21.4.1 Cancer

The onset and progression of various cancers involve substantial dysregulation of HDAC activity. The antitumor effects of HDACIs are suggested to be attributed to both transcriptional repression of proto-oncogenes and transcriptional reactivation of silent tumor suppressor genes.[73] Their effects may also be mediated by the regulation of DNA repair, inducing cell cycle arrest and apoptosis, inhibiting angiogenesis and long-term stimulation of immune response.[74] HDACIs are considered to be very promising candidates in cancer treatments since these agents preferentially kill neoplastic cells and are relatively non-toxic to normal cells,[75] though the molecular mechanisms of this selectivity remain to be elucidated.

A wide range of HDACIs are emerging as promising anticancer pharmaceuticals.[75–77] HDACIs such as belinostat, panobinostat, SAHA and FK228,[72] as well as TSA, sodium butyrate, vorinostat, valproic acid and romidepsinor,[78] showed substantial activity in both haematological and solid tumors in different tissues. In the last few years, HDACIs have undergone a rapid phase of clinical development in different cancer types, either as monotherapy or combined with other anticancer modalities. To date, three HDACIs have been approved by the FDA for the treatment of cutaneous/peripheral T-cell lymphoma,[79] and four HDACIs, namely vorinostat, belinostat, romidepsin and panobinostat, have been approved by the FDA for the treatment of hematologic cancers.[80] Many other HDACIs are at different stages of clinical development for the treatment of hematological malignancies and solid tumors.[79]

21.4.2 Metabolic and Cardiovascular Pathology

The FDA's approval of HDACIs as anticancer agents has provided the motivation for using these medicines as treatment options for non-malignant diseases. The beneficial outcomes of HDAC inhibition were obtained in treatment of various types of inflammatory, neurodegenerative and cardiovascular disorders.[80] In particular, experimental evidence has indicated that inhibitors of Class I HDACs can attenuate the development of cardiac hypertrophy and preserve cardiac function in several small animal models.[81] In addition, HDACIs have been found to be beneficial in preventing myocardial infarction, hypertension, atherosclerosis, vascular calcification, supraventricular arrhythmia, cardiac remodeling, fibrosis, and neointima formation.[82] The putative mechanisms mediating beneficial effects of HDACIs on the heart function include suppression of oxidative stress and inflammation, enhancement of cardiac protein aggregate clearance and autophagic flux, as well as inhibition of MAP kinase signaling.[83] In addition, since HDACIs were reported to promote β-cell proliferation, differentiation and function, and positively affect late diabetic microvascular complications, HDAC inhibition was proposed as a novel treatment strategy for type 2 diabetes.[84]