Globally, tuberculosis (TB) from infection with *Mycobacterium tuberculosis* (MtB) causes more deaths than any other bacterial infectious disease. TB is highly prevalent in low- and middle-income countries and patients with active TB may present with fever, weight loss, and tiredness. Current treatments either directly target and kill MtB or they amplify immune-response mechanisms to fight the infection. However, treatments are not fully effective and new treatments as well adjunctive therapies (those that complement existing treatments) are needed.

Following infection, an inflammatory response ensues, and if this inflammation is not eventually resolved it can cause lung damage, pulmonary dysfunction, and/or pulmonary fibrosis (a disease marked by lung scarring and tissue damage). Consequently, TB can have profound effects on patients’ quality of life. Through their research, Dr Esmeralda Juárez and her team provide vital insights into lung immune-response mechanisms and work to identify potential therapeutic targets which help reduce inflammation without affecting the body’s ability to destroy the bacteria. The research team also explore the utility of a non-invasive method to collect biomarkers and markers of inflammation and oxidative stress from the lungs in exhaled breath condensate (EBC).

Their recent pilot study published in the journal *Antioxidants* revealed different quantities of biomarkers in exhaled breath of TB patients compared to healthy individuals. This suggests measurement of such biomarkers associated with lung damage can be used to both monitor patients over time to assess disease progression and to develop therapeutics.

**THE IMMUNE RESPONSE AND INFLAMMATION IN TB**

Pathogens need to be recognised by the body in order for the innate immune response to be triggered and the pathogen to be removed. Pattern recognition receptors such as Toll-Like receptors (TLRs) and nucleotide-binding oligomerization domain (NOD) receptors on cells such as macrophages (a type of white blood cell), have important roles in recognising foreign pathogens and launching an innate immune response to eliminate them. Macrophages have a key function of phagocytosis (the process of a cell ingesting and eliminating pathogens). Consequently, they evoke an immune response to help eliminate those pathogens. Macrophages are found throughout the body and are present in the lungs in the form of alveolar macrophages. These alveolar macrophages stimulate the release of pro-inflammatory cytokines which in turn recruit further immune cells, commencing the inflammatory process. Alveolar macrophages also have important anti-microbial activities and are vital in the defence and clearance of MtB from the lungs.

During infection, cytokines induce macrophages to release tumour necrosis factor alpha (TNF-α) which kills MtB by releasing reactive oxygen species (ROS) and reactive nitrogen species (RNS). An increase in ROS alters the redox state (the presence and balance of ROS) which causes oxidative stress. Eicosanoids (polyunsaturated fatty-acid-derived signalling molecules) have a critical role in balancing inflammation and resultant oxidative stress with the resolution of inflammation. The inflammatory response is needed to clear infection, but a prolonged inflammatory state and lack of antioxidant mechanisms can result in damage to lung tissue. Once the infection is eliminated, the inflammation must be reduced so that the cells and tissues can return to a homeostatic state. This requires pre-resolving eicosanoids which include the omega-3 fatty-acid-derived mediators such as Resolvins D1 and Maresin 1.

**ADJUNCTIVE THERAPIES FOR TB**

Host directed therapy (modulating the host’s inflammatory response to eliminate the bacteria as opposed to targeting it directly) is a key area of focus for Juárez’s research team. By regulating or stimulating the body’s immune response, the removal of MtB from the lungs can be accelerated. Innovative studies published by Juárez and colleagues in 2012 and 2014 elucidated the role of NOC02 and NOC01, respectively, in alveolar macrophage response to TB infection. The 2012 study discovered a new function of NOC02 in...
Behind the Research

Dr. Esmeralda Juárez

Research Objectives

Dr. Esmeralda Juárez and her team research TB disease mechanisms through biomarker discoveries.

Detail

Address

Calle 4502, Sección XVI, Tlalpan, 14080 Mexico City, Mexico

Bio

Esmeralda Juárez studied lung immune responses for over 20 years at the Department of Research in Microbiology in the National Institute of Respiratory Diseases in Mexico City, Mexico. She believes that by looking into the alveolar space, we will find answers for better treatment, following up, and management of pulmonary tuberculosis.

Institute

INSTITUTO NACIONAL DE ENFERMEDADES RESPIRATORIAS ISMAEL COSÍO VILLEGAS

References


Personal Response

Does your research team have plans to study the utility of EBC in patients with latent TB?

Yes, of course. We have several projects in mind. We want to understand the exhaled metabolites patterns in latent TB patients. Also, determine whether the exhaled metabolites patterns change along with the treatment in susceptible and multi-drug resistant TB patients. In either case, we could find signatures with the potential to aid in treatment success evaluations.

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