

although deacetylase activity has not been reported for all members, all sirtuins contain a conserved catalytic core domain of 275 amino acids and require nicotinamide adenine dinucleotide (NAD⁺) as an essential co-factor.^{2,3} Sirtuins also differ in subcellular locations. SIRT1, SIRT6 and SIRT7 are nuclear proteins with distinct subnuclear localizations. For example, SIRT1 is detected in the nuclei but not the nucleoli, whereas SIRT7 is a widely expressed nucleolar protein associated with active rRNA. SIRT2 is predominantly a cytoplasmic protein, but it can also be located in the nucleus. SIRT3, SIRT4 and SIRT5 are mitochondrial proteins, although SIRT3 has also been reported to move from the nucleus to mitochondria during cellular stress.⁴ Sirtuins are controlling the activity of many proteins related to cell survival, inflammation, lifespan regulation, metabolism, cell cycle regulation, apoptosis and senescence, DNA repair and genome stability. Moreover, sirtuins can modulate lifespan in worms and flies, and their activities may underlie the beneficial effects of caloric restriction and moderate exercise, which are the best known experimental interventions leading to healthy aging and lifespan extension.^{4,5} Thus, sirtuin activation may help in preventing the aging-related decline in heart function and neuronal loss, as well as tumorigenesis.

Cancer can be considered as a collection of related diseases where its key feature is the uncontrolled rate of cell division. In the evolution from a normal to a neoplastic state, cells acquire different hallmarks that make them tumorigenic and ultimately malignant. These hallmarks are implicated in sustaining proliferative signaling, evading growth suppressors, avoiding replicative senescence, reprogramming energy metabolism, inducing angiogenesis, activating invasion by regulation of the cell motility and epithelial-to-mesenchymal transition, and increasing genome instability.⁶ Different sirtuins are key regulators of this wide variety of cellular and physiological processes, and can act either as tumor suppressors or as tumor promoters, depending of the cellular context. In this sense, sirtuins can be recognized as multiple functional proteins acting solely as tumor suppressor, as described for SIRT4, having a role as tumor suppressor or oncogene, as described for SIRT1, SIRT2, SIRT3 and SIRT6, or showing only oncogene-like activity, as SIRT5 and SIRT7.⁷ In those models where sirtuin activation favors cell transformation, pharmacological inhibition of sirtuins can be a valuable tool to aid in the fight against cancer. In this chapter we review the potential use of sirtuin inhibitors in the treatment of cancer.

12.2 Expression of Sirtuins in Cancer Cells

SIRT1, which is an orthologue of the yeast Sir2 protein,⁸ is the most studied among sirtuins, which have attracted great interest as a result of reports that calorie restriction (CR) could extend lifespan in mammals by inducing SIRT1 expression, promoting the long-term survival of irreplaceable cells and reducing cancer incidence.⁹ SIRT1 is a multiple functional protein that deacetylates various substrates, including histones, transcription factors, DNA repair factors and signaling proteins, thereby modulating their activity