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FIRST PERSON

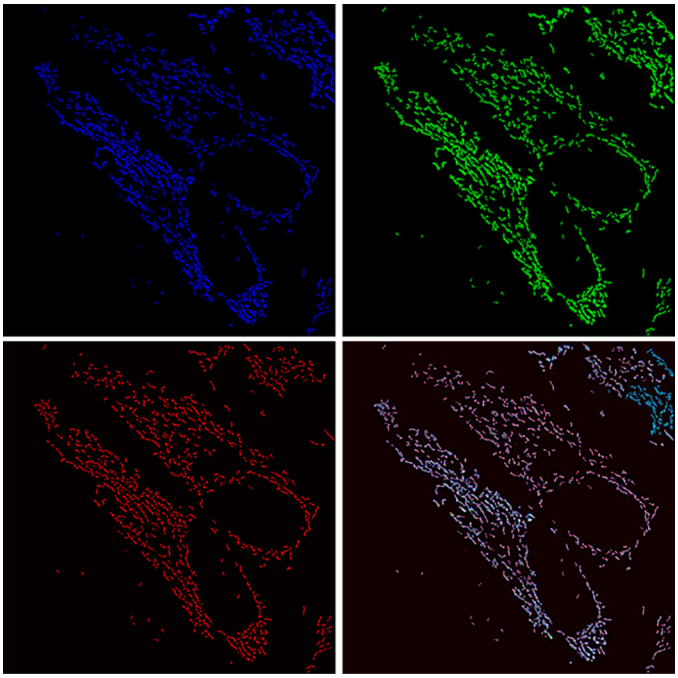
First person – Gergő Szanda

First Person is a series of interviews with the first authors of a selection of papers published in Journal of Cell Science, helping early-career researchers promote themselves alongside their papers. Gergő Szanda is the first author on 'Mitochondrial cAMP exerts positive feedback on mitochondrial Ca^{2+} uptake via the recruitment of Epac1', published in Journal of Cell Science. Gergő is an assistant professor and leads a group at Semmelweis University, Budapest, Hungary, investigating Ca^{2+} signaling and mitochondrial biology, and the role of endocannabinoids in metabolism.

How would you explain the main findings of your paper in lay terms?

Cells translate stimuli from outside the cell (extracellular) into information within the cell (intracellular) by changing the concentration of specific intracellular molecules called second messengers. These molecules decode the extracellular stimulus and then adjust the cell's behaviour accordingly. We study how second messengers modify the function of mitochondria, intracellular organelles responsible for energy production, to adjust mitochondrial function to the actual needs of the cell.

In the present work, we identified a previously undiscovered interaction between two key second messengers, cAMP and calcium ions (Ca^{2+}), within mitochondria. It was already known that during cell stimulation, Ca^{2+} within mitochondria activates the soluble adenylyl cyclase enzyme (sAC) which in turn produces cAMP. Eventually, Ca^{2+} and cAMP together fine-tune the energy production of the mitochondrion. Now, we have found that the above mechanism also works the other way around. Ca^{2+} activates sAC and cAMP production in mitochondria but, at the same time, cAMP can also speed up the rise in mitochondrial Ca^{2+}. This phenomenon caught our attention as we knew that increased mitochondrial Ca^{2+} can have important consequences; it can modify energy production, and also affect cell survival and the secretion of hormones. Indeed, we were able to show that accelerating the rise of mitochondrial Ca^{2+} with the help of sAC and cAMP boosts the production of aldosterone, a hormone essential to surviving fluid loss or bleeding.



HeLa cells expressing both the mitochondrial cAMP sensor (blue and green) and the mitochondria-targeted soluble adenylyl cyclase enzyme (red). Overlay is shown on bottom right.

Gergő Szanda.

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"It came up rather casually that we may actually have a case of positive feedback here."

Were there any specific challenges associated with this project? If so, how did you overcome them?

We had a hard time effectively targeting the sAC enzyme into mitochondria. We routinely target recombinant proteins into the organelle by stitching a mitochondrial target signal (a sort of cellular postal code) to the protein of interest. We usually use two or four repeats of the same signal for precise targeting. For some unknown reason, this strategy did not work reliably with sAC. The solution: five is the magic number! We needed to repeat the target signal exactly five times to achieve a satisfactory mitochondrial localization of sAC. Why five? We don't know, but luckily it worked, as can be seen in the picture above.

When doing the research, did you have a particular result or 'eureka' moment that has stuck with you?

The mechanism we describe in this paper, namely that mitochondrial Ca^{2+} activates cAMP production and then cAMP increases Ca^{2+} further, is an example of positive feedback

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regulation. This is not very common in living systems. Our lab had previously established that the production of aldosterone is largely dependent on mitochondrial Ca^{2+} and we also knew that mitochondrial cAMP somehow modulates aldosterone synthesis. But we didn't dare to think that positive feedback between mitochondrial Ca^{2+} and cAMP could underlie our observations. It came up rather casually that we may actually have a case of positive feedback here. At first, we thought of it as a provocative idea; then we realized that this could in fact elegantly explain our observations. It was a turning point in our thinking.

What changes do you think could improve the professional lives of scientists?

I have the impression that nowadays we (I am no exception, I am afraid) all expect to read about striking, glamorous findings. It is very hard to get negative data published; this can be frustrating sometimes. We should be able to publish negative findings as well, as long as the question was scientifically relevant and the experiments were designed and performed carefully. Such findings may be just as important. The notion that potentially important discoveries are piling up unpublished just because their conclusion is negative is a disturbing one and possibly a serious hindrance to progress. Besides, selecting for positive results is bad practice.

"We should be able to publish negative findings as well, as long as the question was scientifically relevant and the experiments were designed and performed carefully."

Tell us something interesting about yourself that wouldn't be on your CV

I am a devoted amateur photographer. Not a particularly good one, but an enthusiast nonetheless. I don't mind standing in the rain or waiting in the freezing wind for hours to catch the best light. Somehow, it is a spiritual experience for me.

Reference

Szanda, G., Wisniewski, É., Rajki, A. and Spät, A. (2018). Mitochondrial cAMP exerts positive feedback on mitochondrial Ca^{2+} uptake via the recruitment of Epac1. *J. Cell Sci.* **131**, jcs215178.