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Popular Article

Mitochondria and its role in immunity

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Abstract

Mitochondria, often referred to as the "powerhouses of the cell," play a crucial role in immunity. These double-membraned organelles are responsible for generating adenosine triphosphate (ATP), the cell's primary energy source. In the context of immunity, mitochondria contribute to several key functions. First, they are involved in the production of reactive oxygen species (ROS), which serve as signalling molecules in immune responses. Additionally, mitochondria regulate cellular metabolism, influencing the differentiation and activation of immune cells, such as T cells and macrophages. Mitochondria also participate in the activation signalling cascade of various immune response. Dysfunctional mitochondria can lead to compromised immune responses, as seen in various diseases. In summary, mitochondria play an essential role in the orchestration of immune responses through energy production, signalling, metabolic regulation, and ROS production, highlighting their significance in maintaining immune system function.

1. Introduction

Mitochondria are vital, double-membraned organelle present in the cells of almost all eukaryotes. Often nick named as the "powerhouses of the cell," these remarkable structures play a central role in energy production and various cellular processes. Mitochondria are so peculiar as they contain its own genetic material as DNA and can replicate independently, suggesting an ancient evolutionary origin from symbiotic bacteria. They convert nutrients, mainly fatty acids (FA's) and glucose, into adenosine triphosphate (ATP) through a process known as oxidative phosphorylation. ATP are one amongst high energy molecule that fuels cellular activities, making

mitochondria indispensable for the survival and functioning of eukaryotic cells. Beyond energy production, they are also been part of numerous other essential functions, such as regulating cell apoptosis (programmed cell death), maintaining calcium levels, and influencing cellular metabolism such as intermediary metabolism. These organelles are highly dynamic and can change their shape and number to adapt to the cell's energy demands. Mitochondrial dysfunction has been linked to a range of diseases, including neurodegenerative disorders and metabolic conditions. It was first noticed by Albert von Kolliker in 1856 and the term mitochondria was coined by Carl Brenda in the year 1898. It derived from 2 words; Mitos means “thread” and chondros means “grain”.

2. Origin & evolution

The genesis and evolution of mitochondria represent a fascinating chapter in the story of life on Earth. Mitochondria are believed to have originated over 1.5 billion years ago through a symbiotic relationship between ancestral eukaryotic cells and alpha-proteobacteria. This theory is known as endosymbiosis, which was put forward by Lynn Margulis in 1967. According to the endosymbiotic theory, a host cell engulfed an alpha-proteobacterium, forming a symbiotic relationship where the bacterium provided energy to the host cell through oxidative phosphorylation (a process that generates ATP) in exchange for protection and nutrients. Over time, this relationship became mutually beneficial, and the engulfed bacterium evolved into the modern mitochondrion, losing some of its independence but gaining a stable home within the host cell through the process of endosymbiotic gene transfer and lateral gene transfer which is supported by CoRR (Co-location for redox regulation hypothesis).

Other evidence supporting this theory includes the structural similarities between mitochondria and free-living alpha-proteobacteria, the presence of mitochondrial DNA resembling bacterial DNA, and the fact that mitochondria replicate independently within the cell, much like free-living bacteria. This symbiosis allowed eukaryotic cells to become more efficient and diverse, leading to the development of complex multicellular organisms. The incorporation of mitochondria facilitated the evolution of oxygen-dependent metabolism, making it possible for eukaryotes to thrive in oxygen-rich environments, that we see today.

3. Mitochondria; providing energy to the immune cells

Immune cells, such as T cells, B cells, macrophages, and neutrophils, have specific energy requirements to carry out their roles in the immune system. Here's how mitochondria quench the energy thirst of immune cells:

1. **Activated Immune Cells***:* When immune cells are triggered to the stimulus of an infection or

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other immune challenges, they need to rapidly replicate, differentiate, and carry out their immune functions, such as phagocytosis or the release of signalling molecules. This increased metabolic activity requires higher ATP production, which is facilitated by mitochondria.

