Vigyan Patrika

Biopatrika

Tracing back the origin of craniofacial defects during early embryonic development

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Work done in the lab Prof. Sanjeev Galande at IISER Pune and Carl-Philipp Heisenberg at IST Austria

Dr. Saurabh Jagdish Pradhan obtained his bachelor's (B.Sc.) and Master's (M.Sc.) in Biotechnology from Modern College, Ganeshkhind (University of Pune). During his Master's, he got his first exposure to experimental science in the laboratory of Dr. Gopal Kundu at N.C.C.S Pune, where he worked on understanding the mechanism by which flavonoids inhibit tumor progression using melanoma models. He subsequently moved to the laboratory of Prof. Sanjeev Galande at IISER Pune to learn about chromatin dynamics and epigenetics. Initially, he worked as a project assistant and contributed to varied topics of research before starting his work towards a Ph.D. thesis focusing on chromatin dynamics during early embryonic development particularly in taking cell fate decisions. He used zebrafish as a model and worked in close collaboration with Dr. Mahendra Sonawane (TIFR-Mumbai) and Prof. Carl-Philipp Heisenberg (IST Austria). A part of this thesis work was recently published in Nature Communications. His primary interest lies in performing cross-species comparisons to understand developmental processes. To pursue his interest further, he recently joined the laboratory of Dr. Nicolas Rivron and is using stem cell-based embryo models to study cell fate decisions.

How would you explain your research outcomes to the non-scientific community?

Mutations in DNA sequences leading to perturbed biological functions result in rare genetic disorders. In our study, we focused on characterizing the genetic basis of craniofacial defects (related to the skeleton of the skull and face) which often results in abnormal jaw structures. Previous studies have successfully used mouse models to understand mechanisms. However, due to the limitations of the model system in use, it was difficult to probe into the very first events controlling craniofacial development. The use of zebrafish provided unique advantages because external fertilization and development can be followed up from a single cell to adulthood. Mutations in genetic loci of the SATB2 gene have been associated with craniofacial abnormalities in humans. Therefore, we decided to develop an experimental model by generating mutants for Satb2 in zebrafish. During this study, we observed mutations in Satb2 result in defective specification of a special type of cells called 'neural crest'. To support the early stages of development, the mother deposits many important ingredients in the form of RNAs and Proteins. Interestingly, our study also provided insights into how Satb2 protein when deposited by the mother behaves differently than when it is synthesized by the embryo itself. We believe our contribution will further strengthen our knowledge about developmental genetic disorders and can perhaps lead towards enabling early diagnosis of the same.

How do these findings contribute to your research area?

Early embryonic patterning and morphogenesis are regulated by the maternally deposited RNA and protein determinants. Subsequently, at the mid-blastula transition, maternal determinants are degraded as the quiescent zygotic genome is activated. Zygotic genome activation (ZGA) is essential for the initiation and maintenance of regionalized gene expression profiles crucial for the acquisition of unique cellular identities throughout development. In vertebrate embryos, pluripotency factors have been shown to provide transcriptional competence to activate the zygotic genome. However, how the precise timing of the onset of ZGA is controlled is unknown. More importantly, how changes mediated in the chromatin landscape during ZGA are channelized into patterns of gene expression during the specification of cell types is less explored. In this study, we have addressed the molecular mechanisms underlying these intertwined processes. We have described a biphasic and bimodal requirement for the Satb2 during early embryonic development in zebrafish. Interestingly our study highlights the switch between functions of SATB2 from a repressor of transcription during ZGA to an activator of a special subset of neural crest progenitor cells during organogenesis.

What was the exciting moment during your research?

There were a couple of moments that particularly stand out in this exciting journey. Perhaps they were also moments of conviction and satisfaction. The first, when we created a mutant for SATB2 and its micro-CT scans revealed similar phenotypes observed in human pathological conditions. We were excited about this because we realized we have a very powerful tool in hand that will enable us to systematically investigate the early onset of these disorders. The second moment was when we realized that maternally deposited SATB2 regulates zygotic genome activation by acting as a repressor molecule. This completely blew us as very few factors have been documented to perform contrasting functions during such a small developmental window.

What do you hope to do next?

Galande lab will further focus on understanding the molecular mechanisms by which SATB2 protein can perform these contrasting functions in such a short developmental period. I have now moved for my post-doctoral studies at IMBA Vienna where I am performing cross-species comparisons between mice and humans during early embryonic development.

Where do you seek scientific inspiration?

