JCB Journal of Cell Biology

PEOPLE & IDEAS

Brajendra Tripathi: Keeping an eye out for translational research

Marie Anne O'Donnell

Tripathi investigates how the tumor suppressor DLC1 is regulated by oncogenic kinases.

Brajendra Tripathi's family moved to the city of Gwalior, India, so Tripathi and his siblings could access education resources that were unavailable in their rural home, which set Tripathi on the path to fulfilling his childhood dream of becoming a scientist. The possibility of learning new things every day and the opportunity to improve lives for others were Tripathi's main motivation for pursuing a career in science. Tripathi's research has encompassed diverse areas of biology but each project had clear implications for human health, from how to tackle plant pests to how to promote corneal wound healing in the eye. More recently, Tripathi has been focusing on how the focal adhesion protein DLC1, a tumor suppressor that inhibits cancer cell growth and metastasis, is regulated by several kinases. These new insights into the phosphoregulation of DLC1 by oncogenic kinases, and how this may be exploited for cancer therapy, have resulted in several first author papers for Tripathi in the *Journal of Cell Biology*.

We contacted Tripathi to learn more about how he became a cancer biologist.

Where and with whom have you studied?

Most of my education was completed in India. As an undergraduate student, I learned the fundamentals of biochemistry and molecular biology. During my Master's degree, I learned routine laboratory techniques at the National Botanical Research Institute where I was doing a research project on hybrid delta-endotoxin and its expression in tobacco and cotton for the control of a polyphagous pest, *Spodoptera litura*. It was fascinating to work in plant science, but due to limited opportunities for plant science in India, I decided to pursue a scientific career in human health disparity and medicine. So, I moved to the CSIR-Central Drug Research Institute where I studied the signaling mechanisms of insulin sensitivity and resistance in alcoholism and received my PhD in biochemistry from Jawaharlal Nehru University, New Delhi, India. After my PhD, I joined Dr. Peggy Zelenka at the Laboratory of Molecular and Developmental Biology at the National Eye Institute of the National Institutes of Health (NIH) for my postdoctoral training. In Peggy's laboratory, I performed research on signal transduction mechanisms that regulate epithelial cell adhesion and migration in the lens and cornea. In addition, we developed animal models for studying corneal wound healing and evaluated the therapeutic potential of cyclin-dependent kinase 5 (CDK5) inhibitors on wound healing of the cornea (1). We demonstrated that CDK5 inhibitors may be therapeutically useful for treatment of corneal epithelial erosions. In addition, we have investigated the role of the serine/threonine kinase CDK5 in the regulation of Rho-dependent myosin phosphorylation, cytoskeletal organization, and contraction in epithelial cells and found that CDK5 activity is a physiological regulator of myosin-dependent cytoskeletal contraction and cell migration (2). After my postdoctoral training, I joined Dr. Douglas Lowy's Laboratory at the National Cancer Institute, where I am currently working and exploring the functions of the tumor suppressor DLC1 and the mechanisms by which DLC1 is regulated posttranslationally.

What are you currently working on?

We are currently focusing on the functions of the tumor suppressor protein Deleted in Liver Cancer 1 (DLC1) and the kinases that regulate its functions in normal physiology and in cancer. *DLC1* is a tumor suppressor gene that is down-regulated in a variety of cancers through genetic and epigenetic modifications. The DLC1 protein possesses a Rho–GTPase-activating protein (GAP) activity, which negatively regulates RhoA-GTP (3, 4). RhoA-GTP is involved in several cell biological processes such as proliferation, migration, and cytokinesis and is frequently activated in advanced cancer, contributing to the maintenance of the oncogenic phenotype. We have found that the oncogenic kinases AKT and SRC directly phosphorylate DLC1 and attenuate its Rho-GAP and tumor suppressor activities (5, 6). The potential reversibility of these phosphorylations prompted us to evaluate whether the antitumor activity of SRC or AKT inhibition might be more potent in tumors that express DLC1, compared with tumors that do not. We have found that in DLC1-positive tumor lines, combined treatment with AKT and SRC inhibitors results in a remarkable decrease in tumor weight in contrast to DLC1-negative tumor lines. The combination treatment induced β-galactosidase and annexin V expression, markers of cellular senescence and apoptosis, respectively, exclusively in different

Dr. Brajendra Tripathi. Image courtesy of Dr. Brajendra Tripathi.

modonnell@rockefeller.edu.

Dr. Brajendra Tripathi, his spouse Dr. Veenu Tripathi, and their daughters Isha and Anika celebrating Anika's second birthday. Image courtesy of a friend, Dr. Sandhya Sanduja.

populations of treated cells (see micrograph). The combination treatment lowered levels of RhoA-GTP and induced senescence and apoptosis more effectively than treatment with either inhibitor alone. These observations suggest it might be clinically useful to combine drugs that use distinct mechanisms to reactivate the tumor suppressor activity of DLC1.

