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TRPM7 protein key to breast cancer metastasis in animal models

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The protein transient receptor potential melastatin-like 7 (TRPM7) is a critical determinant of breast cancer cell metastasis, according to study results published in *Cancer Research*, a journal of the American Association for Cancer Research.

"The most important discovery that we report in this paper is that TRPM7 is required for metastasis, at least in a xenograft model of breast cancer metastasis," said Frank van Leeuwen, Ph.D., assistant professor at the Radboud University Medical Center in Nijmegen, the Netherlands. "While this fundamental biological finding will not have an immediate impact on patient care, we believe that it opens the door to a previously under-explored area of cancer therapeutics.

"TRPM7 functions as a cation channel. As such, it is in a class of proteins that is already therapeutically targeted to treat diseases; for example, cation channel blockers are used to treat several heart conditions. Given that cation channels are druggable, our data provide clear rationale for probing whether drugs that target this class of proteins could block metastasis."

Central to tumor metastasis are changes in the capacity of tumor cells to adhere to other cells and tissue at the original tumor site and changes in their ability to migrate. As TRPM7 was known to be involved in regulating cell adhesion and migration, van Leeuwen and his colleagues, including researchers at The Netherlands Cancer Institute in Amsterdam, set out to investigate whether TRMP7 had a role in cancer cell

metastasis.

They evaluated whether the level of expression of the TRPM7 gene correlated with breast cancer progression. In primary breast tumors removed at diagnosis from a cohort of 368 women, high levels of expression from the TRPM7 gene were associated with significantly shorter times to both recurrence of disease and occurrence of distant metastases. This association was validated in an independent cohort of 144 breast cancer patients.

"We were able to show that high levels of TRPM7 expression independently predicted poor patient outcome in these two cohorts of women," said van Leeuwen. "Whether this is useful for forecasting patient prognosis awaits further validation. Moreover, it has become increasingly clear that it is not possible to stratify breast cancer patients into prognostically meaningful groups based on the level of expression of a single gene. TRPM7 would, therefore, need to be part of a panel of markers predictive of metastasis."

Having established a clinically relevant link between TRPM7 levels and metastatic disease in breast cancer patients, van Leeuwen and his colleagues examined the underlying molecular mechanisms using in vitro and in vivo assays.

The results indicated that knocking down TRPM7 expression in invasive human breast cancer cells impaired their ability to migrate in vitro and their metastatic potential when transferred into mice. Further analysis pinned down molecular and cellular reasons for these observations.

"Our working hypothesis is that TRPM7 has a key role in the cross-talk that goes on between breast cancer cells and their environment," van Leeuwen said. "Breast cancer cells are very sensitive to environmental cues. We think, but have no formal proof as yet, that TRPM7 channels

are sensors that enable breast cancer cells to perceive changes in their environment."

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