« Scraping » lymphocyte activation biophysics

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Responses of living systems to external inputs are surprisingly fast and robust. Such responsiveness has recently been attributed to living systems being poised at criticality, ready to transition from a meta-stable state to another. Although the idea is extremely enticing from the physics point of view, there is a lack of specific biological examples where well-defined observables of criticality have been identified and quantified. Here we propose to study a fundamental biological system that shows critical behaviour which is moreover sensitive to mechanical cues, is relevant for cell biology and immunology and is at the core of our immune response: the activation of a T lymphocyte (a crucial type of immune cell) by a so called antigen presenting cell (Puech et Bongrand 2021). This system involves communication (chemical and mechanical) between two isolated cells. We hypothesise that both cells are poised at criticality, i.e., near a phase transition, and that their mutual control interlocks them at a self-organised critical point (Blom et Godec 2021).

We propose to dissect the physical basis of reciprocal mechanotransduction in the immunological synapse, the interface between an antigen-presenting cell (APC) and a lymphocyte. Lymphocytes, either T or B, are cells that live and function as single cells. They need to contact an APC in a one-to-one manner to activate before acting to defend the body. Central to this recognition, the T-Cell Receptor (TCR) has been shown to act as a mechanosensor molecule (i.e., a molecule whose function is modulated by a mechanical stress) (Limozin et Puech 2019). Besides, T cells also sense substrate mechanics at the cellular scale. As such, T-cell activation inherently involves mechanotransduction at different scales in space and time (Wahl et al. 2019; Mustapha 2022). Similarly, B cells are mechanically activated upon encountering an antigen (Pierobon et Lennon 2016).

Upon activation, lymphocytes switch from a quiescent to an activated state. This drastic transition consists of a plethora of biochemical responses, as well as profound morphological and material changes. Indeed, we recently reported that cell surface physico-chemical and mechanical properties of lymphocytes are rapidly modulated (secs to min) when contacting a substrate bearing activating molecules, related to their function. Remarkably, lymphocyte activation is triggered by very small changes in substrate properties, such as a tiny increase in antigen concentration, with this threshold being modulated by substrate rigidity. Activation is carefully regulated, to finely sense antigen concentration while avoiding unprompted or excessive activation, which could lead to a pathological autoimmune response. The underlying mechanisms that make activation fast, specific, sensitive and highly robust remain largely unknown. Moreover, the role of the T/B cell interface in regulating activation constitutes a fundamental open question in biology.

As such, the amount of information about the early T (and B) cell early activation when contacting decorated substrates, potentially of different composition, relative molecaular densities, elasticities and structures, has been dramatically increasing in published articles and preprints.

Here, we propose to use modern tools of data bases « scraping » (pubmed, web of science, google scholar), with adapted programming languaages (eg.python) as proposed in other fields (Tshitoyan et al. 2019), to :
1, identify relevant publications from selected imaging modalities and experimental designs
2, qualify the information they content from material and methods
3. recover this information in a tractable format (eg. pandas dataframe)
4. condense this data into « phase plots » (in term of physical phase transitions as in vapour> water > ice) to be defined as a function of the collected data type

The goal is to use the existing data as a guide to define the experimental strategy to further dissect the critical behaviour of lymphocytes when activating upon recognition of a cognate substrate.

Selected references

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