx of ions serves as a signal that triggers various cellular responses, including the activation of immune pathways or the release of signaling molecules to alert neighboring cells about the presence of the pathogen. This mechanism helps the cell recognize and respond to pathogens, initiating immune responses to fight against infections or prevent further invasion.

As we all inhabit a world which is a haven for millions of living forms, human beings are a part of the complex atmospheric milieu. In order to survive our immune system has various strategies thus alerting us from existing infection that pose a threat to de-stabilize homeostasis leading to disease states (Figure 1). Transient Receptor Potential (TRP) channels are group of ionic channels, polymodal sensors and are gated by multiple types of stimuli. They are found in various cell types, including immune cells and they play a significant role in sensing environmental changes, including responding to pathogens. Bacterial infections cause inflammation as well as somatic or visceral pain [3]. The development of these symptoms has been linked to nociceptors becoming activated as a result of immunological activation. However, neuronal activity in the vagal ganglia was shown to occur before the intercellular signaling cascades of the immune system had the time to mature [4]. This review mainly focusses on the significance of TRP as sensors of bacterial toxins and consequently as crucial participants in the detection of pathogens.

The Pathogen-Associated Molecular Patterns (PAMPS) and Damage-Associated Molecular Patterns (DAMPS)

Mammals, have a first-, second-, and third-line immune defense system that is built-in and comprises Pattern Recognition Receptors (PRRs) that are germline-encoded and identify the threat posed by infections and prompt defenses against them. Pathogen-Associated Molecular Patterns (PAMPs) are comprising bacterial cell's membrane and cell wall fragments, toxins, DNA, RNA, etc. which are recognized by these mammalian PRRs and are essential for the pathogenesis, survival and reproduction of microbes. Following PAMP detection by PRRs, a series of events takes place that activate host defense systems to prevent infections, thus strengthening subsequent adaptive immune response. Likewise, PRRs are also capable of identifying molecules such as ATP that are generated following a pathogen invasion that results in tissue injury, and these molecules are known as microbial Damage Associated Molecular Patterns (DAMPs). Therefore, mammalian immune cells recognize bacterial infection through PAMPs and DAMPs [5].

Mammalian Pattern Recognition Receptors (PRRS)

The Toll-Like Receptors (TLR)

A well-known class of PRRs with leucine-rich repeats, namely the Toll-Like Receptors (TLR), are expressed widely by a variety of mammalian cells. When these TLR recognition molecules detect invading pathogens, such as bacteria, viruses, fungi and parasites, they quickly activate our innate and adaptive immune response. TLR1 to TLR10 have been identified as the 10 human TLRs so far [6]. TLRs 2 and 4 trigger an inflammatory immune response during infection, which ultimately results in the invading pathogens' elimination. The first stage in a series of events that result in strong innate immune responses and the establishment of adaptive immunity to pathogens is TLR2 formation of heterodimers with TLR1 and TLR6 [6].

The Human Transient Receptor Potential (TRP) Family of Cation Channels

Transient Receptor Potentials (TRPs) are multimodal cation channels which are emerging as possible therapeutic targets with their role in the modulation of inflammation via innate immune system. There is a member of the TRP channel family expressed in nearly every cell of the body and having a multitude of functions, including as controlling temperature, pain perception, carcinogenesis, and the equilibrium of Ca^{2+} and glucose. Due of their heightened sensitivity to strong mechanical, thermal, and irritating chemical stimuli, sensory neurons are also equipped to detect danger. They exhibit many of the same biochemical mechanisms involved in sensing danger.

Tauseef et al. [7] demonstrated that LPS induces lung endothelial barrier breakdown and inflammation, after TLR4-driven diacylglycerol synthesis, which in turn causes TRPC6-dependent Ca^{2+} flow in endothelial cells. Similarly, Santoni et al. [8] also provided strong evidence to the major role of TRP channels in mediating bidirectional signaling with known PRRs, PAMPs, and DAMPs, which in turn leads to inflammasome activation. As a result of expression of PRRs, such as Toll-like receptors 3, 4, 7, and 9, this activation causes TRP sensitization and the generation of inward currents. Furthermore, a function for TRPs in inflammasome-mediated neurodegenerative disorders is strongly supported by the presence of inflammasomes in neurons and the involvement of TRPs in illnesses of the central nervous system. In this review we attempt to throw light into the pathophysiology of inflammatory illnesses by summarizing our current understanding of the interactions between immune cells and PRRs and ion channels of TRP families with PAMPs and DAMPs.

TRP channels are mostly noted for their role in various sensory functions [9,10] *viz*.

