TUMOUR RESISTANCE IN INDUCED PLURIPOTENT STEM CELLS DERIVED FROM NAKED MOLE-RATS

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The naked mole-rat (NMR, *Heterocephalus glaber*), a eusocial subterranean mammal native to Africa, is the longest-lived rodent (maximum lifespan, 30 years); its body mass, however, is similar to that of the house mouse, *M. musculus* (Ms). NMRs exhibit extraordinary resistance to cancer, which has never been detected in long-term observations of captured NMR colonies. Here, we report that NMR somatic cells exhibit a tumor suppressor response to reprogramming induction. Using retroviral transduction of mouse Oct4, Sox2, Klf4, and cMyc, we obtained NMR induced pluripotent stem cells (NMR-iPSCs). Although NMR-iPSCs exhibit pluripotency *in vitro*, they do not have teratoma-forming tumourigenicity *in vivo*. We show that the tumour-suppressor alternative reading frame (ARF), which is strongly suppressed in Ms-iPSCs and several types of cancers, is activated in NMR-iPSCs. Furthermore, NMRs harbour a unique frameshift mutation in oncogenic ES cell-expressed Ras (ERAS), which positively regulates the tumourigenicity of Ms-ESCs. On knockdown of ARF and expression of Ms-ERas, NMR-iPSCs acquired *in vivo* tumourigenicity and formed teratomas. Forced expression of Ms-Arf in Ms-iPSCs markedly reduced tumourigenicity. Moreover, ARF knockdown in ARF derepressed NMR-fibroblasts induced by several stressors, such as reprogramming, oncogenic stress, or serial passage, caused cellular senescence. We termed this phenomenon ARF suppression-induced senescence (ASIS), which appears to be an NMR-specific tumour suppression mechanism. ASIS may eliminate ARF-suppressed cells and result in the selection of an ARF- activated cell population during the generation of NMR-iPSCs. Thus, NMR-specific ARF regulation and disruption of ERAS regulate tumour-resistance in NMR-iPSCs. Our findings obtained from NMR-iPSCs provide new insights into mechanisms of tumourigenicity in iPSCs and cancer resistance in the naked mole-rat.