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Targeting triple-negative breast cancer by inhibiting cancer stem-like cell (CSC) expansion

Triple negative breast cancer (TNBC) is highly progressive and lacks established targets for therapeutic intervention. p38 γ mitogen-activated protein kinase (MAPK) (gene name: MAPK12) is overexpressed in TNBC but overexpressed p38 γ contributes to TNBC remains unknown. Here, we show that p38 γ activation promotes TNBC development and progression by stimulating cancer stem-like cell (CSC) expansion and may serve as a novel therapeutic target for TNBC. p38 γ silencing in TNBC cells inhibits mammosphere formation and reduces levels of key CSC drivers' expression including NANOG, Oct3/4, and Sox2. Moreover, p38 γ MAPK-forced expression alone is sufficient to stimulate CSC expansion and to induce malignant transformation with a phenotype resembling to TNBC *in vitro* and *in vivo*. Furthermore, p38 γ depends on its activity to stimulate CSC expansion and breast cancer progression, indicating a therapeutic opportunity by application of its pharmacological inhibitor. Indeed, the non-toxic p38 γ specific pharmacological inhibitor pirfenidone selectively inhibits TNBC growth *in vitro* and/or *in vivo* and significantly decreases CSC population. Mechanistically, p38 γ stimulates NANOG expression through AP-1 via interaction with c-Jun. These results together demonstrate that p38 γ drives TNBC development and progression and may be thus a novel therapeutic target by stimulating CSC expansion. Inhibiting p38 γ activity with pirfenidone may be a novel strategy for the treatment of TNBC.

Biography

Guan Chen completed his PhD from Heidelberg University, Germany and Post-doctoral Training from Dana-Farber Cancer Institute, Harvard University, Boston, USA. He has been a tenured full-Professor of Pharmacology at Medical College of Wisconsin for more than 10 years. He serves as an Editorial Board Member of several international Journals.

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