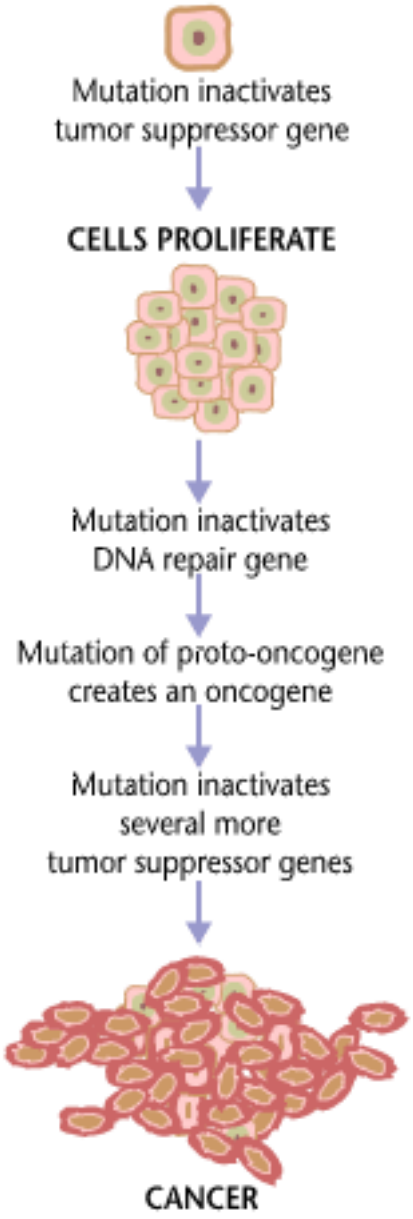
Resveratrol effects



The mechanisms of resveratrol's apparent effects on life extension are not fully understood, but they appear to mimic several of the biochemical effects of calorie restriction. Some studies indicates that resveratrol activates Sirtuin 1 (SIRT1) and PGC-1α and improve functioning of the mitochondria. Other research calls into question the theory connecting resveratrol, SIRT1, and calorie restriction. In addition resveratrol's ability to directly activate sirtuin 1 has been called into question.

A paper by Robb et al. discusses resveratrol action in cells. It reports a fourteen-fold increase in the action of MnSOD (SOD2). MnSOD reduces superoxide to hydrogen peroxide (H2O2), but H2O2 is not increased due to other cellular activity. Superoxide O2- is a byproduct of respiration in complex 1 and 3 of the electron transport chain. It is "not highly toxic, [but] can extract an electron from biological membrane and other cell components, causing free radical chain reactions. Therefore it is essential for the cell to keep superoxide anions in check." MnSOD reduces superoxide and thereby confers resistance to mitochondrial dysfunction, permeability transition, and apoptotic death in various diseases. It has been implicated in lifespan extension, inhibits cancer, (e.g. pancreatic cancer) and provides resistance to reperfusion injury and irradiation damage. These effects have also been observed with resveratrol. Robb et al. propose MnSOD is increased by the pathway RESV → SIRT1 / NAD+ → FOXO3a → MnSOD. Resveratrol has been shown to cause SIRT1 to cause migration of FOXO transcription factors to the nucleus[105] which stimulates FOXO3a transcriptional activity and it has

been shown to enhance the sirtuin-catalyzed deacetylation (activity) of FOXO3a. MnSOD is known to be a target of FOXO3a, and MnSOD expression is strongly induced in cells overexpressing FOXO3a.

Resveratrol interferes with all three stages of carcinogenesis—initiation, promotion and progression. Experiments in cell cultures of varied types and isolated subcellular systems in vitro imply many mechanisms in the pharmacological activity of resveratrol. These mechanisms include modulation of the transcription factor NF-ϰB, inhibition of the cytochrome P450 isoenzyme CYP1A1 (although this may not be relevant to the CYP1A1-mediated bioactivation of the procarcinogen benzo(a)pyrene), alterations in androgenic actions and expression and activity of cyclooxygenase (COX) enzymes. In vitro, resveratrol "inhibited the proliferation of human pancreatic cancer cell lines." In some lineages of cancer cell culture, resveratrol has been shown to induce apoptosis, which means it kills cells and may kill cancer cells. Resveratrol has been shown to induce Fas/Fas ligand mediated apoptosis, p53 and cyclins A, B1 and cyclin-dependent kinases cdk 1 and 2. Resveratrol also possesses antioxidant and anti-angiogenic properties.

Resveratrol was reported effective against neuronal cell dysfunction and cell death, and in theory could help against diseases such as Huntington's disease and Alzheimer's disease. Again, this has not yet been tested in humans for any disease.

Research at the Northeastern Ohio Universities College of Medicine and Ohio State University indicates that resveratrol has direct inhibitory action on cardiac fibroblasts, and may inhibit the progression of cardiac fibrosis.

Resveratrol also significantly increases natural testosterone production from being both a selective estrogen receptor modulator and an aromatase inhibitor.

In December 2007, work from Irfan Rahman's laboratory at the University of Rochester demonstrated that resveratrol increased intracellular glutathione levels via Nrf2-dependent upregulation of gamma-glutamylcysteine ligase in lung epithelial cells, which protected them against cigarette smoke extract induced oxidative stress.