Cell Reports

CellPress
OPEN ACCESS

Q&A

Q&A with Suneil Koliwad and Martin Valdearcos

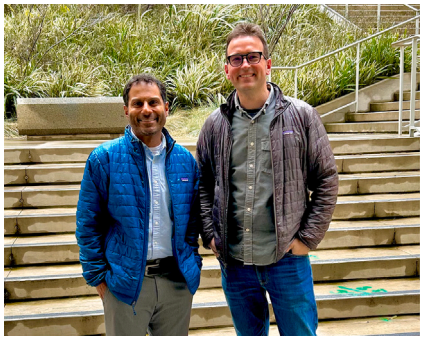
Suneil Koliwad (S.K.) and Martin Valdearcos (M.V.) spoke with *Cell Reports* about their scientific journeys leading to their recent paper investigating the role of microglia in shaping blood glucose homeostasis. They discuss the challenges and future directions of their work and share their publishing experience.

What is the take-home message of your new *Cell Reports* paper?

S.K./M.V.: We've long known that early life is a critical period that determines an individual's susceptibility to developing metabolic diseases, such as diabetes, in adulthood. However, the details of what underlies this "metabolic programming" in the brain are still being worked out. In our new *Cell Reports* paper (https://www.cell.com/cell-reports/fulltext/S2211-1247(25)00180-9), we show that neonatal microglia play a key role in this process, facilitating the formation of glucoregulatory circuits between the hypothalamus and beta cells, the pancreatic cells that secrete insulin in response to rising blood sugar levels. By understanding how microglia shape this connectivity, we might unveil new ways to augment our ability to control blood sugar and preserve metabolic health.

Was there a particularly difficult or challenging aspect of this study?

S.K./M.V.: Yes! Our work here brought us right up against the technical limits of this field. We have used intracerebroventricular approaches to chemogenetically stimulate microglia or inhibit the action of cytokines they produce in the mediobasal hypothalamus, our brain region of interest, with a degree of anatomical specificity. However, this work was confined to adult mice. Here, we specifically focused on neonatal mice, which are much smaller in size, precluding us from effectively using these sorts of approaches. Indeed, there is currently no clear way to our knowledge that reliably targets solely mediobasal hypothalamic microglia in neonatal mice. Future studies building on our work will need to overcome this major technical challenge. We ourselves are actively trying to specifically mark microglia living in this unique anatomical region of the brain in order to overcome this hurdle.



Suneil Koliwad (left) and Martin Valdearcos (right)
Diabetes Center, University of California, San Francisco, San Francisco, CA, USA

How do you think microglia are capable of functioning in a region-specific manner in the brain? How do microglia know which neurons to target in response to changes in diet?

S.K./M.V.: Microglia are highly dynamic and region specific in their functions, partly due to their ability to sense local signals from neurons and other glial cells. They are equipped with a wide variety of receptors allowing them to detect molecular cues from the environment, including changes in diet. Additionally, microglia can respond to changes in neuronal activity or stress signals, which are also modulated by diet. A lot of this knowledge has come from research focused on demyelinating or neurodegenerative diseases. It will be interesting to see how this work can be translated to understand microglial sensing and cell-cell crosstalk in the hypothalamus.

What do you think determines the critical period for microglia-mediated influence on beta cell function before weaning?

S.K./M.V.: A lot of things are changing during the period prior to weaning. For one, hypothalamic circuits undergo substantial rewiring during this period, along with the formation of important hypothalamic projections needed for peripheral metabolic regulation. Our work highlights the importance of microglia in shaping newly forming synaptic connections to target sites. Hormonal levels are also changing dynamically during this time period. For example, leptin levels are well known to surge upward prior to weaning. What role this surge plays in the process we explore here remains to be determined. Clearly, nutritional signals also shift dramatically during this period. Changes in the maternal diet during lactation as well as the switch from maternal milk to a more varied diet upon weaning have impacts on systemic and brain-restricted cytokine levels, growth factors, and the microbiome composition, to name a few. Each of these inputs could help guide microglial activity in the hypothalamus during this precise chronological window.

