Detecting origins of interferons signalling sensitivity

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Interferons (IFNs) signalling is a key mechanism to coordinate antiviral, anti-proliferative and immunomodulatory effects (1). A substantial amount of molecular details is known regarding IFNs signalling pathways and their effectors. IFNs induce JAK-STAT pathway that transmits extracellular chemical signals to the nucleus through cascade of protein-protein interactions (2,3). Nevertheless, understanding, how information about complex mixture of IFNs with other cytokines is processed and translated into distinct cellular responses remains elusive (5,6). Our studies on interferons signalling on mouse embryonic fibroblasts have shown that prior exposure to IFN type-I modify cellular response to IFN type-II stimulation. Precisely, information-theoretic analysis indicate that higher sensitivity of pre-stimulated cells to the presence of IFN type-II in the environment.

Although the sensitising effect of IFN type-II is well known, its impact on signalling fidelity and biochemical mechanism that lead to these changes has not been recognised so far. Due to the complexity of signalling networks identification of origins of this cellular mechanism cannot be addressed with solely experimental methods (7). Here we propose integration of high-throughput experimental single-cell measurements with a mathematical modelling of JAK-STAT pathway in order to provide better understanding of mediation between IFNs type-I and -II signalling. Our solution is based on stochastic modelling of intrinsic and extrinsic cellular heterogeneity using unscented transformation (8,9). We show that origins of increasing sensitivity of pre-stimulated cells are changes in the initial cellular concentration of main transcription factors in the JAK-STAT pathway.

Deciphering the mechanism that lead to more sensitive response informs further research on

novel therapeutic and diagnostic strategies to utilise the clinical potential of IFNs (5).

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