Environmental stiffness regulates intracellular Ca2+ signals through the proton-sensing receptor OGR1

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Extracellular acidification and changes in tissue stiffness accompany a range of different diseases including solid cancers and are sensed by cells through activation of cell surface proton-sensing and mechanosensitive receptors, respectively [1, 2].

We find that activation of a particular proton-sensing receptor critically depends on the stiffness of the substrate that cells expressing the receptor are exposed to. The stiffer the substrate, the more reliably and profoundly can the receptor be activated by increases in extracellular proton concentration. Moreover, modulation of proton-sensing receptor activation is a dynamic process; acute changes in substrate stiffness affect proton-sensing receptor activity on a minute time scale. Our results suggest that substrate stiffness-dependent changes in cell shape play a pivotal role in the ability of the proton-sensing receptor to respond to substrate stiffness. Since the activity of the proton-sensing receptor depends on both substrate stiffness and extracellular proton concentration, it acts as a coincidence detector of these two parameters.

Activation of the proton-sensing receptors leads to complex intracellular Ca^{2+} signals that can link to gene transcription [3]. We would like to propose that the coincidence detector of tissue acidification and changes in tissue stiffness is a key player in the progression of certain diseases.

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[2] V. P. Hytönen and B. Wehrle-Haller. Exp. Cell Res. 343, 35-41 (2015)

[3] W. C. Huang et al. Curr. Biol. 18, 781-5 (2008)