What motivated you to pursue a career in research?

S.K.: I applied to UCLA's undergraduate research program during my sophomore year there and was placed in a lab focused on nerve regrowth following injury. Among the usual litany of basic lab tasks and protocols, I learned how to take whole-cell electrophysiological recordings from neurons in frogs. Seeing a live action potential triggered from a neuron right in front of me for the first time, I fell in love with the idea that we can try to understand how cells and organisms do such precise and elegant things. Taking a class where we met patients with diseases that correlated with what we were studying in class made me want to be a physician-scientist. The obesity pandemic, which was emerging as I was finishing medical school, along

with the fact that type 2 diabetes runs in my family, as it does for many South Asian people like me, cemented my desire to pursue metabolic research.

What events or discoveries have shaped your specific research interests?

S.K.: The year I started my clinical fellowship in endocrinology and metabolism, a paper from Tony Ferrante, Rudy Leibel, and colleagues came out showing that obesity is associated with a build-up of macrophages in the adipose tissue, a phenomenon that was observed not only in rodent models but also in people with obesity. Subsequent work indicating that these macrophages are laden with lipids influenced me to focus on lipid sensing and nutrient sensing by myeloid cells more broadly. A 2012 study by Josh Thaler, now a close collaborator, and colleagues indicated that obesity also induces hypothalamic microglia, specialized myeloid cells of the brain, to accumulate in an eerily similar way. Our microglial research, including the research leading to our current study, was heavily influenced by this seminal work.

What is the focus of your lab?

S.K.: Our lab focuses on molecular and cellular mechanisms at the intersection of nutritional physiology, inflammation, and metabolic function in multiple tissue environments. This focus aims to impact multiple diseases manifesting at this intersection, including obesity, diabetes, fatty liver disease, and atherosclerosis. Over the years, we have expanded this focus to include downstream hallmarks of metabolic tissue dysfunction, such as fibrosis, and have built a large and growing human obesity cohort aimed at allowing us to translate our findings in reductionist systems into the clinical context.

What is your mentoring philosophy?

S.K.: Scientists are competitive and have egos, just like people from other walks of life. Because of this, we sometimes view the success of those in our labs as an offshoot of our own success and discoveries. However, I think it's really the other way around; good mentorship is defined by the long-term success and satisfaction of those who train with us. This view requires putting ego and competitiveness aside and focusing on the supportive acts that set our mentees up to succeed. For me, this includes basing my approach on each trainee's background, prior experiences, strengths, and goals. The process also requires a lot of trust. Martin Valdearcos was the first postdoc I recruited to my lab. He now has his own laboratory and is set to explore fascinating new frontiers related to how microglia influence metabolic control. I couldn't be prouder. He is knocking it out of the park, and I will always be happy that I played a small role in helping him reach his goals. Being able to work with your mentees as a collaborative partner after their careers take off, like Martin and I did here, is an added bonus.

If you could do it over again, is there another career or area of study that you would pursue? If so, why?

S.K.: I've always loved writing. I was an editor of my high school yearbook and a writer for our newspaper, and I thought a lot about writing for a living. My dad, a NASA scientist, steered me to look at science, and this eventually took root. Interestingly, journalism and science share one thing in common: they both strive to find out the truth and are both subject to the harmful effects of bias. So, if I had to do it over again, I might be very happy as a journalist. Even now, I spend a great deal of my time writing and making our work accessible to a broad audience through effective communication. My role as a physician keeps me attuned to how the public views health and disease, concepts that help influence my writing as a scientist. My absolute dream job would have been to be a professional baseball player. I only lacked the necessary height, speed, and strength!

How did you become interested in science?

