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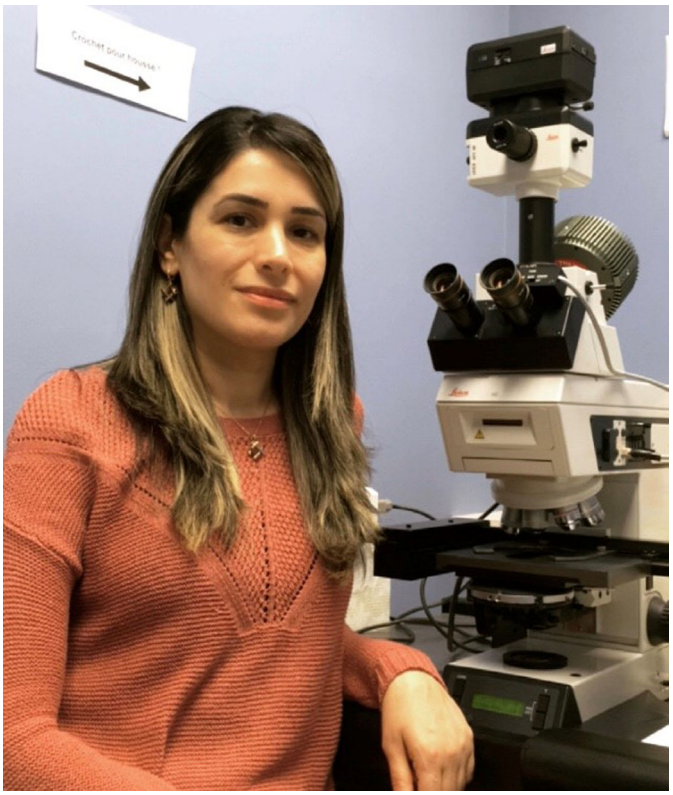
FIRST PERSON

First person – Sepideh Fallah

First Person is a series of interviews with the first authors of a selection of papers published in Biology Open, helping early-career researchers promote themselves alongside their papers. Sepideh Fallah is first author on 'Src family kinases inhibit differentiation of intestinal epithelial cells through the Hippo effector YAP1', published in BiO. Sepideh is a postdoctoral researcher in the lab of Prof. Jean-François Beaulieu at Université de Sherbrooke, Quebec, Canada, investigating how SFKs negatively regulate the differentiation of absorptive and goblet cells through upregulating of YAP1 activity.



Sepideh Fallah

What is your scientific background and the general focus of your lab?

After completing a degree in veterinary medicine, I decided to pursue graduate studies in cell biology. I began my PhD research under the guidance of Prof. Jean-François Beaulieu in the Intestinal Physiopathology Laboratory at the Université de Sherbrooke. The gastrointestinal tract and accessory organs of digestion (pancreas, liver and gall bladder) are responsible for more cancers and subsequent deaths than any other system in the human body. In our lab we study the identification of important signals involved in human intestinal inflammation and cancer. My research interests lie in finding the mechanisms involved in differentiation, stemness and proliferation of intestinal epithelial cells by investigating the role of the Hippo pathway effectors Yes-associated protein 1 (YAP1) and its paralog transcriptional co-activator with PDZ-binding motif (TAZ or WWTR1) in colorectal cancer cell lines.

How would you explain the main findings of your paper to non-scientific family and friends?

The inner part of the intestinal tract is covered by a single layer of epithelial cells that are continuously replaced by new cells provided by stem cells. The stem cells expand and generate new stem cells and progenitor cells. Progenitor cells multiply before differentiating into absorptive and secretory cells, which are required for the absorption of nutrients and protection against pathogens. Various factors have been known to be involved in the replication and differentiation of intestinal epithelial cells. In our study, we used human colorectal cancer cells to investigate the mechanism by which intestinal stem cells give rise to differentiated and mature epithelial cells. To do so, we alternately removed some specific proteins to determine their effects on differentiation.

What are the potential implications of these results for your field of research?

The Hippo pathway plays a significant role in intestinal homeostasis and regeneration, while its effector YAP1/TAZ is known to be a driver of tumor formation and progression in many cancers including colorectal cancers. Studies using several experimental models have shown that tumor growth and metastasis can be inhibited by restricting the aberrant activation of YAP1/TAZ. Therefore, YAP1/TAZ may be considered to be a therapeutic target. However, considering that YAP1/TAZ plays an important role in normal tissues, preventing YAP1/TAZ activity in cancer patients may lead to adverse side effects. On the other hand, Src family kinases, which are associated with tumor development and metastasis, have been reported to act as regulators of the YAP1/TAZ co-activator in other systems. Therefore, knowing the mechanisms by which YAP1/TAZ activity is regulated could lead to the discovery of new cancer treatment strategies for colorectal cancer.

