Naked mole-rats appear to have unusual biological traits that protect against both the vagaries of aging and cancer. These mouse size rodents exhibit extreme longevity with maximum lifespan exceeding 30 years and unlike most mammals show a markedly attenuated age associated change in physiological and molecular features. Moreover, in contrast to the case of laboratory mice which are notoriously short-lived and highly susceptible to spontaneous neoplasia, cancer is exceedingly rare in naked mole-rats. Astonishingly, we have observed only one incidence of spontaneous neoplasia within our large (>2800), long-maintained (35+ year) captive colony, despite careful assessment of >2500 individual necropsies. Further evidence of the marked resistance of naked mole-rats to cancer is indicated by attempts at oncogenic transformation of naked mole-rat cells. Unlike cells from other mammals, in which transformation by oncogenes RAS and SV40 T antigen causes invasive xenograft tumors, naked mole-rat fibroblasts transformed with these oncogenes have no tumorigenic effects. Similarly, topical treatment with chemical carcinogens as well as prolonged exposure to UV did not induce skin cancers in the naked mole-rat. Pronounced differences in epidermal hyperplasia, cell senescence and molecular responses to these experimental treatments were evident between mice and naked mole-rats. Although both experimental treatments induced considerable DNA damage within 24h, pronounced species differences in the upregulation of several molecular pathways including Nrf2 signaling, DNA repair and apoptosis were evident. Data acquired to date confirm our hypothesis that naked mole-rats have mechanisms in place that protect against experimental induction of cancer by both chemical and physical stressors and highlight several cytoprotective mechanisms in the naked mole-rat and that are likely to play a key role in preventing cancer initiation and progression.