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AN INSIGHT INTO CROSSTALK'S BETWEEN HOST ASSOCIATED-TRANSIENT RECEPTOR POTENTIAL CHANNELS AND BACTERIAL TOXINS: A FUTURE POSSIBILITY AS TARGETS FOR DRUG DEVELOPMENT

Microbiology

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ABSTRACT

The role of transient receptor potential (TRP) channels as pathogen sensors presents a compelling narrative in understanding cellular defence mechanisms against microbial invasion. We dwell into 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 signalling pathways. These signalling cascades orchestrate a robust immune response, encompassing the activation of immune cells, release of cytokines, and the priming of neighbouring cells to fortify their defences against the invading pathogens. Understanding the intricacies of TRP channels as pathogen sensors unveils promising avenues for therapeutic interventions. Targeting these channels holds potential in manipulating immune responses, strategies to bolster the host defence against infections, and potentially mitigating immune-related disorders. Unravelling the nuances of TRP-mediated pathogen sensing, offers promising prospects for novel therapeutic interventions aimed at bolstering the body's defence mechanisms.

KEYWORDS

endotoxin, lipopolysaccharides, transient receptor potential, pathogen-associated molecular patterns.

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 [Szentirmai É *et al.,* 2021]. 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 [Martinac, B, 2004]. The influx of ions serves as a signal that triggers various cellular responses, including the activation of immune pathways or the release of signalling molecules to alert neighbouring 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.

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. The 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 [Fernández-Ballester G *et al,* 2023]. The development of these symptoms has been linked to nociceptors becoming activated as a result of immunological activation. 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 defence system that is built-in and comprises Pattern Recognition Receptors (PRRs) that are germline-encoded and identify the threat posed by infections and prompt defences against them. Pathogen-associated molecular patterns (PAMPs) are comprising bacterial cell's membrane and cell wall fragments, toxins, DNA, RNA, etc. which are recognised 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 defence 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 recognise bacterial infection through PAMPs and DAMPs [Amarante-Mendes GP *et al*, 2018].

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, they quickly activate our innate and adaptive immune response [Oliveira-Nascimento L *et al,* 2012].

THE HUMAN TRANSIENT RECEPTOR POTENTIAL (TRP) FAMILY OF CATION CHANNELS

Here, we emphasize the multimodal cation channels, namely the Transient receptor potentials (TRPs) 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.

Tauseef and colleagues (2012)[6] demonstrated that LPS induces lung endothelial barrier breakdown and inflammation, after TLR4-driven diacylglycerol synthesis, causes TRPC6-dependent Ca^{2+} flow in endothelial cells. Similarly, Santoni *et al.* (2015)[7] also provided strong evidence to the major role of TRP channels in mediating bidirectional signalling with known PRRs, PAMPs, and DAMPs, which in turn leads to inflammasome activation. Expression of PRRs, such as Toll-like receptors 3, 4, 7, and 9 causes TRP sensitization and the generation of inward currents of Ca^{2+} ions inside cell. 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 highlight the pathophysiology of inflammatory illnesses by summarising our current understanding of the interactions between immune cells and PRRs and ion channels of TRP families with PAMPs and DAMPs.

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 (Boonen et al., 2018). 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 modulators. According to studies, LPS causes the production of bactericidal nitric oxide (Figure 1) and an increase in the frequency of the mammalian ciliary beat by activating TRPV4 channels in airway epithelial cells [Boonen *et al,* 2018].

cells [Boonen *et al,* 2018].

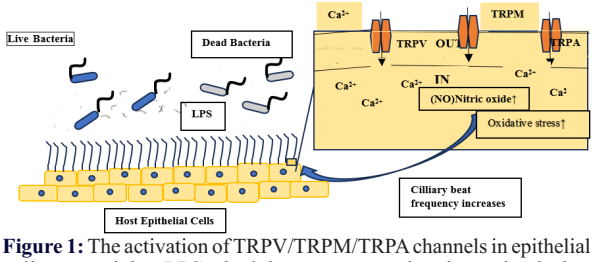

Figure 1: The activation of TRPV/TRPM/TRPA channels in epithelial cells caused by LPS shed by gram-negative bacteria during colonisation near the epithelial surface results in a Ca^{2+} influx. This influx sets off acute cellular responses, including the production of bactericidal nitric oxide and an 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.

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 signalling 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, signalling 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 (Vrenken et al., 2016). Several factors make TRP cation channels attractive as drug targets:

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 signalling systems, including those that are mediated by cell surface receptors (for example, G protein-coupled receptors (GPCRs) and growth factor receptors).

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 (Koivisto et al., 2022).

In fact, the variety of functions performed by TRP channels is not fully captured by the general classification of them as environmental cue sensors. Certain TRP channels work on intracellular membranes and many TRP channels are triggered by second messenger signalling 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. These encompass targeting one or more TRP channels may reduce symptoms or have therapeutic effects, in both genetic and acquired channelopathies.

CONCLUSION

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 defence machinery while averting immune-related disorders [Bose P *et al*, 2015]. 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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