Crack the state of silence: Tune the depth of cellular quiescence for cancer therapy

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ABSTRACT

The regulation of cellular quiescence underlies numerous physiopathological phenomena. We recently found that quiescence depth can be tuned as to adjust a dimmer switch, by altering the expression of genes in the Retinoblastoma (Rb)-E2f pathway. Reducing quiescence depth may wake dormant cancer cells and make them susceptible to treatment.

Quiescence is a sleep-like cellular state in which cells are dormant but retain their ability to re-enter the cell cycle and divide upon growth signals. This “reversibility” is a salient feature that distinguishes quiescence from other coma-like irreversibly arrested cellular states such as terminal differentiation and senescence. The reactivation of quiescent cells, including stem and progenitor cells in the body, is fundamental to tissue repair and homeostasis. Quiescence also protects cells against cellular stress and toxicity. In this regard, dormant cancer cells present a therapeutic challenge by often evading drug treatments, which may later lead to cancer relapse.

Quiescence is not a homogeneous but rather a heterogeneous cellular state. There are remarkable variations among quiescent cells in their likelihood to re-enter the cell cycle upon growth stimulation, which we term quiescence depth. In vitro, when cultured longer under quiescence-inducing signals (e.g., serum starvation or contact inhibition), cells progress into “deeper” quiescence, from which they require longer time and stronger serum stimulation to resume proliferation. Meanwhile, considerable heterogeneity in quiescence depth exists among cells in the same population under the same culture conditions. The heterogeneity of quiescence depth is also seen in vivo. Muscle stem cells and neural stem cells upon collateral or neural injury respectively become “alerted” and move to shallower quiescence, exhibiting an increased likelihood to proliferate upon the next stimulation.

Our recent work demonstrates that quiescence depth can be tuned continuously in the cell. Previously we have found that the Rb-E2f pathway (here Rb stands for retinoblastoma protein family, including Rb1, Rbl1/p107, and Rbl2/p130, and E2f stands for activator E2f transcription factors, including E2f1, E2f2, and E2f3a) functions as a bistable switch, converting graded and transient growth signals into an all-or-none E2f activation, which underlies the all-or-none transition from quiescence to proliferation. By experimentally testing the predictions generated from a mathematical model, we now show that the E2f-OFF state of the Rb-E2f bistable switch can be adjusted to different levels, as to adjust a dimmer switch, by altering the expression of genes in the Rb-E2f pathway (Fig. 1A).

Many cellular factors and mechanisms may affect quiescence depth by impinging on the Rb-E2f bistable switch and modulating its activation threshold (Fig. 1A). One such example is cell growth. We recently found that prior cell growth affects the depth of quiescent cells, likely by affecting the sensitivity of the Rb-E2f bistable switch to serum growth signals. Specifically, given the same immediate division history, quiescent cells that had more growth at the time of quiescence induction (i.e., those that had progressed further along the preceding cell cycle) exhibit a shallower quiescence depth. Further, we showed that the deterministic cell-growth memory, coupled with the stochasticity of the Rb-E2f bistable switch, quantitatively explains the quiescence heterogeneity in a population of isogenic cells under the same culture condition.

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growth, we anticipate that other quiescence regulatory activities, such as autophagy, DNA damage response, and stress response, to name a few, crosstalk with the Rb-E2f bistable switch and form an interconnected quiescence regulatory network (QRN). In the QRN, the Rb-E2f bistable module performs the necessary integration and conversion of various positive and negative growth signals into a binary E2f-OFF/ON output, while the other quiescence regulatory activities modulate the activation threshold of this Rb-E2f bistable module, which sets the ultimate metric of quiescence depth.

Elucidating the molecular mechanisms controlling quiescence depth may provide novel strategies to combat cancer, aging, and other hyper- or hypo-proliferation related diseases. As one example, dormant cancer cells, including many metastatic cells, evade chemotherapies that typically kill off actively dividing cells. These dormant cancer cells are, by nature, pro-proliferative with frequent mutations in the Rb-E2f pathway (e.g., the loss of Rb or Cdk inhibitors, or the amplification/over-expression of cyclins or Cdkks). Thus, dormant cancer cells are likely poised at shallower quiescence than healthy cells due to altered Rb-E2f network dynamics (Fig. 1B).³ Treatments that reduce the activation threshold of the Rb-E2f switch are then likely to first push dormant cancer cells but not healthy cells out of quiescence and expose them to chemotherapy. In this regard, we have recently identified two natural compounds purified from a medicinal mushroom *Ganoderma lucidum*. These two compounds, ergosterol peroxide and ganoderma-nondiol, were found to reduce quiescence depth by increasing basal E2f level, and appeared to preferentially target quiescent cancer cells (MCF7) instead of their normal counterpart (MCF10A) for apoptosis.¹⁰ Further investigating the nature of quiescence heterogeneity, especially how the Rb-E2f switch interacts with other regulatory activities to control quiescence depth in different cell types under different conditions, will help the development of novel strategies to better target dormant cancer cells, and correspondingly, cancer metastasis and recurrence.

Disclosure of potential conflicts of interest
No potential conflicts of interest were disclosed.

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