

Moreover, it promoted cell proliferation, migration and lung metastasis in osteosarcoma cell lines and patient clinical samples, as compared to matched non-tumor tissue.⁴³

High SIRT3 expression in the cytoplasm significantly correlates with high tumor grades in positive lymph node status, and poor prognosis in colon cancer patients.⁴⁴ Again highlighting the double face of sirtuins in cancer, low levels of SIRT3 have been associated with poor outcome in breast cancer⁴⁵ but high levels of SIRT3 expression also predicted a poor prognosis in patients, increasing lymph node metastasis, pathological grade and tumor size for breast cancer.^{46,47} Only SIRT3 and, to a lesser extent, SIRT7 were overexpressed in three cell lines of oral squamous cell carcinomas (OSCC) compared with primary keratinocytes.⁴⁸

SIRT5 and SIRT7 have been described acting only as oncogenes in relation to tumorigenesis. SIRT5 was significantly increased in human NSCLC tissues at both protein and mRNA levels compared with adjacent normal lung tissues; it was associated with large tumor volume, metastasis and high disease stage, and predicted poor overall and disease-free survival.⁴⁹ Meanwhile, SIRT7 overexpression has been detected in hepatocarcinoma, thyroid and breast cancers.^{12,46,50} In addition to SIRT1, microRNAs are direct suppressors of SIRT7 and may function as tumor suppressors by controlling aberrant expression of SIRT7 in HCC tumorigenesis.⁵¹

12.3 Sirtuins and the Hallmarks of Cancer

The main feature during tumorigenesis is the increase in the number of cells. This increment can be produced by different mechanisms: by increasing the rate of cell proliferation, by avoiding apoptosis, or by a combination of both. The first non-histone substrate found for SIRT1 was p53, where the acetylation in lysine residues is indispensable for p53 activation. The tumor suppressor p53 inhibits the formation of tumors by controlling the cell cycle, apoptosis and DNA repair in response to various forms of genotoxic stress.⁵² Luo *et al.* and Vaziri *et al.* found that SIRT1-mediated deacetylation, with a specificity for its C-terminal Lys382 residue, antagonized p53-dependent transcriptional activation and apoptosis. SIRT1 activation avoided the increase in the levels of acetylated p53 upon exposure of cells to ionizing radiation. Conversely, levels of acetylated p53 were enhanced when the cells were treated with nicotinamide, a general competitive inhibitor of sirtuin activity.^{10,53} SIRT2 is also able to deacetylate and downregulate the transcriptional activity of p53 in HEK293 cells,⁵⁴ and recently it has been reported that p53 levels are also regulated by SIRT7 in NIH3T3 and U2OS cells.⁵⁵ SIRT7 overexpressing cells resisted both senescent and apoptotic effects of doxorubicin relocalizing SIRT7 from the nucleolus to the nucleoplasm, which resulted in decreased accumulation of p53 as well as its transcriptional targets, the well-known tumor suppressor p21.⁵⁵ Epigenetic suppression of p21 has been also reported in patients with HCC where SIRT7 gene expression was significantly upregulated and mediated mitotic stimulation of cells.⁵¹