Vigyan Patrika

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Targetable metabolic vulnerabilities in HER2+ breast cancer brain metastasis

First author: Pravat K. Parida

Work done in the lab of Dr. Srinivas Malladi at UT Southwestern Medical Center, Dallas.

Pravat K. Parida is from Balasore, Odisha, India. He received his Bachelor of Science (Zoology) degree from Fakir Mohan University, Odisha, India, in 2009. He topped in his master's degree in Life Science from National Institute of Technology Rourkela, Odisha, India in 2011. During his master's degree, his research was focused on formulating Chitosan nanoparticles for the delivery of drugs and therapeutic proteins under the supervision of Dr. Bismita Nayak. He then joined Bose Institute, Kolkata under the joint supervision of Dr. Kuladip Jana, Prof. Kaushik Biswas and Prof. Anup Kumar Misra as CSIR-JRF in 2012. His doctoral studies majorly focused on anticancer activity of trans-stilbene derivative Z-DAN-11 which inhibits cancer progression through disruption of microtubule dynamics, driving G2/M arrest, and p53-dependent apoptosis. In the year 2019, he was awarded a Doctorate in Philosophy (Biochemistry) from Bose Institute, University of Calcutta, WB, India. He is currently working as a Postdoctoral Fellow at UT Southwestern Medical Center, Dallas, Texas-USA under the mentorship of Dr. Srinivas Malladi from May 2019. In the year 2020 he got the prestigious CPRIT postdoctoral trainee grant for two consecutive years for his project "Metabolic determinants of brain metastatic HER2+ breast cancer cells". His research interests includes Cancer Metabolism, Metastasis, Metastatic latency/dormancy, tumor recurrences, Tumor Microenvironment.

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

Patients with stage III or IV breast cancer with amplified human epidermal growth factor receptor 2 (ERBB2; HER2) have a high chance of developing brain metastasis which is one of the major causes for their poor survival. Brain metastases develop following the spread of cells from the primary tumor to the brain through the vasculature. The majority of disseminated tumor cells in the brain parenchyma perish. The surviving few may initiate synchronous metastases(S-BM) that are detected along with the primary tumor or adapt and stay latent (Lat) for months to years before triggering a metachronous metastatic outbreak or late relapse(M-BM) as shown in Figure 1. The survival dependencies of cancer cells with a similar genomic profile that have differentially adapted to the brain parenchyma are unknown. Understanding these differences is vital to devise effective strategies that identify and treat patients presented with synchronous or delayed metachronous metastases.

The differential disease presentation in a given distal organ can be well explained by "The seed and soil hypothesis". If we consider disseminated of tumor cells as seeds and brain micro-environment as soil then, in similar nutrient-enriched soil majority of seeds can perish, the surviving few based on their differential survival potential can either grow as big plant (S-BM) or persist as slowly germinating seed (Lat) and/or delayed growing moderate plants (M-BM), Figure 2.

Through a phenotypic screen in athymic mice, we isolated HER2+ synchronous (S-BM), latent residual (Lat) and metachronous (M-BM) brain metastatic cells. By investigating these brain tropic cells, we uncovered that the metabolic diversity within these cells and its impact on varied disease outcomes. Our key findings from the study can be summarized as follows: Tumor cell secreted lactate attenuates NK cell cytotoxicity and facilitates overt metastasis. Attenuating lactate secretion in S-BM impedes brain metastasis significantly, while M-BM adapts and survives as residual disease. In contrast to S-BM, Lat and M-BM survive in equilibrium with innate immunosurveillance, oxidize glutamine and maintain cellular redox homeostasis through the anionic amino acid transporter xCT. Moreover, xCT expression is significantly higher in matched metachronous brain metastatic samples compared to primary tumors from HER2+ breast cancer patients. Inhibiting xCT function attenuates residual disease and metastatic relapse/tumor recurrence in these preclinical models.

How do these findings contribute to your research area?

HER2+ breast cancer brain metastasis is a major challenge in clinics. Systemic anti-HER2 therapies are highly effective for extracranial metastasis but ineffective on brain metastases, despite adequate delivery and activity in the brain parenchyma. Although small-molecule brain permeable tyrosine kinase inhibitors are approved for treating HER2+ breast cancer patients with intracranial metastasis, the overall survival benefit to patients is short lived. Current systemic therapies targeted towards HER2+ brain metastatic disease are not curative and patients with synchronous, latent residual or metachronous brain metastases are treated with the same regimens despite differences in clinical presentation. Our study suggests several potential approaches to limit residual disease and outgrowth of brain metastasis. First, targeting lactate metabolism reactivates innate immune surveillance and results in elimination of aggressive metastatic cells that lack redox modulating capabilities. Second, pharmacological inhibition of xCT (with erastin) or glutamine metabolism in combination with current standard of care anti-HER2 drugs is therapeutically beneficial to limit residual disease, potentially delaying metastatic relapse. The erastin analogue PRLX 93936 is currently undergoing clinical testing in multiple myeloma (NCT01695590); clinical use or trials of this strategy to delay brain metastasis in HER2+ metastatic breast cancer patients are warranted. Finally, these findings may also have broader therapeutic applicability to other cancer with a propensity to disseminate to the brain.

