

Study explores emerging role of NAD⁺ in innate and adaptive immune responses

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Researchers at Brigham and Women's Hospital (BWH) have discovered a new cellular and molecular pathway that regulates CD4⁺ T cell response—a finding that may lead to new ways to treat diseases that result from alterations in these cells. Their discovery, published online in the *Journal of Allergy and Clinical Immunology*, shows that administering nicotinamide adenine dinucleotide (NAD⁺), a natural molecule found in all living cells, shuts off the capacity of dendritic cells and macrophages to dictate CD4⁺ T fate. Researchers found that NAD⁺ administration regulated CD4⁺ T cells via mast cells (MCs), cells that have been mainly described in the context of allergy, exclusively.

"This is a novel cellular and molecular pathway that is distinct from the two major pathways that were previously known. Since it is distinct and since it has the ability to regulate the immune system systemically, we can use it as an alternative to bypass the current pathways," said Abdallah ElKhal, PhD, BWH Department of Surgery, senior study author.

CD4⁺ T [helper cells](#) and dendritic cells play a central role in immunity. Alterations or aberrant dendritic cells and T cell responses can lead to many health conditions including [autoimmune diseases](#), infections, allergy, primary immunodeficiencies and cancer.

As of today, two major pathways have been described to regulate CD4⁺ T cell response. The first pathway was described by Peter C. Doherty and Rolf M. Zinkernagel (1996 Nobel prize winners) showing the

requirement of MHC-TCR signaling machinery. More recently, a second mechanism involving the Pathogen or Damage Associated Molecular Patterns (PAMPs or DAMPs) was unraveled by Bruce A. Beutler and Jules A. Hoffmann (2011 Nobel Prize winners). Of importance, both pathways require antigen presenting cells (APCs) in particular [dendritic cells](#) (DCs) or macrophages (Mφ). Elkhal's novel pathway is distinct from the two previous ones and may offer a path forward for novel therapeutic approaches.

For the current study, BWH researchers performed pre-clinical trials using an experimental infection model. They showed that mast cell-mediated CD4+ T cell response protects against lethal doses of infection (*Listeria monocytogenes*). Mice treated with NAD+ had a dramatically increased survival rate when compared to the non-treated group.

"Collectively, our study unravels a novel cellular and molecular pathway that regulates innate and adaptive immunity via MCs, exclusively, and underscores the therapeutic potential of NAD+ in the context of a myriad of diseases including autoimmune diseases, hemophilia, primary immunodeficiencies and antimicrobial resistance," said Elkhal.

More information: Hector Rodriguez Cetina Biefer et al, Mast cells regulate CD4+ T cell differentiation in absence of antigen presentation, *Journal of Allergy and Clinical Immunology* (2018). [DOI: 10.1016/j.jaci.2018.01.038](#)

Provided by Brigham and Women's Hospital

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