

*Im Rahmen des Physikkolloquiums spricht*

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über

## **HOW CALCIUM SHAPES HUMAN HEALTH AND DISEASE ON A MOLECULAR LEVEL**

### Abstract:

All human life starts with a calcium ( $\text{Ca}^{2+}$ ) wave<sup>1</sup>. Upon fertilization,  $\text{Ca}^{2+}$  is the first signalling molecule emerging within the oocyte and later in life,  $\text{Ca}^{2+}$  is quantitatively the most abundant mineral in the human body.  $\text{Ca}^{2+}$  serves as second messenger within cells, shaping intracellular molecular processes responsible for development, gene regulation and transcription, function of cells and tissues, apoptosis, muscle contraction and immune responses<sup>2</sup>. For cells, it is mandatory to tightly maintain their  $\text{Ca}^{2+}$  balance, as a permanent imbalance in the cytosolic  $\text{Ca}^{2+}$  concentration is toxic and inevitably leads to malfunctions, like autoimmune attacks, inflammation of tissues or other pathophysiological conditions<sup>3</sup>.

Mechanistically, humans adapted the use of various pumps, ATPases, uniporters and ion channels to control intracellular  $\text{Ca}^{2+}$  levels at all times. Upon ligand binding,  $\text{Ca}^{2+}$  is released from intracellular stores such as the endoplasmic reticulum (ER), a process which increases the cytosolic  $\text{Ca}^{2+}$  concentration by 1000-fold<sup>4</sup>. As ER stores have limited capacity, they must be refilled with extracellular  $\text{Ca}^{2+}$ . The primary route of  $\text{Ca}^{2+}$  influx from the extracellular milieu is through membrane channels belonging to the family of store-operated  $\text{Ca}^{2+}$  channels (SOCCs).

These types of channels open in response to a signal of empty ER stores. The prototypic SOCC is the  $\text{Ca}^{2+}$  release activated  $\text{Ca}^{2+}$  (CRAC) channel with its two key players, STIM1 residing in the ER, and Orai1, the actual ion conducting pore within the plasma membrane<sup>5</sup>. Since their identification in 2005 and 2006, respectively, these two proteins have been intensively studied.

Using various interdisciplinary experimental techniques like molecular biology and biochemical methods, cell biology, protein science, molecular dynamics simulations and biophysical techniques, we have been able to decipher the molecular structure and choreography of STIM1 and Orai1 proteins, their interplay and downstream cellular effects. Hence, main experimental approaches focused on the molecular structure-function relationship of CRAC channel proteins and just in the last few years, research was directed towards the connection of protein function to human disease. By now, we know that  $\text{Ca}^{2+}$  dysregulation is involved in serious clinical human phenotypes like immunodeficiency, muscle weakness or cancer development; cellular calcium dynamics are even affected during viral infections<sup>6</sup>.

Within this talk, I discern the molecular basis of STIM1 and Orai1 proteins, their interplay and physiological relevance, extending the focus to human  $\text{Ca}^{2+}$ -dependent diseases. The knowledge gained can be applied to the development of new therapeutic drugs, treating  $\text{Ca}^{2+}$  dependent diseases.

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