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Women and Future in Science Seminar

Selective Translation Orchestrates Key Signaling Pathways in Primed Pluripotency

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Cellular senescence induction leads to progressive cell death via the INK4a-RB pathway in naked mole-rats

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13:00-14:00 JST

← via Zoom Register here

https://riken-jp.zoom.us/meeting/register/tJYrf--hqjwqH9bxFLhSFeLa67AMhY2oRQQO

Selective Translation Orchestrates Key Signaling Pathways in Primed Pluripotency

Pluripotent stem cell identities, such as differentiation and infinite proliferation, have long been understood within the frameworks of transcription factor networks, epigenomes, and signal transduction, yet remain unclear and fragmented. Directing attention toward translational regulation, as a bridge between these events, promises to yield new insights into previously unexplained mechanisms. Our functional CRISPR interference screening-based study revealed that EIF3D maintains primed pluripotency through selective translational regulation. The loss of EIF3D disrupts the balance of pluripotency-associated signaling pathways, impairing primed pluripotency. Moreover, we discovered that EIF3D ensures robust proliferation by controlling the translation of various p53 regulators, which maintain low p53 activity in the undifferentiated state. Therefore, this study establishes a paradigm for selective translational regulation as a defining feature of primed pluripotent stem cell identity.

Cellular senescence induction leads to progressive cell death via the INK4a-RB pathway in naked mole-rats

Naked mole-rats (NMRs) have exceptional longevity and are resistant to age-elated physiological decline and diseases. Given the role of cellular senescence in aging, we postulated that NMRs possess unidentified species-specific mechanisms to prevent senescent cell accumulation. Here, we show that upon induction of cellular senescence, NMR fibroblasts underwent delayed and progressive cell death that required activation of the INK4a-retinoblastoma protein (RB) pathway (termed “INK4a-RB cell death”), a phenomenon not observed in mouse fibroblasts. Naked mole-rat fibroblasts uniquely accumulated serotonin and were inherently vulnerable to hydrogen peroxide (H2O2). After activation of the INK4a-RB pathway, NMR fibroblasts increased monoamine oxidase levels, leading to serotonin oxidization and H2O2 production, which resulted in increased intracellular oxidative damage and cell death activation. In the NMR lung, induction of cellular senescence caused delayed, progressive cell death mediated by monoamine oxidase activation, thereby preventing senescent cell accumulation, consistent with in vitro results. The present findings indicate that INK4a-RB cell death likely functions as a natural senolytic mechanism in NMRs, providing an evolutionary rationale for senescent cell removal as a strategy to resist aging.