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On-target PIM-1 and STAT3 inhibition thwarts disease progression in xenografts of gastric cancer stem-likecells

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Background: Peritoneal dissemination is characterized by an aggressive clinical course, therapeutic resistance, and striking molecular heterogeneity. Cancer stem-likecells (CSCs) closely model this molecular heterogeneity and likely have a key role in tumor recurrence and therapeutic resistance. Emerging evidence indicates that signal transducer and activator of transcription3 (STAT3) is an important mediator of tumor cell survival, growth, and invasion in peritoneal dissemination that correlated with PIM-1 expression. Herein, we generated characterized 12 clones cells populations in gastric tumors with distinct properties that have stem cell-like characteristics, to evaluate the translational potential therapeutics by PIM-1 inhibitors.

Methods: CSCs were cultured inDoxorubicin resistant condition;condense sphericity and highlyexpression of stem cells marker (CD133, CD44, DLL4 and LGR5) were determined by soft agar, real-time PCR. Endogenous PIM-1 and STAT3 activity was assessed in human gastric tissue, CSCs and animal xenografts by immunohistochemistry, PET/CT and Western blotting. PIM-1 inhibitors were used to inhibit PIM-1 and STAT3 activity *in vitro* and *in vivo*.

Results: Both PIM-1 and STAT3 activity was demonstrated to be highly activated in human gastric tissue, molecularly heterogeneous CSCs tumors and CSCs xenografts. PIM-1 inhibitors or PIM-1 siRNA knockdown administration resulted in on-target STAT3 inhibition and dramatically reduced CSCs survival, soft agar assay and stem cells markers. CSCs animal xenografts maintained high levels of activated PIM-1 and STAT3 activity seen in their parent tumors. Intraperitoneal PIM-1 inhibitors reduced intratumoral PIM-1 and STAT3 activity,stem cells marker and prolonged animal survival.

Conclusion: Our study demonstrates the *in vitro* and *in vivo* efficacy of on-target PIM-1 and STAT3 inhibition in heterogeneous CSCs that closely emulate the genomic and tumorigenic characteristics of molecular heterogeneityin cancer stem-likecells.

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Application of proteomic variations in personalized medicine of cancer

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Tumor heterogeneity and individual difference are actually derived from individualized variations. No two completely same individuals exist in the world. Variations are involved in each aspect of healthcare. Cancer contains highly heterogeneous cell types that are the distinguishing pathophysiological basis and causes the proteomic variation. In combination with multiple endogenous and exogenous factors, that proteome variation is the basis for personalized patient treatment. Differences in the proteins (the proteome) can distinguish among those heterogeneity structures. The components of a proteome dynamically change as a cancer progresses. Changes in protein expression, protein modifications, and protein molecular network, individually or in combination, might be biomarkers to predict the disease, monitor the tumor progression, and develop an accurate molecular classification for personalized patient treatment. The modalities of proteomic variation might also be useful in the interventional prevention and personalized treatment of patients to halt the occurrence and progression of a tumor.

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