2. **Mitochondrial Respiration:** Immune cells primarily rely on mitochondrial respiration to generate ATP. During this process, glucose and other energy substrates are broken down within the mitochondria to produce ATP and other products. The electron transport chain, embedded in the inner wall of double membrane, is a crucial component of this process.
3. **Fatty Acid Oxidation***:* In addition to glucose, immune cells can also use fatty acids as an energy source. Fatty acid oxidation occurs within mitochondria, where fatty acids are broken down to generate ATP. This is particularly important for immune cells in tissues with high fatty acid content, like adipose tissue.

The energy utilization in immune cells depends on the specific ligands and receptors engaged and also the microenvironment in which they operate. Monocytes and M2 macrophages predominantly utilize mitochondrial energy metabolism. This means they primarily rely on oxidative phosphorylation (OXPHOS) within their mitochondria to generate ATP when responding to particular signals and operating in specific microenvironments. In contrast, M1 macrophages primarily rely on glycolysis, which is a less efficient but faster way to generate energy from glucose, indicating a preference for this metabolic pathway when activated under different conditions. Activated B and T lymphocytes are mostly dependent on oxidative phosphorylation (OXPHOS), emphasizing the importance of mitochondrial energy production in supporting their immune functions when they engage specific ligands and operate in particular microenvironments.

In summary, mitochondria are vital for immune cells to meet their energy demands and carry out their functions effectively. These organelles are central to the metabolism and activation of immune cells, allowing them to respond to infections and other immune challenges.

4. **Mitochondrial DNA; as DAMP**

Mitochondrial DNA (mt-DNA) can act as a Damage-Associated Molecular Pattern (DAMP) when it is spill over to the extracellular space in response to cellular damage or stress. DAMPs are molecules that signal tissue injury or cellular stress to the immune system and trigger an inflammatory response. When cells are damaged due to various factors, such as infection, trauma, or cellular stress, they can release their contents, including mt-DNA, into the surrounding tissues. Extracellular mt-DNA can be recognized by the receptors of immune system as a signal of cellular damage, similar to how pathogen-associated molecular patterns (PAMPs) from bacteria

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or viruses are recognized as signals of infection, due to their conserved CpG islands which are non-methylated which cannot be seen in eukaryotes. Mitochondrial DNA is been recognised by the TLR 9 receptors of innate immune system to activate p38MAPK pathways to activate the neutrophils. Similarly, the formyl peptides present on the mitochondrial proteins also bind to the FPR1 (formyl peptide receptor 1) to recruit PMN cells to the site. Similarly, cardiolipin seen in the mitochondrial membrane also activate the NLRP3 inflammasome through the activation of TLR4 receptors.

Recognition of mt-DNA as a DAMP can led to the activation of the immune system, resulting in an inflammatory response. This inflammatory response can be beneficial in many cases, as it helps recruit immune cells to the site of damage, clears cellular debris, and promotes tissue repair and regeneration. Its also speculated that mt-DNA also activates IL-1β through an unknown receptors.IL-1 β is considered as a potent cytokine involved as an major activator of monocytes and pathways in the pro-inflammatory pathway cascades. However, in some situations, excessive or uncontrolled release of mt-DNA can lead to chronic inflammation and be associated with various diseases, including autoimmune disorders and inflammatory conditions.

5. Mitochondrial DNA; as extra cellular DNA traps

Extracellular DNA traps, often referred to as DNA traps or extracellular traps (ETs), are structures composed of chromatin (DNA and associated proteins) that are released by certain immune cells, primarily neutrophils and other granulocytes, during conditions like infections and inflammation. These DNA traps, formed by immune cells is composed of mt-DNA, histones, antimicrobial peptide LL-37, neutrophil elastase, cathepsin G, proteinase 3, lactoferrin, and tryptase. These extracellular DNA traps are typically designed to capture and immobilize pathogens, such as bacteria, fungi, and parasites, as working arm to the innate immune response. Mitochondrial DNA (mt-DNA), as a specific subset of cellular DNA, can indeed be found within these extracellular DNA traps, especially when the immune cells are under conditions of stress, infection, or inflammation. mt-DNA being a genetic material can evoke the immune response, and when released into extracellular traps, it can contribute to the overall effectiveness of these structures in pathogen capture and immune defence.

