Mechanoreceptors initiate innate immunity in response to microbial infections.

Giulia Stucchi[1], Laura Marongiu[1], Giuseppe Rocca[1], Marco Galli[1], Anna Celant[1], Stefano Cozzi[1], Martina Molgora[1], Alessandra Polissi[2], Alessandra Maria Martorana[2], Marina Vai[1], Ivan Orlandi[1], Metello Enzo Innocenti[1], Francesca Granucci[1],
E-mail: giulia.stucchi@unimib.it
[1] University of Milano-Bicocca, Italy
[2] University of Milan, Italy

Keywords: Innate immunity, microbial sensing, tissue mechanosensing

Abstract:

How mammals mount an effective immune response against infectious agents remains an unresolved
fundamental issue in biology. Here, we discovered an unforeseen two-tier mechanism of neutrophil recruitment during infections, in which mechanosensing is key to initiating innate immunity. Leveraging a skin infection model and pathogenic bacteria and fungi, we demonstrate that the early recruitment of neutrophils is mainly danger-driven and partly reminiscent of sterile inflammation. Mechanistically, neutrophil recruitment is initiated by a mechanosensor-dependent pathway,

involving the activation of PIEZO1 channels. This leads to LTB4 production, which, along with IL-1α, induces the release of CXCL1, promoting neutrophil arrival to the site of infection. In contrast,

later neutrophil recruitment is TLR- and CXCL2-dependent, highlighting a shift towards a pathogen-driven response to sustain inflammation. These findings advance our understanding of innate

immunity by uncovering that mechanical and biochemical signals integrate into a circuit that initiates innate immune responses to microbial infections.