Targeting Quiescent Cancer Cells: Conquering Treatment Resistance and Recurrence

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Abstract:

Introduction: Tumour heterogeneously consist of proliferating and quiescent cancer cells. Cancer cells can enter a quiescent state (G0 phase) to survive unfavourable conditions like nutrient and oxygen deprivation. Quiescent cancer cells (QCCs) are resistant to treatment and can reinitiate proliferation, driving tumour growth and metastasis. Despite their clinical impact, there is a lack of clinically available QCCs-targeting agents. Understanding factors governing the survival of QCCs is crucial for developing targeted treatments.

Materials and Methods: We first provide an overview of the mechanisms that regulate QCCs include CDK signaling pathway, CDK inhibitors, cyclins, c-Myc pathways, DYRK1B, non-coding RNAs, OXPHOS, autophagy-induced quiescence, quiescence-inducing microenvironment, etc. In the case of QCCs in bone, osteoblast-mediated bone formation helps initiate and maintain their quiescent state, while osteoclast-mediated bone resorption can re-activate QCCs, leading to re-proliferation. Therapeutic strategies involve maintaining the quiescent state of QCC, eliminating QCCs, re-activating QCCs to sensitize them to cancer treatment, and inducing quiescence in proliferating cancer cells.

Results: Next, we discuss natural compounds potentially target QCCs. Examples include Guttiferone K (isolated from Garcinia *yunnanensis* Hu.), Safranal (derived from saffron), and citric acid (from citrus peel extracts), which can maintain QCCs in a quiescent state and prevent re-proliferation. Saikosaponin A (SSA) extracted from Bupleurum DC. eliminates QCCs by enhancing autophagy, leading to cell death. All-trans retinoic acid, a derivative of vitamin A, induces quiescence in cancer cells through its action on neighbouring normal cells and inhibition of the extracellular matrix.

Conclusions: Developing effective QCCs-targeting agents is crucial for inhibiting cancer growth, progression, and recurrence. Challenges exist in translating these agents to the clinic. Combining

QCCs-targeting agents with conventional treatments may enhance response and disrupt recurrence, and suppress metastasis including of bone.

References:

1. Nik Nabil, WN, *et al*. Towards a framework for better understanding of quiescent cancer cells. *Cells*. 2021;10(3):562;
2. Nik Nabil, WN, et al. Advances in therapeutic agents targeting quiescent cancer cells. *Acta Materia Medica*. 2022;Vol. 1(1);
3. Dai, R, et al. Osteoblasts and osteoclasts: an important switch of tumour cell dormancy during bone metastasis. *J Exp Clin Cancer Res*. 2022;41(1):316.