Proposal for M2 internship 2020/21

Title:

Mechanical properties of neutrophils in acute inflammation

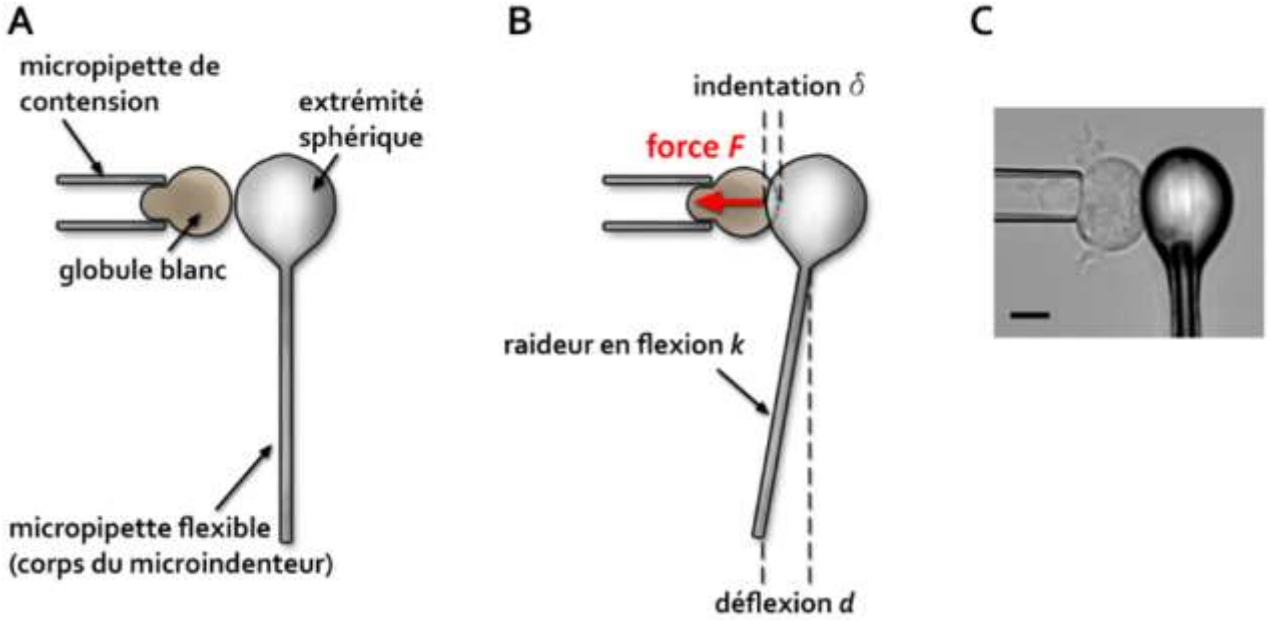
Supervision: Oliver Nüsse (University Paris-Saclay,Institute of Physical Chemistry, Orsay) and
Julien Husson (Ecole Polytechnique, Palaiseau)

Internship description:

The ongoing Covid-19 pandemic has caused over 800 000 deaths worldwide in 9 months. The disease mainly affects the lungs. The immune response of many patients gets out of control and massive liberation of inflammatory cytokines ("cytokine storm") induces major damage.

In fact, most Covid-19 patients in intensive care units suffer from acute inflammation and 2/3 develop acute respiratory distress syndrome (ARDS). One of the characteristics is a massive influx of a particular type of white blood cell, the polymorphonuclear neutrophils, into the lungs. The activation of these leukocytes is probably an essential factor in the destruction of the lungs. In order to control the inappropriate arrival and activation of neutrophils, it is necessary to better understand the underlying mechanisms.

During ARDS the neutrophils are trapped in the pulmonary microvasculature. The mechanism of this leukocyte blocking has not yet been elucidated. Yap et al. (J Appl Physiol 2005) have shown that the passage of neutrophils through very narrow capillaries (~ 5 µm) causes the remodeling of their actin cytoskeleton, itself being directly associated with the mechanical properties of a cell. Preira et al. (Crit Care 2016) showed that serum cytokines from ARDS patients slow the time it takes for neutrophils to pass through narrow microfluidic channels, an indirect measure of the mechanical properties of cells. Cytokines are therefore another factor that can alter the mechanical properties of neutrophils and block them in narrow capillaries. Knowing the mechanical changes of neutrophils during inflammation is important to better understand ARDS and develop therapeutic strategies.



The specific objectives of this project are:
Objective 1: To quantify the evolution of the mechanical properties of leukocytes when they incubate in the presence of cytokines whose concentrations are high in Covid-19 patients.
Objective 2: Determine whether these mechanical changes can be blocked by specific antibodies against the cytokine or its receptor.

The host team has more than 30 years of experience with primary neutrophils and neutrophil-like cell lines. The collaborating team is expert in single cell mechanics. Together, we have successfully conducted a thesis on the mechanical properties of phagocytes.

Keywords : Acute inflammation, neutrophil, mechanics, cytokines

Techniques used during the internship:
The project is taking place in close collaboration with J Husson's team at the Institut Polytechnique de Paris. The mechanical properties will be determined with a microidentification device on single cells under a microscope, developed by J Husson. The project will use neutrophil-like PLB-985 cells (cell line) and primary human neutrophils. We are going to test the amplitude of mechanical changes in neutrophils and the time scale on which they occur. In parallel, we will check the presence of interleukin receptors (primarily IL6 and IL8) on PLB985 cells in comparison with the primary neutrophils. The project requires solid knowledge in mechanics. The experiments involve cell culture, purification of blood cells, microscopy, manipulation of cells under a microscope, flow cytometry.

References
Zak, A. et al. 2019 Single-cell immuno-mechanics: rapid viscoelastic changes are a hall-mark of early leukocyte activation. bioRxiv 851634.

Song, Z.M. et al. 2017. Phosphoinositol 3-phosphate acts as a timer for reactive oxygen species production in the phagosome. J Leuk Biol. 101:1155-1168.

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