PhD Position - 3 years - Starting October 2020

Title

Role of the anion channel LRRC8/VRAC in NLRP3 inflammasome activation

Abstract

Chloride channels are used by cells to regulate a wide variety of cellular functions such as transepithelial transport, membrane excitability, cell volume or intracellular pH. However, the lack of specific inhibitors and the diversity of families of chloride channels strongly limited their studies. Thus, the lack of information on their locations, structures and functions leads to their underuse as therapeutic targets.

This is particularly the case of the LRRC8 family (Leucine-Rich Repeat Containing 8) newly identified and expressed in a ubiquitous manner. The LRRC8 family contains 5 subunits, LRRC8A to E, which form heterohexameric channels. LRRC8A is the only mandatory subunit but the stoichiometry of the different subunits within the molecular complex remains unknown. The LRRC8 channels are essential for generating the VRAC current (volume-controlled anion channel) which governs the cellular volume regulation.

In macrophages, the inflammasome NLRP3 is a multiprotein complex activating caspase-1 which controls the maturation of the pro-inflammatory cytokines IL-1β and its subsequent release. This molecular complex is activated by certain molecules originating from pathogenic agents (TLR ligants) and various cellular danger signals such as ATP. This mechanism is the cornerstone of many inflammatory diseases. Dogma admits that the loss of K + mediated by activation of P2X7 receptors induced by extracellular ATP is the main physiological pathway leading to activation of NLRP3. However, this classic view has been challenged by the discovery that extracellular hypotonicity triggers the secretion of IL-1β independently of P2X7. In this process, the processing and secretion of IL-1ß is highly dependent on the loss of intracellular Cl- ions linked to the RVD process and can be blocked by generic inhibitors of the chloride channels.

In this thesis project, we will explore the hypothesis that LRRC8 is a major player in the inflammatory response through three axes:

1- Identify the cellular pathways which connect the activity of the LRRC8 channel to the activation of NLRP3. In particular, we will investigate how variations in intracellular Cl-, redox potential and purinergic pathways control the activation of NLRP3. We will develop macrophage lines whose different LRRC8 subunits have been genetically inactivated to study their contribution to the different signaling pathways leading ultimately to the release of IL-1ß.

2- Look for specific inhibitors of the LRRC8 channels through a pharmacological strategy by screening for venoms and animal toxins.

This project is based on solid preliminary results obtained within the framework of the LabEx consortium "Ion Channel Science and Therapeutics",

This project represents a unique opportunity to better understand the physiology of the chloride channels, with the prospect of developing innovative therapeutic strategies in the context of inflammation.

Keywords

Cellular biology
Electrophysiology
Molecular biology
Pharmacology

Related publications

- Qiu Z, Dubin AE, Mathur J, Tu B, Reddy K, Miraglia LJ et al. SWELL1, a plasma membrane protein, is an essential component of volume-regulated anion channel. Cell 2014; 157: 447–458.
- Voss FK, Ullrich F, Münch J, Lazarow K, Lutter D, Mah N et al. Identification of LRRC8 heteromers as an essential component of the volume-regulated anion channel VRAC. Science 2014; 344: 634–638.
- Compan V, Baroja-Mazo A, López-Castejón G, Gomez AI, Martínez CM, Angosto D et al. Cell volume regulation modulates NLRP3 inflammasome activation. Immunity 2012; 37: 487–500.
- Friard J, Corinus A, Cougnon M, Tauc M, Pisani DF, Duranton C, Rubera I. LRRC8/VRAC channels exhibit a noncanonical permeability to glutathione, which modulates epithelial-to-mesenchymal transition (EMT). Cell Death Dis. 2019 Dec 5;10(12):925.

Funding

The 3-year doctorate will be funded by the LABEX ICST and must imperatively start from October / November 2020 at the Molecular Physiomedecine Laboratory, CNRS-UMR7370, Nice, France, in the Physiology and physiopathology of ion transport group.
The PhD will be carried out under the supervision (co-direction) of Christophe Duranton and Isabelle Rubera.

How to apply : Interested and motivated students should send as soon as possible a CV, a motivation letter, master scores/ranking and reference letters to

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