3 Inhibitors of Histone Deacetylases as Anti-inflammatory Drugs

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Abstract. This review addresses the issue of histone deacetylase (HDAC) inhibitors as developed for the treatment of cancer and for the investigation of the inhibition of inflammation. The review focuses on both in vitro and in vivo models of inflammation and autoimmunity. Of particular interest is the inhibi-
tion of pro-inflammatory cytokines. Although the reduction in cytokines appears paradoxical at first, upon examination, some genes that are anti-inflammatory are upregulated by inhibition of HDAC. Whether skin diseases will be affected by inhibitors of HDAC remains to be tested.

3.1 Introduction

In order to maintain the compact nature of DNA, chromatin is tightly wrapped around nuclear histones in distinct units called nucleosomes. The enzyme family called histone deacetylases (HDAC) maintains the histone proteins in a state of deacetylation so that DNA can bind tightly. A natural balance exists between histone acetylases (HAC) and HDAC. Synthetic inhibitors of histone deacetylases result in hyperacetylation of histones and the unraveling of the chromatin tightly wrapped in the nucleosome and allow transcription factors to bind and initiate gene expression. Developed for the treatment of cancer, inhibitors of HDAC increase the expression of a variety of genes, which are silenced in malignant cells. As such, the anti-tumor effects of HDAC inhibitors increase the expression of genes driving cell cycle, tumor suppression, differentiation and apoptosis (Marks et al. 2000, 2001; Richon et al., 1998, 2000, 2001). Suberoylanilide hydroxamic acid (SAHA) belongs to the class of hydroxamic acid-containing hybrid polar molecules that inhibit HDAC. SAHA suppresses the proliferation of cancer cells in vitro and reduces the growth of experimental tumors in vivo (Butler et al. 2000; Marks et al. 2001; Richon et al. 2001). SAHA, trichostatin A and butyrate are well-studied inhibitors of nuclear HDAC. However, SAHA also binds to S3 protein in the cytosol, a component of the ribosome (Webb et al. 1999). There are ongoing clinical trials of SAHA (Marks et al. 2001), and patients with cancer have been injected with increasing doses of SAHA (300–600 mg/m²) intravenously (O’Connor et al. 2001). Although solid tumors are treated in clinical trials with HDAC inhibitors, leukemias and multiple myeloma are often cancers that are first studied for treatment with HDAC inhibitors.