

FIRST PERSON

SPECIAL ISSUE: CELL BIOLOGY OF HOST–PATHOGEN INTERACTIONS

First person – Pragya Chandrakar

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. Pragya Chandrakar is first author on 'Jagged–Notch-mediated divergence of immune cell crosstalk maintains the anti-inflammatory response in visceral leishmaniasis', published in JCS. Pragya conducted the research described in this article while a Senior Research Fellow in Dr Susanta Kar's lab at the CSIR Central Drug Research Institute, Lucknow, India. She is now a Postdoctoral Research Fellow in the lab of Dr John Chan at Albert Einstein College of Medicine, New York, USA, investigating the different possible mechanisms by which foreign pathogens breach the immune system.

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

Our immune system consists of the innate and adaptive arms of immunity that mount an effective immune response during pathogenic challenge. However, several pathogens have developed well-equipped machinery to breach this circle, and one among them is the parasite *Leishmania donovani*, which impairs the coordinated interactions between components of innate and adaptive immunity that span functional crosstalk between macrophages and T cells, resulting in progression of visceral leishmaniasis. In our study, through a series of experiments conducted in *L. donovani*-infected mouse bone marrow macrophages (BMMφs) and CD4⁺ T cells, we observe that *L. donovani* selectively induces Jagged1 expression in BMMφs to kickstart Notch receptor signaling in T cells and conveniently deflect T cell polarization towards an immunosuppressive Th2 phenotype. The resulting skew towards Th2 differentiation acts as a rheostat for host-defensive Th1 responses, creating a conducive niche for the parasite. Taken together, our results imply that *L. donovani* takes advantage of Jagged1–Notch signaling to prevent the bipartite macrophage–T cell crosstalk responsible for mounting anti-leishmanial immune responses.

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

The major challenge in the project was to identify the parasite-derived factor that was responsible for modulating or skewing the macrophage–T cell-mediated immune response. Besides that, another hurdle was to establish a link between parasite lipophosphoglycan (LPG)-mediated Jagged1 induction in BMMφs and the Th2-biased immune response in T cells co-cultured with infected macrophages. We overcame this issue by utilizing a LPG-knockout *Leishmania* parasite, which modulated host cellular events such as activation of various transcription factors, including β-catenin, Egr1, RBPJk and GATA3, as well as the PI3K/Akt pathway, establishing an anti-inflammatory crosstalk between macrophages and T cells.

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

The turning point for my project was when I saw that siRNA-mediated knockdown of Jagged1 and functional blocking of Notch1



Pragya Chandrakar

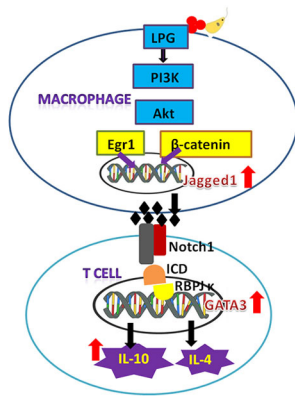
in T cells markedly attenuated both IL-10 and IL-4 cytokine levels in the T cells co-cultured with infected BMMφs. This suggested a role for Jagged1–Notch signaling in governing T cell-specific anti-inflammatory immune responses during experimental visceral leishmaniasis. Later on, during the course of subsequent experiments, we were able to figure out that the parasitic factor LPG was primarily responsible for upregulating the Jagged1 ligand and enabling macrophage–T cell crosstalk via activation of Jagged1–Notch signaling. Further investigating the in-depth mechanism, such as the transcription factors and the intracellular pathways responsible for activation of Notch signaling, made this project even more thrilling and exciting.

Why did you choose Journal of Cell Science for your paper?

As Journal of Cell Science is a peer-reviewed journal that is committed to publishing and representing a wide range of research in cell biology, and because our entire study was focused on exploring the different aspects of immune cell biology, we chose this journal to represent our findings. Choosing the Journal of Cell Science for publication of our research article aligned with our research direction, and we believed that it would also help in our aim of stimulating the interest of readers from different areas of cell biology.

Have you had any significant mentors who have helped you beyond supervision in the lab? How was their guidance special?

My significant mentor was my supervisor Dr Susanta Kar, who actually introduced me into the scientific arena. He changed my vision, helping me to admire and understand the world of immune cells and guiding me to make my willpower strong enough to



Schematic representation of *L. donovani* induced Jagged/Notch signaling in host: Leishmanial LPG-mediated induction of PI3K/Akt pathway activates β -catenin and Egr1-driving Jagged1 expression in macrophages, which then activates Notch signalling in T cells with increased ICD nuclear translocation, followed by RBPIK activation and its binding on GATA3 promoter, which all together increase the anti-inflammatory cytokines, IL-10 and IL-4 production.

Host–pathogen interactions in visceral leishmaniasis.

overcome a vulnerable period in my life – when my fellowship ran out but many experiments were still to be completed. He convinced me to have patience, stating that the best is yet to come and that “This is the time when your cultivated flowers are going to blossom in the scientific field”. These words were invaluable to me.

What motivated you to pursue a career in science, and what have been the most interesting moments on the path that led you to where you are now?

My curiosity to understand human immune biology developed at the time of my undergraduate degree. I was fascinated by the concept of how well organized our immune system is when it comes to responding to any foreign pathogen. Later on, it became my passion when I started learning about how pathogens breach such a highly organized shield as the immune system. All of this served collectively to drive me to pursue a research career in the field of host–pathogen interactions.

Who are your role models in science? Why?

Firstly, Marie Curie. Not only was she the first woman to win the Nobel Prize, but she won it twice in two different fields of science. I admire her for her courage; in order to believe in her idea, she went her own way. She faced many obstacles while being a scientist among men to establish herself in the scientific community. I hold her in high regard for her scientific accomplishment and her road leading to success. Secondly, Dr A. P. J. Abdul Kalam – ‘A Man beyond Science’. He was a person who made an outstanding contribution in the field of aerospace; however, very few people know of his contribution in the field of medical science research. He worked in collaboration with Dr Somaraju Bhupathiraju to benefit the common man of India by reducing the price of a cardiac stent to a quarter of the original market price. Thirdly, Mark M. Davis. I really look up to him for his outstanding discovery in the field of immunobiology, especially for his contribution to set up an *in vitro* organoid culture system to study human immune cell reactions that includes the germinal centers.

What’s next for you?

Currently, I am working as postdoc at Albert Einstein College of Medicine, New York and simultaneously looking out for suitable scientist posts in various parts of India. As a scientist, I would like to lead my own team to explore different aspects of the role of germinal centers in the arena of infectious disease biology.

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

When I face failure in my experiments, I decide to take a break and visit a science museum or watch some scientific movies to learn more about the failures of different great scientists. This helps me to regain my passion for science and strengthens my willpower to face the challenges ahead.

Reference

Chandrakar, P., Seth, A., Rani, A., Dutta, M., Parmar, N., Descoteaux, A. and Kar, S. (2021). Jagged–Notch-mediated divergence of immune cell crosstalk maintains the anti-inflammatory response in visceral leishmaniasis. *J. Cell Sci.* 134, jcs252494. doi:10.1242/jcs.252494