M.V.: My interest in science began early in high school. Sadly, when I was 13, I lost my father to Langerhans cell histiocytosis (LCH), a rare disorder caused by immune system dysregulation that leads to an abnormal accumulation of macrophages and dendritic cells in non-target tissues. This experience motivated me to study biology with a focus on immunology. Later, I was fortunate to receive excellent training in innate immunity and lipid metabolism, along with outstanding mentorship, as a PhD student in the labs of Maria A. Balboa and Jesus Balsinde at the Eicosanoid Research Division at the Institute of Molecular Biology and Genetics (IBGM by its initials in Spanish). This is where my journey in macrophage biology began, and it continues today, as I study brain macrophages in my own lab.

What motivated you to pursue a career in research?

M.V.: I once considered going to medical school, but at the time, I mistakenly believed that doctors only treated patients. The idea of spending my days in a clinic solely seeing patients did not appeal to me. Instead, I wanted to contribute to curing diseases through research. During my final year as an undergraduate at the University of Granada (UGR), I had the opportunity to spend the summer in Querétaro, Mexico, collaborating on a project focused on Chagas disease, an infectious disease caused by the parasite *Trypanosoma cruzi*, which is transmitted by triatomine bugs. We visited numerous rural villages to collect these insects and brought them to the lab to assess disease incidence. I fell in love with lab work, and that experience cemented my decision to pursue a career as a scientist.

Why did you choose to pursue your postdoctoral training with Dr. Koliwad?

M.V.: During my PhD, I received a fellowship for an internship abroad. At the time, I was studying lipid droplets in macrophages and reached out to Robert V. Farese Jr. to request an internship in his lab at the Gladstone Cardiovascular Research Institute for the summer of 2009. Instead of hearing directly from Bob, I received a response from Suneil Koliwad, a postdoctoral fellow studying myeloid cells in his lab. That summer turned out to be a life-changing experience; working closely with Suneil inspired me, and I returned home determined to move to the US as soon as I completed my PhD. Shortly after, Suneil secured a faculty position to start his own lab at the University of California, San Francisco (UCSF), and I joined his lab as a postdoc a few months later.

What are your goals for the future?

M.V.: I recently established my own laboratory at UCSF, where my primary goal is

to conduct high-quality research while actively recruiting and mentoring young scientists. Over the past two decades, immunology has undergone a major revolution, particularly with the development of immunotherapy, harnessing the power of the immune system to combat not only infections but also diseases such as cancer. My ultimate goal is to uncover mechanisms that enable the immune system to treat metabolic and brain diseases.

What are you most excited about in the lab now?

M.V.: Over the past decade, we have developed tools to manipulate microglia, gaining valuable insights into their role in the central regulation of energy and glucose homeostasis. However, the cellular and molecular mechanisms underlying these processes remain poorly understood. I am eager to further investigate glia-glia and glia-neuron interactions, with a particular focus on microglia, to identify therapeutic targets for preventing and treating hypothalamic dysfunction and metabolic diseases.

How did you decide to submit to *Cell Reports*?

S.K./M.V.: Our first landmark paper on this topic of research was published in 2014 in *Cell Reports*, where we described that hypothalamic microglia are metabolic sensors (https://www.cell.com/cell-reports/fulltext/S2211-1247(14)00972-3). This paper has over 600 citations.

How was your experience publishing with *Cell Reports*?

S.K./M.V.: The process was smooth, and we really appreciate the formatting commonalities within the *Cell* family of journals, making the process of finalizing a manuscript for submission relatively quick and easy. It was also easy to communicate directly with editors, editorial staff, and the acceptance coordinators whenever we had a question or concern.

What suggestions do you have for potential *Cell Reports* authors?

S.K./M.V.: Don't overlook *Cell Reports*. It may be topically broad, but it organizes published papers by field and has a substantial worldwide readership. We're confident that researchers in our field of metabolism will quickly see our new work now that it's published in *Cell Reports*.

DECLARATION OF INTERESTS

The authors declare no competing interests.

https://doi.org/10.1016/j.celrep.2025.115473