Prion-like p53 amyloids and their link to cancer pathogenesis

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Dr. Ambuja Navalkar’s interview with Bio Patrika hosting “Vigyaan Patrika,” a series of author interviews. Dr. Ambuja is currently working as an Institute postdoctoral fellow at IIT Bombay. She has completed her doctoral studies under the guidance of Prof. Samir K. Maji in the department of Biosciences and Bioengineering, Indian Institute of Technology Bombay. Previously, she has pursued her M.Sc degree in Biotechnology from the Maharaja Sayajirao University of Vadodara, Baroda, and her B.Sc degree in Biotechnology from Ruia College, University of Mumbai. She is interested in exploring the protein aggregation linked with cancer and neurodegenerative disorders. Apart from research, she enjoys reading, good food, and solving puzzles. She wants to pursue scientific research focused on fundamental processes in cells which can answer disease-relevant questions. Here, Ambuja talks about her work on prion-like p53 amyloid formation and its link to cellular transformation leading to tumorigenesis published in the Journal of Cell Science.

How would you explain your paper’s key results to the non-scientific community?
Our body cells grow, proliferate, and die in a balanced manner. Several proteins inside the cells regulate the proliferative pathways to maintain cellular homeostasis. If the cells experience stress conditions, many unwanted changes, like DNA damage and mutations, can accumulate in the cell causing deregulation of cell division, leading to diseases like cancer. Our research focuses on one of the possible causes of cancer by studying the p53 tumor suppressor protein, which is a cellular brake against tumor formation. p53 has evolutionarily conserved segments, which are aggregation-prone, that can drive its misfolding. p53 amyloid aggregates have been detected in cancer biopsies linking it directly to cancer.

In their altered conformation (misfolded and aggregated), prion proteins act as infectious and transmissible particles similar to viruses in human prion diseases like Creutzfeldt-Jakob Disease (CJD) and kuru. Our current study asks whether cancer can be a prion-like disease caused by p53 amyloid infection. We establish that induction of p53 amyloids in non-cancerous cells can enhance the oncogenic traits like resistance to apoptosis with high migrative and proliferative rates. p53 prions can be transferred to the next generation of cells, propagating transformative characteristics and increasing cell survival. Cells with p53 amyloids in mice can establish tumors in mice models in vivo. Interestingly, the oncogenic traits in cells are reversed when we disaggregate p53 using an in vitro synthesized peptide inhibitor against p53 aggregates. Hence, our results provide evidence to directly link p53 amyloid formation to cancer progression and provide a model wherein the transfer of p53 prions in an infectious manner across cells can potentially spread the cancerous phenotype.

What are the possible consequences of these findings for your research area?
Our findings establish the possible mechanism of cancer initiation and how the amyloid formation and spread of p53 aggregates contribute to the cancerous properties of the cells. The study also further highlights the possibility that cancer can be an infectious disease, although further in vivo studies are required to confirm this. Additionally, the disaggregation of p53 amyloids may be implemented for targeting, if not all, but a subset of cancers where p53 aggregation is responsible for cancerous transformation. Hence, this work paves the path towards the study of anti-aggregation therapeutics focusing on the p53 amyloid formation pathway to combat cancer uniquely.

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What was the exciting moment (eureka moment) during your research?
During my research, there were several exciting moments as we were exploring the consequences of p53 amyloid formation. My most memorable ‘eureka’ moment was when I was performing microscopic imaging of the cells induced with p53 aggregates, and I saw that the p53 amyloids are capable of transmitting through cell generations. This observation was pivotal to establish the prion-like transmissibility of p53 amyloid aggregates and led us to our in...
What do you hope to do next?
Currently, I am working as a postdoctoral researcher to understand the alterations in cellular pathways due to p53 amyloids, which lead to the transformation of cells. I look forward to exploring novel avenues to add to my expertise and keep me motivated every day. In the long run, I am interested in pursuing research on the unexplored aspects of human diseases like neurodegeneration and cancer for designing targeted therapeutics.

How do you intend to help Indian science improve?
Since I am in a learning phase, I seek to make the maximum contribution through dedicated research in biology as a scientist. In India, talent in young scientists should not suffer due to a lack of exposure to challenging opportunities, research funding, and mentorship. Being a part of this scientific ecosystem, I hope to resolve these issues as a researcher in my future journey. I believe that science should not be restricted by geographical boundaries and intend to contribute to interdisciplinary research beneficial to humankind globally.

Where do you seek scientific inspiration?
To quote Richard Feynman, “Study hard what interests you the most in the most undisciplined, irreverent and original manner possible.”

I believe that my scientific inspiration essentially comes from the desire to seek answers to biology’s unsolved puzzles. My passion for science is the alarm clock which wakes me up every morning, and I enjoy the thrill of designing new experiments. Apart from this, my mentor and lab mates have always been enthusiastic about scientific discussions, which have got me through the crests and troughs of academia.

Reference

Prof. SK Maji lab: https://www.bio.iitb.ac.in/~maji/

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