Cellular Signaling Gone Awry: How Extracellular Vesicles Promote Cancer Angiogenesis

By Laura Powell, Graduate Student

Over 65,000 people develop head and neck squamous cell carcinoma (HNSCC) each year, and the 5-year survival rate is less than 50%. These statistics highlight the importance of research performed by Vanderbilt University postdoctoral fellow Shinya Sato, Ph.D., in the lab of Alissa Weaver, M.D., Ph.D., Professor of Cell and Developmental Biology. Sato's work, published in *JCI Insight*, has looked at a signaling pathway in HNSCC that leads to blood vessel formation in the tumors.

Sato originally aspired to be a pediatrician and completed medical school in Japan, but realized research was his greater passion. During his graduate studies at Nagoya City University in Japan, Sato became interested in cancer research, in part, because of the lack of effective therapies for advanced-stage cancer patients.

"It was very sad for me," Sato says of the lack of effective therapies. "My dream was to cure these patients completely, but I realized it is very difficult to cure cancer. Now, my hope is to improve patient lifespan."

His own interests in cancer angiogenesis, and the recommendation of a former Weaver lab member and fellow native of Japan, led Sato to move to the US to join the Weaver lab. His work has focused on extracellular vesicles (EVs), or particles that are released from cells and help cells communicate. In order to grow, tumors need a constant supply of oxygen and nutrients which they access by stimulating new blood vessel formation in a process known as angiogenesis. Researchers hypothesized that EVs may contribute to angiogenesis, but the mechanism by which this occurred was not understood.

Shinya Sato, Ph.D. (left) with his wife and son. (Photo submitted)

To address this question, Sato and his colleagues performed a proteomic analysis of EVs purified from HNSCC cells. Their analysis identified several proteins in the ephrin receptor (Eph) family that had previously been shown to regulate angiogenesis and one of the Eph proteins, EPHB2, is overexpressed in some patients. This overexpression correlated with decreased patient survival.

Additionally, Sato's study revealed that when HNSCC cells release EVs expressing EPHB2, they bind to ephrin-B2 on endothelial cells, resulting in phosphorylation of STAT3 and promotion of angiogenesis, likely through alterations in gene expression. Sato is optimistic about the potential use of drugs that would inhibit EPHB2, especially if used in combination with pre-existing therapies, but says there are some caveats to consider.

"EPHB2 is a good target for anti-angiogenesis therapy, but we should screen patients that would benefit from such a drug, since not every patient's tumor expresses EPHB2."

Sato's postdoctoral work at Vanderbilt led to his current role as Chief Physician at Kanagawa Cancer Center Research Institute in Yokohama, Japan. While he was thrilled to accept the prestigious position, Sato says returning to Japan required adjustment for his family, especially his 5-year-old son who was at first sad to leave the US.

"He's adjusting though. One month after returning to Japan, he's back in his routine and enjoying Japanese sushi again."

Learn More:

Sato, S, et. al., EPHB2 carried on small extracellular vesicles induces tumor angiogenesis via activation of ephrin reverse signaling. *JCI Insight* (2019) 4(23): e132447.