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Dasatinib sensitizes triple negative breast cancer cells to chemotherapy by targeting breast cancer stem cells

Jun Tian

McGill University, Canada

Patients with triple negative breast cancer (TNBC) exhibit poor prognosis and are at high risk of tumor relapse and metastasis due to the resistance to conventional chemotherapy treatments. Tumor recurrence and resistance to chemotherapy have been in part attributed to the presence of breast cancer stem cells (BCSCs), a subpopulation of breast cancer cells that possesses stem-like properties. Therefore, targeting BCSCs is a priority to overcoming chemotherapy failure in TNBCs. We generated chemotherapy-resistant TNBC cells through cyclic treatments with paclitaxel (pac). The pac-resistant cells displayed increased self-renewal potential and higher percentage of BCSC subpopulations compared to the parental TNBC cells. A screen with various kinase inhibitors revealed dasatinib, a Src kinase family inhibitor, as a potent suppressor of BCSC numbers and a blocker of self-renewal ability in chemotherapy-resistant breast cancer cells. We also found dasatinib to block pac-induced BCSC enrichment and Src activation in both parental and pac-resistant TNBC cells. Interestingly, dasatinib induced an epithelial differentiation of the pac-resistant mesenchymal cells, further resulting in their enhanced sensitivity to paclitaxel. The combination treatment of dasatinib and paclitaxel not only decreased the proportion of BCSCs and their self-renewal capacity but also synergistically reduced cell viability of pac-resistant cells. *In vivo* studies, using xenograft mouse preclinical models of breast cancer further demonstrated the efficiency of the dasatinib/paclitaxel combination treatment in inhibiting tumor growth. Together, these results highlight dasatinib as a promising anti-BCSC drug that could be used in combination with paclitaxel to overcome chemotherapy resistance in TNBC.

Biography

Jun Tian is currently a fifth year PhD student in Department of Medicine, McGill University, Canada. She has received her Bachelor of Science degree from Nankai University, China in 2013. Her research interest focuses on studying the role of breast cancer stem cells in breast cancer initiation, metastasis and chemotherapy resistance. So far, she has published seven co-authored scientific articles in peer-reviewed journals.

jun.tian3@mail.mcgill.ca

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