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Exosomes: the stiffness-tuned nano-boosters of cancer progression

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Work done in the lab of Dr. Shamik Sen at IIT-Bombay & Dr Sejal Patwardhan at ACTREC-Tata Memorial Centre.

Dr Sejal Patwardhan is a Principal Investigator at Advanced Centre for Treatment Research and Education in Cancer (ACTREC)-Tata Memorial Centre and Assistant Professor, Homi Bhabha National Institute (HBNI), Mumbai. Dr. Patwardhan completed B.Sc. in Biotechnology from Mumbai University and did her Masters in Biotechnology from Maharaja Sayajirao University of Baroda, Gujarat. She then earned her Ph.D. in Life Sciences from Bhabha Atomic Research Centre; where she explored biochemical aspects of tumor microenvironment with respect to survival, metastasis, and therapy resistance in response to cancer radiotherapy. She then moved to IIT Bombay for her post-doctoral studies, wherein she focused on biophysical cues of the tumor microenvironment.

After her post-doctoral studies, Dr Patwardhan wrote an independent competitive extramural grant which was funded by DBT in the form of 'Innovative Young Biotechnologist Award'. As a young investigator, she chose to probe the effect of ECM stiffening on exosome secretion of cancer cells and its influence on cancer invasion. Dr. Patwardhan commenced this work in Dr. Shamik Sen's Lab in IIT-Bombay. After securing a faculty position in ACTREC, she continued and concluded the project in her own lab at ACTREC. She triumphed to publish her findings in a highly prestigious and high-impact journal, Biomaterials. Dr. Patwardhan is the first as well as corresponding author of this publication.

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

Any tissue is made up of cells held together by a cementing material called extracellular matrix (ECM). As cancer progresses, the tumor tissue becomes stiff due to increased deposition and crosslinking of collagen fibers in ECM. Tough ECM makes cancer cell's life easy. There is a direct effect of ECM mechanics on cellular processes, which helps in cancer cell proliferation & metastasis. Numerous studies have highlighted the role of cytokines & soluble factors secreted by cancer cells in ECM rigidity and cancer spread. However recently, a new form of the acellular, tiny component has been identified to be secreted by cells, namely exosomes. Exosomes are the tiny courier guys, almost 1000 times smaller than cells from which they are secreted in the surrounding. They help in exchanging signals, carrying metabolites and other cargo between cancer and normal cells. Exosomes are hitherto not explored as mediators of ECM and cancer cells crosstalk.

To address this, we grew human breast cancer cells on ECM substrates of varying rigidity. Interestingly, we noticed that cells grown on stiff ECMs secrete more exosomes than those grown on soft ECM. We further observed that cancer cells, when grown on stiff ECMs, migrate fast. However, if we block the exosome secretion, the motility of cells is reduced drastically, suggesting the key role of stiffness-regulated exosomes in breast cancer metastasis.

We then dissected the content of exosomes using various approaches, which identified thrombospondin-1 as a vital molecule that is elevated by several folds in exosomes secreted under stiff ECM conditions. Analysis of human patient tumor samples also suggested the potential role of exosomal thrombospondin-1 in breast cancer metastasis. Our study identified a culprit which can be targeted to deal with ECM hardening coupled breast cancer spread.

How do these findings contribute to your research area?

Gaining an in-depth understanding of steps involved in cancer spread and its regulation by many factors prevailing in tumor microenvironment is imperative to design smart strategies to control disease progression.The field of ECM dynamics and mechanotransduction (transmission of mechanical signals into biological signals) majorly revolves around the direct effects of ECM mediated by integrins. These membrane sensor proteins trigger the signaling cascade further.

Adding a new dimension to current understanding, our findings for the first time revealed that ECM hardening modulates exosomes content and its secretion. We further showed how these ECM modulated exosomes play an instructive role in breast cancer cell motility and invasion. Our study sheds light on the indirect yet profound effects of ECM stiffening on cancer motility featuring exosomal thrombospondin-1 as a master regulator. These pioneering findings have opened a myriad of avenues to explore exosomes and especially exosomal thrombospondin-1 as a promising theranostic target.

What was the exciting moment during your research?

The journey was a roller coaster ride! In every segment, after a series of futile efforts (which are inevitable in research), I experienced a couple of breathtaking, super exciting moments. The very first of it was when we succeeded in the isolation of exosomes, the moment I saw the exosomal pellet, and there was a visible difference in pellet size in stiff ECMs compared to soft ECM, I was thrilled. When I visualized the exosomal samples under electron microscope revealing high quality, pure preparations, it was satisfaction at another level.

While digging the mechanism of the phenomena observed, the approach was totally exploratory; we didn't have any hypothesis or candidate molecules in mind. However, despite a blind and rigorous analysis, proteins involved in ECM modulation, cell adhesion and motility emerged as master regulators. This gave us the confidence that we are on the right track and that something robust will come out, and guess what, every analysis/technique we undertook, thrombospondin-1 unanimously emerged as a master player.

What do you hope to do next?