What has surprised you the most while conducting your research?

I was amazed to learn that hundreds of signals communicate with each other to allow homeostasis of the smallest unit of the body – cells. And that a malfunction of any one of these signals could result in a vast problem for the entire organism. More specifically in my research was the fact that the pharmacological inhibition of Src family kinases results in an almost complete abolition of YAP1 expression without significantly affecting its paralog TAZ.

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

Early-career scientists must work hard to find their place in academia and/or industry. The lack of adequate funding in various laboratories prevents early-career scientists from applying their fresh scientific ideas. In addition, most laboratories/companies

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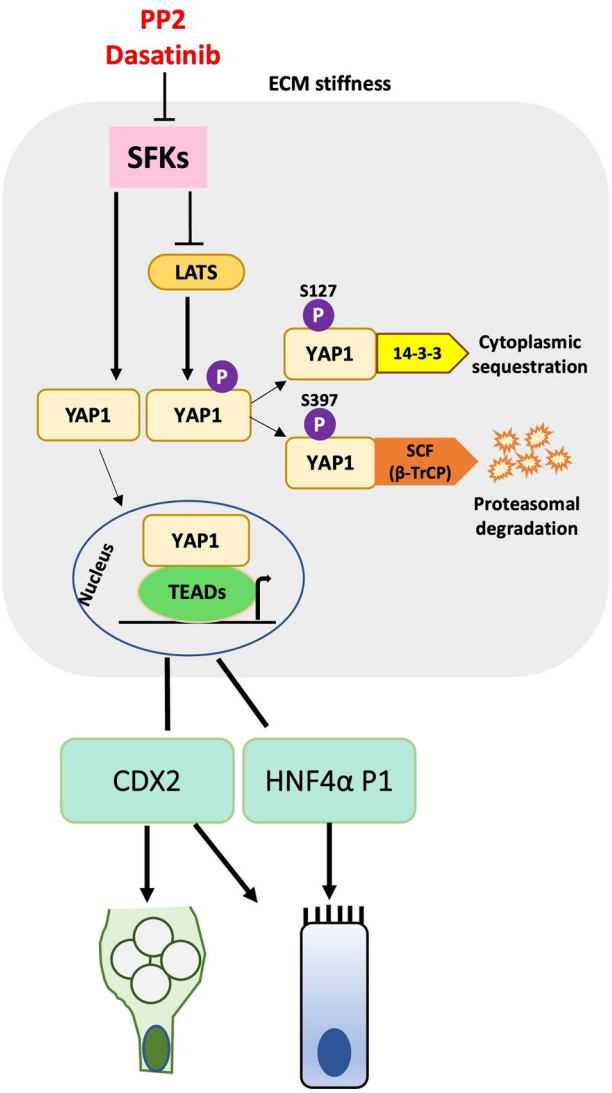

SFKs inhibition was accompanied by an increase in absorptive and goblet cells differentiation as well as YAP1 phosphorylation, which is mediated by P1 isoforms of HNF4α and CDX2 transcription factors. However, regulation of YAP1 paralog TAZ is not directly controlled by SFKs and has a distinct effect on differentiation of absorptive cells.

insist on hiring only scientists with extensive expertise, which may require several years of experience in different work areas. It would be helpful if governments would allocate more funding to support early-career scientists and encourage enterprises to recruit entry-level researchers through paid internships.

"The lack of adequate funding in various laboratories prevents early-career scientists from applying their fresh scientific ideas."

What's next for you?

Due to my keen interest in the research environment, I would like to pursue a future in R&D. Currently, as a postdoctoral fellow, I am studying the role of the YAP1 paralog transcriptional co-activator TAZ on intestinal epithelial cell differentiation. Despite similarities between YAP1 and TAZ, there is growing evidence that they can be distinguished by structural and functional aspects. Therefore, I aim to investigate how they can act individually in differentiation and proliferation. In the near future, I hope to continue exploring cellular mechanisms involved in the regulation of gene expression and cell behavior.

Reference

Fallah, S. and Beaulieu, J.-F. (2021). Src family kinases inhibit differentiation of intestinal epithelial cells through the Hippo effector YAP1. *Biology Open* **10**, bio058904. doi:10.1242/bio.058904