Inflammation: A Double Edge Sword In Immunity

The latest research suggests NAD+ may play a central role in regulating inflammation for an effective—but targeted—immune response to dangerous pathogens such as the Coronavirus.

Taming The Beast Of Inflammation

In the midst of the COVID-19 pandemic, supporting innate immunity is top of mind. The immune system is *essential* for recognizing and destroying cells that have become infected to stop the spread of pathogens.

Inflammation is part and parcel to the immune response. While some inflammation is visible to the naked eye, similar to the skin turning red and itchy after a bug bite, much inflammation that occurs is hidden deep inside the body's organs—but it can still have a powerful, tangible effect. The deadly acute respiratory distress syndrome (ARDS) seen in many coronavirus patients is an example of inflammation gone horribly wrong.

When a virus infects immune cells, the Nod-like receptor family protein 3 (NLRP3) inflammasome activates your inflammatory response. This inflammatory response is a forest fire that burns everything in its path—producing an onslaught of reactive oxygen species (ROS) which

damage viral particles as well as your own DNA and proteins [1].

But the inflammation also activates two major repair proteins, Sirtuins and Polyadenosine diphosphate-ribose polymerases (PARPs), which may be essential in helping the cells survive the infection. Both of these enzymes modify]proteins to try and repair the damage as well as to limit the virus's ability to replicate [2-4].

The Quest For A Coronavirus Cure

Many of these pathways are currently being investigated as potential Coronavirus solutions. The aforementioned PARP proteins have been shown to modify Coronavirus genetic material and proteins, in an attempt to prevent it from replicating and spreading between the cells of the lungs and throughout the body.

Unfortunately, the Coronavirus has evolved a counter-defense to remove the modifications made by PARPs, leading to a "cat and mouse" game that drains cells of vital stores of NAD+ [5].

Likewise, the protective enzymes Sirtuins, also activated by inflammation, rely on the molecule NAD+ to regulate the inflammatory response and prevent excessive DNA damage. The "goldilocks zone" of inflammation struck by PARP and Sirtuins seems to all be powered by the ubiquitous NAD+.

Could Boosting NAD+ Mean Supporting Immunity?

The depletion of NAD+ by the immune response and inflammation may help invaders like the Coronavirus get a foothold in the body.

A study of infected human lungs suggests the virus may even try to suppress cells from producing new NAD+ [6]. COVID has been shown to deplete NAD+ levels by as much as 70%, weakening infected cells in turn [7]. In an essential immune cell called a macrophage, NAD+ depletion has been linked to immune dysfunction [8].

In fact, COVID seems to target high energy expenditure organs, like lungs, kidneys and intestines [9]—organs that need all the NAD+ they can get.

Could boosting cellular levels of NAD+, with NAD+ precursors, actually help fight off infection? That's what is under investigation in preclinical models as well as human subjects at this very moment.

The Ongoing Research On Immunity And NAD+ Precursors

Nicotinamide Riboside (NR) and other NAD+ precursors are currently being studied for their potential role in supporting immunity and containing inflammation.

In preclinical models (like cells and mice) [10], NR has been demonstrated to boost protective Sirtuins and

decrease levels of inflammation-promoting signaling molecules called cytokines. In healthy older men, NR has been shown to decrease the levels of many inflammatory cytokines that have been implicated in the body's overzealous response to COVID [11, 12].

NMN, another NAD+ precursor, has also been shown to play an anti-inflammatory role in preclinical models. In a rodent model of hemorrhagic shock, NMN was found to significantly decrease levels of lactic acidosis and interleukin (IL) 6 levels [13]. Through the reduction of inflammatory cytokines IL-6, as well as a slight decrease of TNF-α, NMN improved shock-induced hyperglycemia—successfully reducing inflammation [13].

Fighting off infections with inflammation is the immune system playing with fire—the inflammation may destroy the virus, but it can also burn the host. Thankfully, scientists are learning more and more about the role of protective enzymes like Sirtuins and PARP, and the importance of the cellular energy molecule, NAD+, in supporting immunity.

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