

Modelling the cytosolic $[Ca^{2+}]$ responses induced by *Shigella* invasion in epithelial cells

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Abstract

Shigellosis is an important problem of public health worldwide. It is mainly caused by the ingestion of contaminated food or water contaminated with *Shigella*. After its ingestion, this bacterium invades the colon and causes an intense inflammatory reaction, leading to destruction of the epithelial tissue. During cell invasion, *Shigella* induces atypical Ca^{2+} signals, but its role in invasion has remained unclear and poorly studied (Tran Van Nhieu *et al.*, 2013).

It is well known that every cell type uses Ca^{2+} as a second messenger to control a wide array of cellular functions, including reorganisation of the cytoskeleton, inflammatory responses and cellular death (Sun *et al.*, 2017). The perturbation of cellular Ca^{2+} homeostasis caused by *Shigella* facilitates the entrance of the bacteria and its dispersion to adjacent cells. This further leads to apoptosis and destruction of the intestinal epithelium. The bacterium induces local responses, described as an increase of Ca^{2+} localised in the invasion area (Tran Van Nhieu *et al.*, 2013), and global responses, that spread in the whole invaded cell. The local versus global character of the responses plays a crucial role in the cytotoxicity of the bacteria, as a high and sustained Ca^{2+} elevation could lead to cellular death and limit the dissemination of the bacteria. Preliminary work was carried out by Tran Van Nhieu *et al.* (2013) and Sun, *et al* (2017) in order to analyse the atypical Ca^{2+} responses induced by *Shigella* using modeling tools. Nevertheless, the models that have been proposed don't take into account the Ca^{2+} coming from the extracellular space, which has been demonstrated to have a crucial contribution to the Ca^{2+} responses. Thus, in this work we present a partial differential equation (PDE) model that takes into account extracellular Ca^{2+} entry through Plasma Membrane Channels, as well as Ca^{2+} and $InsP_3$ diffusion through the cytosol and the conditions caused by *Shigella*, in order to analyse the global vs local character of the cytosolic $[Ca^{2+}]$ responses during bacterial invasion. Numerical simulations show the impact of the plasma membrane channels in the local/global character of the $[Ca^{2+}]$ responses, which implies that controlling extracellular Ca^{2+} entry to the cytosol could be crucial in order to find a mechanism to limit the dissemination of the bacteria.

Keywords: Calcium signalling, mathematical modelling, transport phenomena, systems biology, StoreOperated Calcium Entry

References

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