- **Temperature sensitivity:** TRPM8, TRPV1, TRPV2, and TRPV4 channels.
- **Perception of pain:** TRPV1 channel play a role in pain that can result from tissues becoming inflamed or damaged during infections. In certain situations, pathogen or immune system signals may cause TRP channels to react indirectly.
- **Chemical sensitivity:** TRPA1 and TRPM2 channels senses certain substances like pathogen debris that can activate them as part of the body's reaction to an infection.
- **Calcium signaling:** A large number of TRP channels are permeable to calcium ions. A lot of cellular functions, such as immune cell activation and pathogen defense, depend on the regulation of calcium ion influx by TRP channels.

Moreover, because of their adaptability to different stimuli, they may be able to aid the body's defense mechanisms against pathogens. When bacterial components are present, human TRP is activated, causing the appropriate reactions:

- **Chemotaxis and migration:** It has been suggested that TRP channels are involved in the early immune response to infections by controlling the chemotaxis and migration of immune cells towards areas of infection.
- **Inflammation:** TRP channels are implicated in the inflammatory response. For instance, they might detect danger signals released during infections, activating immune cells and triggering the release of inflammatory mediators. The production and release of inflammatory mediators, as well as the regulation of cell migration and phagocytosis, are only a few of the diverse spectrum of TRP channel-mediated functions in immune cells [11].

TRP channels as Sensors of Bacterial Endotoxins

TRPA1: The identification of TRPA1 as an endotoxin sensor resulted from an initial study involving endotoxin detection by TRP channels. *Escherichia coli* LPS has been demonstrated to stimulate sensory neurons in mice that have been isolated from the nodose and trigeminal ganglia. Rather than depending on TLR4, functional TRPA1 expression was required for LPS activation in sensory neurons [10]. Studies highlight the function of TRPA1 as an LPS sensor, inducing quick responses like pain and directing the course of inflammation. As previously suggested, sensory neurons express many TRP ion channel members, whether or not they co-express TRPA1, which is known to have a significant involvement in neurogenic inflammation.

TRPV1, TRPM3 and TRPM8: In sensory neurons, TRPA1 expression partially overlaps with activated TRPV1 and TRPM3. Both of these latter channels are implicated in neurogenic inflammation and the stimulation-induced release of peptidergic

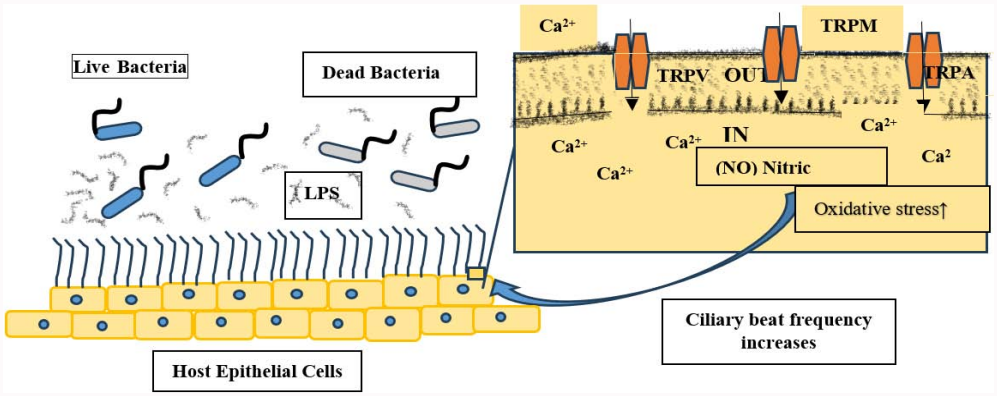

Figure 1: The activation of TRPV/TRPM/TRPA channels in epithelial cells caused by LPS shed by gram-negative bacteria during colonization near the epithelial surface results in a Ca^{2+} influx. This influx sets off acute cellular responses, including the production of bactericidal nitric oxide and an increase in ciliary beat frequency followed by lysis of bacteria due to oxidative stress.
TRP: Transient Receptor Potential; LPS: Lipopolysaccharide; Ca^{2+}: Calcium ion; ↑ increase

modulators. Additionally, cold hyperalgesia in inflammatory conditions is associated with sensory neuron expression of TRPM8. As a result, LPS activity was found on TRPM8, TRPM3, and TRPV1. TRPV1 was found to be a significant factor in the elevation of intracellular Ca^{2+} concentration that is induced by LPS in primary cultured mouse DRG neurons. It is well known that TRPV1 activation in nociceptive neurons causes burning pain and releases neurogenic substances, including substance P and CGRP, which cause neurogenic inflammation. Although TRPM3 activity has been linked to inflammatory pain, there is currently no evidence linking it to pathogen sensing. A future study should examine the TRPM3 synergistic effects with TRPA1, TRPV1 or TLR4-mediated signaling despite the minimal direct effect of LPS [12].