This study has contributed bidirectionally. On one side, it has unraveled the novel mechanism by which ECM stiffening fosters breast cancer spread, which added a new horizon to cancer biology research. On the other hand, it has given rise to many leads, which warrants further investigation. Moving ahead on the path of translating our findings into clinical applications, we intend to validate the diagnostic or prognostic potential of exosomal thrombospondin-1 to predict metastasis in breast cancer patients.

Where do you seek scientific inspiration?

Life itself is a fascinating inspiration for me. As researchers, we are constantly evolving on the spectrum of knowledge and ignorance towards understanding 'life'. As we know more, we identify more things that we don't understand than what we truly appreciate. This process is highly challenging, and the urge to find out more keeps the motivation on for me. One can simply get amazed with the beauty of the life processes, their coordination, intricacy, regulation, timing, and wholesomeness. The farther we move towards being knowledgeable about it, the more puzzled we get as to how this complex system is operating so accurately at such a minuscule level. It is an inexpressible feeling derived from the joy of understanding life, which is the biggest scientific inspiration propelling me to continue with the journey of science.

How do you intend to help Indian science improve?

Since ancient days, Indian science had a glorious past, and it's needless to say that history repeats itself - India is

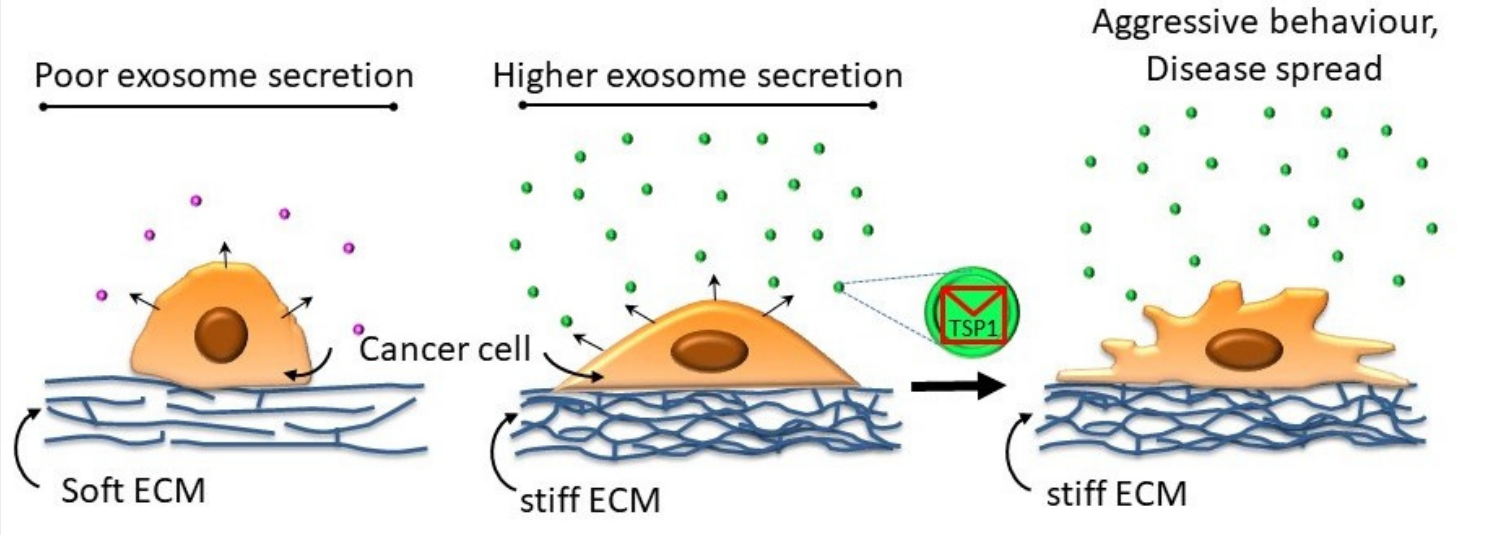
full of talent, ideas, and creativity. India harbors unique pool of extremely talented researchers owing to its diverse segment of population and possess huge untapped potential among the young and motivated researchers. This immensely valuable asset can propel the stature of Indian science to towering peaks in coming time. With rapid policy-making and blossoming funding opportunities, the Government is catering to the need of the budding researchers with some state-of-the-art facilities of international standard across the labs.

In recent years, we have been heading towards building infrastructure to support cutting-edge research due to awareness for research and development with access to precious resources. As a Principal Investigator, I would mentor and nurture young minds to stimulate their scientific inclination. I would educate and scientifically groom them such that they can contribute remarkably to any scientific questions that we pick, leading to the betterment of humankind.

I would also contribute to science awareness and outreach program by writing articles in science magazines to communicate science phenomena, scientific findings, and career options in science to young students, which will motivate them to pursue science.

Reference

Sejal Patwardhan*, Pratiksha Mahadik, Omshree Shetty, Shamik Sen*, ECM stiffness tuned exosomes drive breast cancer motility through thrombospondin-1, Biomaterials, 279,122285, 2021 (* Corresponding author) https://doi.org/10.1016/j.biomaterials.2021.121185



Role of ECM stiffness-modulated exosomes in breast cancer spread: ECM stiffnening leads to excessive exosome secretion. Thrombospondin-1 (TSP-1) packaged in exosomes induce various changes in cells making them more aggressive and motile leading to cancer exacerbation.