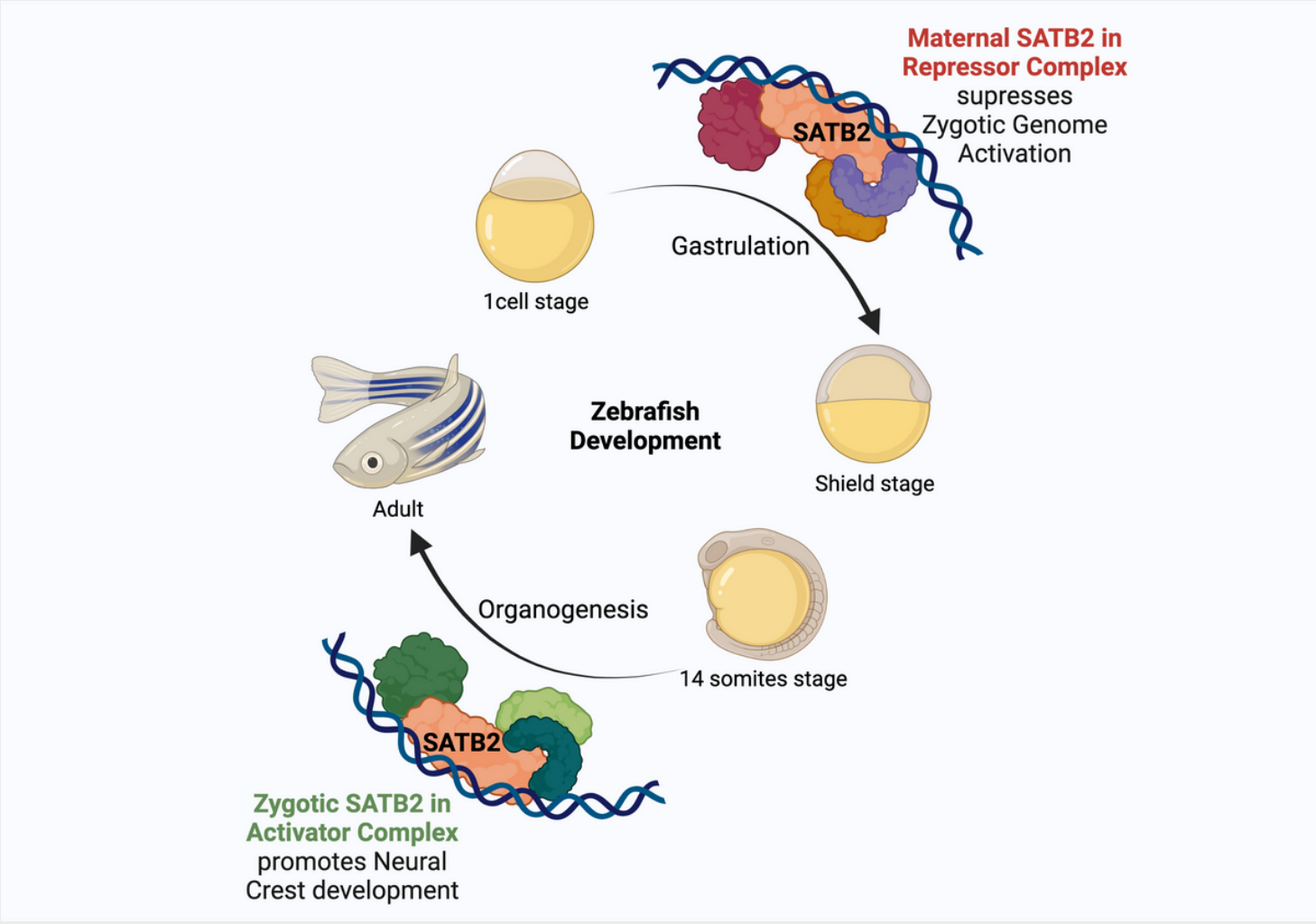
Frankly speaking, I do not have a single source of inspiration, or let's say unlike many other researchers do not have a particular story or incident which I can define as inspiring. I chose this path because I wanted to do something different from my classmates in high school. But as I embarked on this journey, I met many individuals from whom I tried to take a thing or two which I liked and admired. One thing I enjoyed most during this scientific journey is intense discussions with peers and attempting to understand the thought process behind every discovery.

How do you intend to help Indian science improve?

I was fortunate to have many collaborative visits to laboratories in Europe and USA. One thing that struck me very hard is the awareness about research opportunities and research methodologies is extremely poor amongst Indian students. This situation is concerning and needs a lot of attention at the system level. Currently, I am taking small steps by mentoring some students and making them understand how to approach a scientific journey with an open mind towards and embrace the day-to-day learnings. Every student will have their method of choice. However, it is equally important to understand if a particular method is acknowledged in the research community. I believe this will help students to reach their next goal. I am also interested in mentoring at the level of primary schools to expose them to the field of scientific research which I was completely unaware of.

Reference

Pradhan, S.J., Reddy, P.C., Smutny, M. et al. Satb2 acts as a gatekeeper for major developmental transitions during early vertebrate embryogenesis. Nat Commun 12, 6094 (2021). https://doi.org/10.1038/s41467-021-26234-7


Maternal SATB2 in
Repressor Complex
supresses
Zygotic Genome
Activation
SATB2
1cell stage
Gastrulation
Zebrafish
Development
Shield stage
Adult
Organogenesis
14 somites stage
SATB2
Zygotic SATB2 in
Activator Complex
promotes Neural
Crest development