Guarding the gatekeepers

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According to Greek mythology, the guardians of the gates of heaven were known as the Horae or Orai after whom the calcium channel protein, Orai is named. Credit: National Centre for Biological Sciences (NCBS), Bangalore

Information flow in cells relies on calcium as a key agent in several signalling pathways. Calcium dependent signalling is crucial in nearly every aspect of life - muscle movement, immune reactions, nerve function, light sensing and many such processes. In fact, one could consider any cellular function, and calcium signalling is probably involved in it in some way. Now, researchers from the National Centre for Biological Sciences (NCBS), Bangalore have discovered a new player in calcium signalling pathways - a protein named Septin 7 that functions as a 'molecular brake' to Orai activation.

As calcium ions cannot cross cell membranes freely, the rise and fall of calcium levels within a cell are controlled through a set of proteins that act as channels for calcium ions. One such protein is Orai, that forms pores or channels in cell membranes and allows calcium ions to move through them in a regulated fashion. Since these proteins can be likened to 'gatekeepers' of the calcium entryways into cells, they are named after the mythological Greek Orai, also known as Horae or the gatekeepers of heaven. Researchers Bipan Kumar Deb and Trayambak Pathak from Prof. Gaiti Hasan's group at NCBS have discovered that another protein known as Septin 7 acts as a 'guard' of the Orai proteins by regulating their activity.

Previous work from this group had established the critical role of calcium signalling and Orai for maintaining dopamine levels in flight circuit neurons in fruit fly (*Drosophila*) brains. Using this system as a platform, Prof. Hasan's team investigated and established the role of Septin 7 as a 'molecular brake' of Orai in the neurons of these flies. This means that when Septin 7 levels are decreased in a cell, calcium entry via Orai goes up, leading to higher calcium concentrations within cells. The discovery has been published as a paper in the journal *Nature Communications*.

The negative nature of Orai regulation by Septin 7 could be a

therapeutically important one. "Most drugs work by inhibiting the function of a protein, and inhibiting most proteins causes the processes they are involved in to be reduced. In this case, inhibiting Septin 7 can actually raise intracellular calcium levels," says Bipan Kumar Deb, the lead author of the paper.

"In the context of neural function, we know that under some conditions, reduced calcium signalling can lead to neurodegeneration. Rare genetic disorders such as spinocerebellar ataxias are thought to be caused by calcium signalling dysregulations. Future therapies for certain classes of such disorders could focus on Septin 7 as a therapeutic target," adds Prof. Hasan.

The next challenge the team intends to address involves studying the role of Septin 7 in Orai regulation in mammalian cells. Future work also involves studying the role of Septin 7 in cells other than neuronal cells, specifically, in the cells of the immune system. "The Orai gene was first discovered in patients with Severe Combined Immuno-Deficency (SCID) syndrome, and subsequently an essential role for Orai proteins in immune cell function was uncovered," says Deb. "Therefore, it is highly likely that Septin 7 also may play a role in calcium signalling mechanisms of the immune system, and we are already planning experiments to pursue this line of investigation," he adds with enthusiasm.

More information: Bipan Kumar Deb et al, Store-independent modulation of Ca2+ entry through Orai by Septin 7, *Nature Communications* (2016). DOI: 10.1038/ncomms11751

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