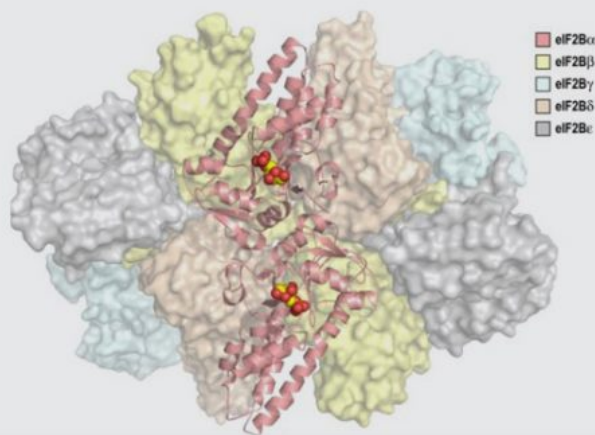


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Calico Stories

A breakthrough in understanding metabolite regulation of a central stress sensor



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Understanding homeostasis in aging and disease could lead to the ability to target specific biological pathways involved in the pathology of disease. That's why Calico scientists, led by [Carmela Sidrauski](#), have been studying the integrated stress response (ISR) pathway since 2014, and specifically the protein complex eIF2B, which is inhibited when cells sense a variety of insults.

By understanding how the stress sensor eIF2B is regulated in cells, it may be possible to develop modulators that attenuate the chronic expression of stress proteins that can lead to neurological conditions like Vanishing White Matter Disease (VWMD) or possibly ALS and restore the proteome to a functional state.

Calico had breakthrough results when we brought our target — eIF2B — and associated expertise to a multiyear collaboration among various Calico labs, the University of Utah and biopharmaceutical partner AbbVie. Together, we uncovered that binding of sugar phosphates to eIF2B can activate it, suggesting a novel and direct link between nutrient status and the rate of protein synthesis in cells.

Calico had already found that synthetic small molecules could activate the eIF2B complex and wondered if there were natural ligands in the cell that would also inhibit or activate it. Based on this hypothesis, the question was, are cellular metabolites directly modulating our target? Research revealed that eIF2B senses how much sugar a cell is getting and tells the cell to adjust the amount of protein it makes based on its energy status.

"This is a significant, fundamental discovery, and it has definitely caught the attention of the academic community," says Carmela. "This protein complex is

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with others in the scientific community.

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