6th IPR Frontier Seminar

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A state of partial Rb inactivation and intermediate E2F activation safeguards proliferation commitment

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Abstract

Tissue repair, immune defense, and cancer progression rely on a vital cellular decision of whether to proliferate or stay in quiescence. Mammalian cells commit to proliferation by triggering a positive feedback whereby the transcription factor E2F activates cyclin-dependent kinase 2 (CDK2), which phosphorylates the E2F inhibitor retinoblastoma (Rb) leading to a further increase in E2F activity to express the genes needed for proliferation. How cells manage to trigger the positive feedback only when needed is a fundamental question since positive feedbacks can inadvertently amplify small perturbations as illustrated by neuronal death by excitotoxicity or hyperinflammatory immune responses. Here we use single-cell analysis of E2F and CDK2 activity dynamics to determine how cells control the positive feedback to safeguard proliferation commitment. Strikingly, cells spend variable times of a few hours to over 20 hours in a reversible state of intermediate E2F activity. The intermediate E2F activity is proportional to the amount of phosphorylation of an evolutionary conserved Threonine 373 (T373) site in Rb. The Rb T373 site is phosphorylated by CDK4/6 or CDK2 before the other Rb sites due to its much slower dephosphorylation rate compared to the other sites. Cells exit this intermediate E2F activity state by slowly dephosphorylating T373 and returning to quiescence, or by increasingly engaging the positive feedback between E2F and CDK2 to fully phosphorylate Rb and start proliferation. Only full phosphorylation releases Rb from chromatin while T373 phosphorylated Rb remains chromatin bound. Together, our study identifies a dedicated molecular state of intermediate E2F activation in which cells integrate fluctuating signals to reliably decide whether to disengage or fully engage the positive feedback that flips the Rb-E2F switch and initiates cell proliferation.