What was the exciting moment during your research?

Our early observations suggested higher glutamate secretion in Lat and M-BM cells. Based on those findings we looked for a possible transporter that is responsible for the same. From RNA sequencing data analysis, we found one of the glutamate transporters xCT (heterodimer of SLC7A11 and SLC3A2) was significantly enriched. I tried 5 times with different approaches to validate the xCT protein expression between S-BM, Lat and M-BM but was not able to detect any signal. During the pandemic, our Institute was shut down for 40 days between March-April 2020. Once it re-opened, I tried the same for the 6th time with little change in the western-blot protocol. Finally got the signal. This is the moment which I will never forget in my life. This reminds me of the statement of Colin Powell "There are no secrets to success. It is the result of preparation, hard work, and learning from failure". I believe my never give-up-mentality guided me to this eureka moment.

What do you hope to do next?

Tumor relapse or recurrence is a common problem associated with cancer. Many patients considered disease-free post-treatment develop secondary tumors within months to decades. Clinical and experimental data suggest that cancer cells disseminate from the primary tumor, early, even prior to initial diagnosis. It is believed that those disseminated latent residual cells that survive in distal organs are responsible for the tumor relapses or recurrences in distal organs like the brain, bone, lungs etc. However, directly working with human patient samples has been a challenge. So, we need a better animal model that can mimic clinical

findings. In the future, I will work on developing new preclinical metastatic models in animals. By studying in detail, I will try to understand the molecular and metabolic determinants of organ-specific metastasis and develop suitable drugs to target against metastatic disease.

Where do you seek scientific inspiration?

My teacher during my bachelor's degree Dr. Janardan Behera has been a great inspiration for me who influenced me to a great extent. Of late my wife Minu's curiosity-driven simple scientific questions have really impelled me in research. My current mentor Dr. Srinivas Malladi's in-depth knowledge and unique approach in interpretation of results has been a great inspiration to me.

How do you intend to help Indian science improve?

Currently, Indian science is way behind developed nations considering cancer patient sample preservation, maintenance of database and use in research. As a cancer biologist, I believe that each and every bit of patient material is very critical not only for diagnosis but also for treatment. We all know how patient-derived xenografts and related preclinical animal models have helped enormously to cancer therapy. I am really motivated to bridge the gap between clinicians and nonclinical cancer research labs in terms of patient material transfer. This will definitely help future cancer research in India.

Reference

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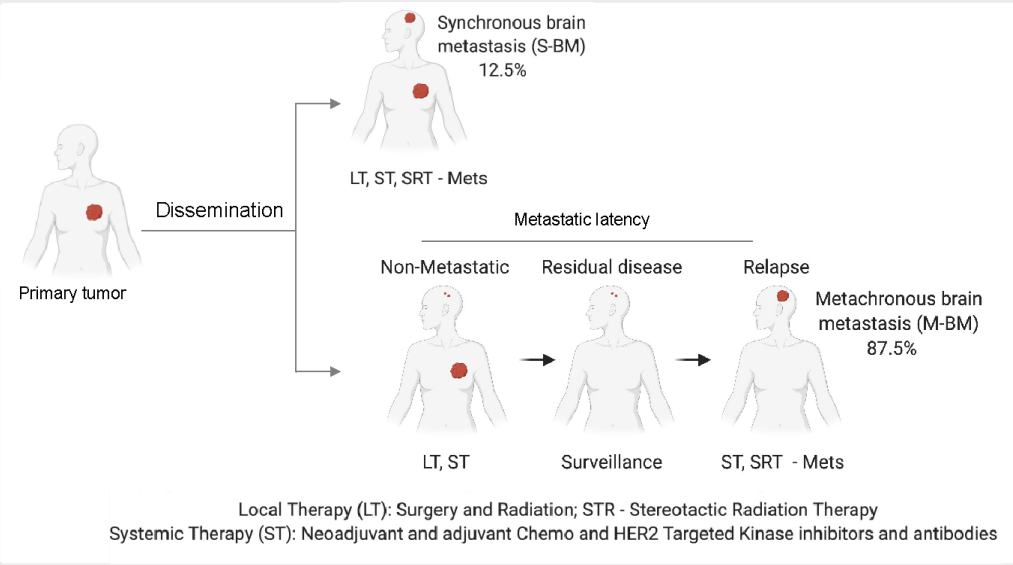

Figure1: Showing disparate metastatic disease presentation (Synchronous and metachronous brain met) in HER2+ breast cancer.

Figure 2: Showing differential metastatic potential of HER2+ disseminated cancer cells (seeds) in brain (soil).