SOD2 exerts a suppressive role in awakening of quiescent prostate cancer cells

Mengfan Liu[1,2], Yang Li[1,2], Rongchen Dai[1,2], Xue Jiang[1,2],
Zhichao Xi[1,2*] and Hongxi Xu[1,3*]

[1] *School of Pharmacy, Shanghai University of Traditional Chinese Medicine;*

[2] *Engineering Research Center of Shanghai Colleges for TCM New Drug Discovery;*

[3] *Shuguang Hospital, Shanghai University of Traditional Chinese Medicine.*

**Correspondence: Zhichao Xi, xizhichaohaerbin@163.com; Hongxi Xu, xuhongxi88@gmail.com.*

Abstract:

Introduction: Recurrence is the leading cause of cancer-related death, which is attributable to the presence and re-activation of quiescent cancer cells (QCCs). QCCs are therapeutically challenging as they can withstand conventional treatment and resume proliferation by awakening. However, effective QCCs-targeting agents are lacking. Focusing on preventing prostate cancer (PCa) recurrence, aim of this study was to identify potential therapeutic target for quiescent PCa, and harness naturally-occurring compound to affect the target.

Materials and Methods: Quiescent PCa cells were established by 7-day serum withdrawal. Proteomics and transcriptomics were employed to identify differentially expressed proteins and mRNAs between quiescent and proliferative PCa cells. Two cell lines with stable knockdown or overexpression of the identified gene were established as experimental model to investigate the mechanisms of the identified gene in maintaining and wakening of quiescent state, using SYBR Green assay, colony-formation, immunoblotting, real-time PCR and flow cytometric analysis. In vivo experiments were conducted to mimic cancer recurrence and evaluate the inhibitory effect of a natural compound.

Results: Superoxide dismutase 2 (SOD2) was highly expressed in quiescent PCa cells. PCa patients with low SOD2 expression was associated with dismal relapse-free survival. SOD2 knockdown promoted the re-proliferation of quiescent PCa cells, whereas SOD2 overexpression induced apoptosis during the awakening of quiescent PCa cells, suppressed recurrent PCa tumour growth, and prolonged mice survival. Pterostilbene (PTE), a natural compound significantly inhibited the re-activation of quiescent PCa cells by elevating SOD2 expression, and SOD2 knockdown partially rescued PTE-induced apoptosis in awakening quiescent PCa cells. PTE additionally impeded relapsed tumour growth of quiescent PCa cells in xenograft nude mice model.

Conclusions: SOD2 exerts a suppressive role in awakening of quiescent prostate cancer cells and represents a promising therapeutic target for preventing PCa recurrence. Naturally-occurring compound PTE impedes awakening of quiescent PCa cells in vitro and in vivo by upregulating SOD2.

References:

1. Wan NNN, et al. Advances in therapeutic agents targeting quiescent cancer cells. *Acta Materia Medica*, 2022. 1(1), 56-71.
2. Wan NNN, et al. Towards a framework for better understanding of quiescent cancer cells. *Cells*, 2021. 10, 562.
3. Jiang X, et al. Safranal prevents prostate cancer recurrence by blocking the re-activation of quiescent cancer cells via downregulation of S-phase kinase-associated protein 2. *Frontiers in Cell and Developmental Biology*, 2020. 8, 598620.
4. Xi ZC, et al. Guttiferone K impedes cell cycle re-entry of quiescent prostate cancer cells via stabilization of FBXW7 and subsequent c-MYC degradation. *Cell Death and Disease*, 2016. 7, e2252.