In addition to resveratrol, three synthetic STACs, SRT1720, SRT2104, and SRT3025, may help prevent metabolic decline and type II diabetes.[15] In both diet- and genetically-induced models of obesity, SRT1720 has been shown to improve insulin sensitivity, lower plasma glucose levels, and increase mitochondrial capacity.[24] Moreover, SRT1720 extends the lifespan of mice fed a high-fat diet and prevents liver steatosis and insulin resistance.[107] Another STAC, SRT2104, also appears to improve insulin sensitivity and boost mitochondrial performance in mice.[108] However, the effectiveness of SRT2104 in humans remains less clear. While dietary supplementation with 2 g day^{-1} of SRT2014 in otherwise healthy cigarette smokers was shown to improve their lipid profile,[120] a recent phase II clinical trial in patients with type II diabetes failed to yield evidence of improved insulin sensitivity or glucose tolerance, ostensibly due to poor drug pharmacokinetics.[121] SRT3025 has been shown to reduce hyperglycemia and promote beta cell expansion in a mouse model of diet-induced type II diabetes, but human studies using this compound have not been attempted.[122]

11.4.3 Cancer

Even before its characterization as a SIRT1 activator, resveratrol had been investigated as a potential anti-tumorigenic agent. One of the first studies to test the effects of resveratrol on cancer, published in 1997, examined its topical application in a model of skin cancer.[123] This study demonstrated that resveratrol shows chemopreventive activity in three major stages of carcinogenesis, including anti-initiation activity, anti-promotion activity, and anti-progression acitivty.[123] Subsequent studies have demonstrated that systemic administration of resveratrol also prevents tumor growth in mouse and rat models of colon cancer,[124] prostate cancer,[125] gastric cancer,[126] and gamma-radiation-induced thymic lymphoma,[73] and that at least some of these effects are SIRT1-dependent.[73,127] However, resveratrol does not appear to protect against all cancers, and at least one study has suggested that it could in fact promote growth of certain tumor types.[27] For example, resveratrol was shown to be ineffective in treating breast cancer[109] and cancer-related deaths in old mice,[102] and to worsen survival in certain models of prostate cancer.[128]

Several classes of synthetic STAC appear to inhibit tumor growth and enhance tumor cell apoptosis. For example, both resveratrol and SRT2183 were recently shown to induce growth arrest and apoptosis of malignant lymphoid cells.[129] In addition, SRT1460, SRT1720, and SRT3025 block tumor growth and chemosensitize pancreatic cancer cells through a mechanism involving SIRT1-dependent lysosomal-mediated cell death.[130] SRT1720, which is the most well-studied synthetic STAC in the context of cancer, induces lysosomal-dependent cell death in breast cancer cells[131] and attenuates tumor growth in a mouse model of multiple myeloma.[132] However, like resveratrol, synthetic STACs may not always be beneficial for cancer treatment. SRT1720 has been shown to promote cell migration of breast cancer tumor cells to the lung[133] and to attenuate the antitumor activity of melatonin, a potent