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Scientists identify potential target to reduce progression of metastases

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A team of researchers at the IRCM, led by Dr. Jean-François Côté, made an important discovery in breast cancer, which will published online this week by the scientific journal *Proceedings of the National Academy of Sciences* (*PNAS*). The Montréal scientists identified the DOCK1 protein as a potential target to reduce the progression of metastases in patients suffering from breast cancer, the most common type of cancer in women.

Dr. Côté's laboratory is interested in metastasis, which is the spread of cancer from an organ (or part of an organ) to another. Nearly 90 per cent of cancer patient deaths are attributable to metastasis, thus explaining the importance of understanding the underlying cellular and molecular mechanisms of this harmful process.

"Despite important breakthroughs in breast cancer treatment, few mechanisms are known to explain the spread of metastases," says Dr. Côté, Director of the Cytoskeletal Organization and Cell Migration research unit at the IRCM. "We are looking to identify the proteins that regulate the metastatic process so that new agents can be developed and combined with current treatments."

Two major breast cancer subtypes, HER2+ and Basal, have a tendency to be metastatic and recurrent, and are ultimately associated to a poor survival rate. Research at the IRCM was conducted on the HER2+ type (Human Epidermal growth factor Receptor 2), which represents approximately 25 per cent of breast cancer cases. HER2 positive

tumours tend to develop and spread more quickly than other types of tumours.

"By studying a genetic mouse model with HER2+ breast cancer, we identified the protein DOCK1 as an important regulator of metastasis," explains Mélanie Laurin, doctoral student in Dr. Côté's laboratory and first author of the study. "When we eliminated this protein in mice, our results showed a significant decrease in lung metastases. We also discovered that the DOCK1 protein contributes to the growth of tumours."

"To show the correlation between the expression of DOCK1 and breast cancer prognosis, we performed an analysis of several databases of patient genic," adds Dr. Benjamin Haibe-Kains, researcher at the IRCM who collaborated with Dr. Côté's team. "We did indeed discover that high levels of DOCK1 in HER2+ or Basal breast cancer patients are associated with a lower prognosis, or recurrence of the disease."

"Our work defined a new molecule required for the progression of breast cancer to the metastatic stage and allowed us to identify new markers that could become potential targets to stop the progression of metastases," concludes Dr. Côté. "We also showed that a chemical inhibitor of the DOCK1 protein, developed by Dr. Yoshinori Fukui, our collaborator in Japan, can stop the migration of cancerous cells. These results could eventually lead to the development of drugs that would limit the progression of metastatic breast cancer and could thereby improve patient prognosis."

"We are proud to fund this research," comments Melody Enguix, Scientific Communication Advisor at the Canadian Cancer Society. "The findings are another important step toward understanding how we can stop metastases, which are the cause of most breast cancer deaths."

More information: Rac-specific guanine nucleotide exchange factor DOCK1 is a critical regulator of HER2-mediated breast cancer metastasis, www.pnas.org/cgi/doi/10.1073/pnas.1213050110

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