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Cancer cells co-opt the neuronal redox-sensing channel TRPA1 to promote oxidative-stress tolerance

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Generation of reactive oxygen species (ROS), a natural byproduct of oxygen metabolism, occurs in all aerobic organisms at a controlled rate. Cancer cells are subjected to numerous cellular insults, including dysregulated oncogenes and dissociation from their natural extracellular matrix niches, leading to the generation of high levels of ROS; therefore, defense system against oxidative stress is critical for cancer cell survival. Here, we show a non-canonical oxidative-stress defense mechanism through TRPA1, the redox-sensing Ca^{2+}-influx channel that we previously found in sensory and vagal neurons (Takahashi et al., *Nature Chem. Biol.*, 2011). In TRPA1-enriched breast and lung cancer spheroids, TRPA1 induces Ca^{2+} influx in response to ROS generated upon matrix deprivation in the inner spheroid cells and suppresses apoptosis, and its inhibition induces clearance of cells from the inner space. TRPA1 is also activated by ROS-inducing chemotherapies and drives chemoresistance, and its inhibition suppresses xenograft tumor growth and enhances chemosensitivity. TRPA1 does not affect cellular redox status but allows cancer cells to tolerate harsh oxidative stress through upregulation of Ca^{2+}-induced anti-apoptotic programs involving MCL-1. Interestingly, NRF2, an oxidant-defense transcription factor, directly controls TRPA1 expression, thus providing an orthogonal program for protection against oxidative stress together with canonical ROS-neutralizing programs that reduce oxidative stress. Thus, our study reveals a previously unrecognized oxidative-stress tolerance program involving a neuronal ROS sensor, TRPA1 and highlights its potential as a therapeutic target.