EMT markers and promotes cell migration and invasiveness in epithelial and mesenchymal cancer cells. SIRT7 cooperates with SIRT1 to repress *E*-cadherin expression interacting physically with SIRT1, with the deacetylase activity of SIRT1 not being required for *E*-cadherin repression, but only the physical interaction between SIRT1 and SIRT7.[95] In accordance with these results, overexpression of SIRT7 also increased the motility of ovarian cancer cells.[96]

High levels of SIRT1 expression have also been associated with the regulation of EMT in other human cancers. SIRT1 expression has been correlated with poor prognosis of colorectal cancer and co-localized with the stem marker CD133. SIRT1 decreased the level of p53 allowing the expression of several genes associated with the stemness, whereas the SIRT1 inhibitor nicotinamide significantly decreased the percentage of $CD133^+$ cells.[27] However, the role of SIRT1 in tumorigenesis is, once again, controversial because overexpression of SIRT1 inhibited migration of OSCC cells *in vitro*, as well as their metastasis to the lung *in vivo*, increasing the expression of *E*-cadherin and decreasing the expression of mesenchymal markers, involving the deacetylation of Smad4, which can influence MMP7 expression, cell migration, invasion, and tumor metastasis in OSCCs.[97]

Finally, unlike other sirtuins, SIRT7 selectively binds to promoter regions of target genes and deacetylates Lys-18 of histone H3, stabilizing the transformed state of cancer cells, including anchorage independent growth and escape from contact inhibition, two important hallmarks of transformed cells.[98] Among the genes regulated by SIRT7, some microRNAs have been reported, with microR-34a downregulation being markedly correlated with tumor size, metastasis, disease stage and prognosis, which played a pivotal role in SIRT7-mediated effects on gastric cancer.[99]

12.4 Sirtuin Inhibitors as Anticancer Agents

In view of their varied functions in cells, sirtuins are a druggable class of enzymes that could have beneficial effects on a number of human diseases when selectively activated or inhibited by different molecules. Mammalian sirtuins are characterized by N- and C-terminal sequences of variable length and a 275 amino acid catalytic core region that consists of a large domain with a Rossmann fold, a small domain containing a three-stranded zinc ribbon motif and a cleft between the domains that form the binding sites for both substrates: NAD^+ and the acetylated Lys residue of a protein substrate.[100,101] This structural similarity means that a given molecule could inhibit different sirtuins simultaneously. Compared with sirtuin activators, which have been mainly developed for SIRT1, more studies have been performed for inhibitors against different sirtuins, especially as anticancer drugs.

12.4.1 Nicotidamine and Its Analogues

In the sirtuin-operated deacetylation of a protein, the enzyme binds acetylated proteins and NAD^+, releasing a molecule of nicotinamide by each acetyl-Lys hydrolyzed.[3] Nicotinamide (Figure 12.1A) has been demonstrated to be