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Molecular biology of the role of CARF in aging and cancer: basic and interventional approaches

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CARF (Collaborator of ARF) was first cloned as an ARF-interacting protein and shown to regulate the p53-p21WAF1-HDM2 pathway, a central to tumor suppression via senescence and apoptosis. CARF inhibition in cancer cells led to polyploidy and caspase-dependent apoptosis. In order to determine the mechanism of CARF silencing-induced apoptosis, we examined various cell death and survival pathways including the mitochondrial stress, ATM/ATR, Ras/MAP kinase and retinoblastoma cascades in cultured CARF-compromised cancer cells. We found that CARF is a pleiotropic regulator with widespread effects; its suppression affected all investigated pathways. Most remarkably, CARF-knockdown elicited DNA damage response as evidenced by increased levels of phosphorylated ATM and gH2AX, leading to induction of mitotic arrest and eventual apoptosis. CARF was upregulated during replicative, oncogenic and stress-induced senescence in cultured cells. We demonstrate the upregulation of CARF beyond a certain threshold level causes shift of cellular phenotype from growth arrest to transformation and hence may provide a potential molecular bridge between aging and cancer.