TRPV4: According to studies, LPS causes the production of bactericidal nitric oxide and an increase in the frequency of the mammalian ciliary beat by activating TRPV4 channels in airway epithelial cells [10].

TRP Channels as Targets for Drug Discovery

TRP (Transient Receptor Potential) channels are being investigated as targets for drug development. Upon interaction with pathogenic cues, TRP channels undergo conformational changes or activation, initiating a sequence of intracellular events. Activation of these channels triggers the influx of ions, predominantly calcium, into the cell. This influx acts as a primary signaling event, stimulating downstream pathways pivotal in orchestrating immune responses.

The activation of immune responses through TRP channels involves intricate crosstalk with various cellular components. This includes interactions with immune receptors, signaling molecules, and pathways. TRP channels not only detect the presence of pathogens but also modulate immune responses by influencing cytokine release, activating immune cells, and regulating the inflammatory milieu [13].

Several factors make TRP cation channels attractive as drug targets

1. Although ion channels have been successful as drug targets, achieving subtype selectivity has always been a major challenge, especially for voltage-gated sodium and calcium channels. Because members of the TRP channel family have less homology with each other, identification of subtype-selective compounds may be more easily achieved. TRP channels act as integrators of several well-described signaling systems, including those that are mediated by cell surface receptors (for example, G Protein-Coupled Receptors (GPCRs) and growth factor receptors).

2. In humans, disease can be caused by mutations in a significant number of TRP channel-encoding genes. According to preliminary studies in the field of pain, specific TRP channels - known as thermos TRP channels have the ability to cause sensory nerve impulses to be triggered in response to thermal and chemical stimuli. Though the most advanced application of TRP channels today is in pain research, an increasing amount of work in human genetic association studies and animal gene deletion studies has demonstrated the critical roles TRP channels play in pathophysiology beyond the sensory nervous system [14].

In fact, the variety of functions performed by TRP channels is not fully captured by the general classification of them as environmental cue sensors. In fact, certain TRP channels work on intracellular membranes and many TRP channels are triggered by second messenger signaling cascades that are started by receptor activation. A number of pathophysiological processes, such as pain, cardiac hypertrophy, respiratory reflex hypersensitivity and ischemic cell death are linked to TRP channels.

Furthermore, a number of human gene association studies have revealed that Single-Nucleotide Polymorphisms (SNPs) in the promoters and/or coding regions of the genes encoding TRP channels are either linked to a higher risk of multifactorial diseases or they seem to be the cause of uncommon heritable conditions. It's interesting to note that these mutant TRP channels typically exhibit increased activity when expressed in recombinant systems, indicating that blocking these channels might have therapeutic benefits.

In contrast, the identification of chemical modulators of TRP channels is still in its infancy. To date, target validation of TRP channels has primarily been generated *via* genetic studies. Numerous naturally occurring ligands, such as menthol and capsaicin, have contributed significantly to our understanding of the pharmacology of TRP channels. These molecules rarely exhibit the potency, selectivity, and/or physical qualities that are desired in contemporary drug discovery programs, despite the fact that they can be instructive when employed as tools for compound screening [15].

Conclusion

Although the majority of TRPs exhibit limited expression patterns, with diverse tissue distribution in humans, their physiological roles and regulatory mechanisms influence how they are connected to various diseases. These encompass a variety of disorders were targeting one or more TRP channels may reduce symptoms or have therapeutic effects, as well as both genetic and acquired channelopathies.

Moreover, TRP channels demonstrate a nuanced ability to integrate multiple stimuli, allowing cells to distinguish between harmless fluctuations in the environment and pathogenic threats. This discriminatory capability enables the immune system to mount precise responses tailored to combat specific pathogens while preventing unnecessary immune activation.

In summary, the intricate interplay between TRP channels and pathogen recognition underscores their pivotal role as sophisticated detectors, orchestrating immune responses against a diverse array of pathogens. Unravelling the complexities of this interplay opens doors to innovative strategies aimed at bolstering the immune defense machinery while averting immune-related disorders. However, the precise mechanisms through which TRP channels could detect pathogens or their constituents directly, however, remain a topic of ongoing investigation and discussion within the scientific community.

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