What drew you to translational cancer research?

I have an abiding interest in the clinical applications of basic research. DLC1 has a critical role in growth regulation, and the attenuation of its tumor suppressor activities by several kinases strongly suggests that DLC1 reactivation by inhibitors of these kinases could be useful for cancer treatment. As most of us know, tumors arise from the combined effects of oncogene activation and tumor suppressor gene inactivation, but most targeted therapies focus on inhibition of growth-promoting oncoproteins, with less consideration given to the reactivation of tumor suppressors. If the tumor suppressor protein DLC1 could be turned back "on" with pharmacological agents, such an approach would be novel in cancer therapy.

What kind of approach do you bring to your work?

I strongly believe that the key aspects to a productive laboratory are centered around maintaining a pleasant and cooperative working environment, along with sharing resources and knowledge. I am a strong supporter of collaboration in research and an advocate for training the next generation of scientists, encouraging them to ask questions and to dive into scientific research early on. I believe that I'm going to learn something new from each experiment whether it works or fails.

Are there any notable differences between working at the NIH and other research institutes?

I don't know if there are any specific differences between working at the NIH compared with other research institutes because NIH is the only place I have worked since my arrival in the United States, now almost 15 yr ago. What I know for sure and can say without any reservation is that the NIH is a great place to work. I have learned a lot and have updated my scientific skills through the various training programs that the NIH offers. The NIH has great educational opportunities and resources as well as a very pleasant work environment. Overall, the NIH has a great mix of people of different cultures and backgrounds coming together to make a difference in people's lives and better health for everyone.

"Most targeted therapies focus on inhibition of growth-promoting oncoproteins, with less consideration given to the reactivation of tumor suppressors."

What did you learn during your training that prepared you for the next stage of your career?

I consider myself extremely fortunate to have had great mentors throughout my scientific career. Dr. Doug Lowy is simply an outstanding mentor and a great person with whom I have learned a lot and from whom I am continuously learning. My experiences as a student and postdoc have made me realize setting up the right culture in the laboratory is extremely important, and Dr. Lowy's laboratory has a very caring, compassionate, and supportive atmosphere, but at the same time is scientifically rigorous. I can say I enjoy all aspects of my job, ranging from performing experiments, teaching junior members of the laboratory, preparing manuscripts and presentations, attending scientific seminars, and working with a passionate team. All of which I believe are prerequisites for becoming a leader in the field.

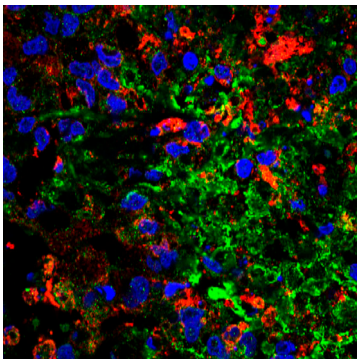
What has been the biggest challenge in your career so far?

A big challenge for me has been balancing my work and family life. My wife (also a scientist at the NIH) and I spend a lot of time in the laboratory, yet we want to have time for our kids as well. I hope that with time this will become easier, as our children grow. Scientifically, I have very limited experience in grant writing, and this is the area where I need improvement.

Any tips for a successful research career?

I don't have any golden advice and will only give tips to others whenever I become successful myself! Having said that, I can only suggest what worked best for me. Having a positive attitude is extremely important in life and also in the research field. There is no substitute for hard work. However, in addition to hard work at the bench, accomplishments in science involve interaction and discussion with peers. Success is the product of knowledge, hard work, sacrifice, and perseverance.

1. Tripathi, B.K., et al. 2008. *Mol. Vis.* 14:542–549.
2. Tripathi, B.K., and P.S. Zelenka. 2009. *Mol. Cell. Biol.* https://doi.org/10.1128/MCB.01098-09
3. Tripathi, B.K., et al. 2014. *J. Cell Biol.* https://doi.org/10.1083/jcb.201405105
4. Tripathi, B.K., and D.R. Lowy. 2017. *Oncotarget.* https://doi.org/10.18632/oncotarget.16805
5. Tripathi, B.K., et al. 2017. *J. Cell Biol.* https://doi.org/10.1083/jcb.201703105
6. Tripathi, B.K., et al. 2019. *J. Cell Biol.* https://doi.org/10.1083/jcb.201810098



The combined treatment of Saracatinib and MK-2206 leads to increased signals for both cellular senescence (green, β-galactosidase) and apoptosis (red, Annexin V) in DLC1-WT tumors. Image courtesy of Dr. Brajendra Tripathi.