Extracellular DNA traps, whether they contain nuclear DNA or mt-DNA, are thought to serve several important functions:

a) **Pathogen Capture:** They can ensnare and immobilize invading pathogens, preventing their spread.

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b) **Localized Immune Response:** The DNA traps help concentrate antimicrobial molecules and enzymes in the vicinity of the trapped pathogens.
c) **Signalling:** They can release inflammatory signals and activate nearby immune cells.
d) **Tissue Damage:** In some cases, excessive DNA trap formation can lead into tissue damage to sets in inflammation, particularly in conditions where the immune response is dysregulated.

Therefore, while nuclear DNA is a major component of these extracellular DNA traps, mt-DNA, with its distinct genetic material and potential immunogenic properties, can also be present and contribute to the immune response, particularly in situations where mitochondrial stress or damage occurs.

6. Mitochondria; as a signalling hub for immune system

Innate immune signalling is intricately regulated by fundamental host metabolic functions, including oxygen consumption, ATP production, and potentially biosynthetic pathways that rely on mitochondrial activity and overall mitochondrial fitness, as suggested by Arnoult et al. One essential component of this regulation is the Mitochondrial Antiviral Signalling Protein (MAVS), which serves as an adaptor protein in the innate immune response. Upon activation, MAVS triggers a cascade of downstream events, which leads to the formation of key signalling molecules. For instance, MAVS activation can stimulate the transcription factors IRF3 and IRF7, resulting in synthesis of type 1 interferons (IFNs), crucial in antiviral defence. Additionally, MAVS activation can also induce the Nuclear Factor-κB (NF-κB) pathway, which culminate in the translation of pro-inflammatory cytokines such as TNF-α and IL-1β. This orchestrated response is crucial in combating infections and mounting an effective immune defence.

Moreover, in the context of innate immunity, there is an evolutionarily well safeguarded signalling molecule known as ECSIT (Evolutionarily Conserved Signalling Intermediate in Toll pathway). ECSIT plays a significant role in various immune responses, particularly within the Toll-like receptor signalling pathway, which is vital for detecting and responding to pathogens. Furthermore, the regulation of innate immune signalling involves intricate molecular interactions within the mitochondria. For example, the internalized NLRX1 protein interacts with UQCRC2, a component of complex 3 of the mitochondrial respiratory chain. This interaction serves as a regulatory mechanism, potentially impacting the overall function of the electron transport chain present in the mitochondria.

Additionally, the production of reactive oxygen species (ROS) is another important regulatory factor in innate immune signalling. ROS can modulate several signalling pathways,

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including NF-κB, JAK-STAT, and the caspase-1 inflammasome. These ROS-mediated adjustments play a integral role in fine-tuning the immune response and maintaining immune homeostasis, ensuring an appropriate and effective defence against various threats.

7. Conclusion

Mitochondria serve as the primary energy source for the immune system, with only a few exceptions. The immune mechanism itself is an energy-intensive process, demanding ample energy to function efficiently. Mitochondrial DNA, referred to as mt-DNA, plays an integral role in immune activation as a Damage-Associated Molecular Pattern (DAMP). This mt-DNA serves as a crucial cue for initiating the innate wing of the immune system, enabling a rapid response to potential threats.

Additionally, mt-DNA acts as extracellular DNA traps, contributing to a vital immune mechanism that helps the body prevent the spread of deadly pathogens. These traps ensnare foreign genetic material and restrict the pathogens' movement, bolstering the body's defence. Furthermore, mitochondria are integral to immune signalling through MAVS (Mitochondrial Antiviral Signalling Protein), enhancing their involvement in orchestrating immune responses and defending the body against various threats.

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