Preface: Histone Deacetylases as Therapeutic Targets

Histone deacetylases (HDACs) play a crucial role in regulating the gene expression underlying various biological processes including differentiation, development, response to stress, and damage. Such enzymes remove acetyl groups from histones at prominent amino-terminal lysine residues—usually promoting chromatin condensation and acting as transcription repressors—and from nonhistone substrates. HDACs seem to be deregulated in tumors and have been implicated in tumor development and progression; they are involved in the silencing of growth regulatory and apoptotic pathways. Indeed, increasing evidence supports a relationship between selected HDACs and tumor aggressiveness. Human HDACs are a large family comprising 18 proteins grouped into 4 classes based on phylogenetic analysis: class I includes HDACs 1–3 and 8; class II, HDACs 4–7, 9, and 10; class IV HDAC11; and class III, unrelated sirtuins. HDACs 1–11 are zinc-dependent enzymes and are targeted by broad-spectrum HDAC inhibitors such as the US Food and Drug Administration–approved drugs vorinostat, belinostat, romidepsin. The therapeutic potential of inhibiting HDACs to enhance the efficacy of treatment is emerging both from basic and translational research. In this special issue the functional role of HDACs in the epigenetic regulation of gene expression and in the modulation of multiple responses, as well as their potential as targets for pharmacological intervention in cancer therapy, is reviewed to provide an overview of relevant aspects of the role of HDACs in tumor biology and treatment.

HDACs play a crucial role in the regulation of gene expression, acting on histones as part of multiprotein complexes. Olzscha and colleagues review how HDACs can regulate gene expression at the molecular level, highlighting the contribution of such enzymes to the fine-tuning of transcriptional activity.

Montezuma and colleagues review the available literature regarding altered expression of HDACs in cancer tissues and describe recent results in the field, with particular emphasis on genitourinary cancer. These authors highlight that a variety of enzymes of the HDAC family have been reported to be upregulated in tumors with poor prognosis, suggesting that selected HDACs may be prognostic markers.

Chen and colleagues present the possible contribution of specific HDACs in selected tumor types, including hematological malignancies, underlying how HDACs participate in the regulation of gene expression by actin on histones and nonhistone substrates.

Regulation of acetylation of chromatin also occurs through the action of sirtuins, known as class III HDACs. Yang and colleagues review the role of one of the enzymes of this class, providing insights into the regulation of cancer cell biology and inflammation by sirtuin 1. Of note, sirtuins, which comprise multiple structurally related enzymes, have been implicated in the regulation of opposite phenomena, that is, oncogenesis and tumor suppression, thereby indicating the need for detailed molecular analyses of their role under different conditions.

The development of inhibitors tailored to HDACs has led to the identification of compounds that selectively inhibit specific enzymes. Such inhibitors are precious tools used to investigate the processes regulated by various isoforms. Haakenson and colleagues provide an example of the complex regulation of HDAC6-dependent functions. A complex interplay seems to occur among HDAC6 and the mitogen-activated protein kinase pathway, which sustains tumor cell survival. This evidence supports the relevance of different post-translational modifications (e.g., acetylation and phosphorylation) in cell survival mechanisms.

Arrighetti and colleagues review recent advances in the use of drug combination strategies based on HDAC inhibitors to improve the antitumor activity of drugs of different classes, including conventional chemotherapeutic agents and targeted agents, as well as immunotherapy. The variable effect of drug combinations in preclinical models likely reflects the complex role of HDACs, which act both in multisubunit transcriptional complexes, where they interact with DNA and are capable of recruiting specific HDACs to silence target genes, and in cellular compartments other than the nucleus, where they modulate the function of cytoskeletal and chaperone proteins.
HDACs play a relevant role in tumor-associated angiogenesis, a field in which relevant mechanistic insights have been achieved by the phenotypic characterization of knockout mice and by the use of pharmacological inhibitors. Turtoi and colleagues review experimental evidence regarding tumor-associated angiogenesis, paying attention to the critical role of HDAC7 and sirtuin1 in the regulation of vasculature development and to the unexpected and unwanted induction of proangiogenic factors triggered upon pharmacological inhibition of HDACs.

In the search for novel treatment options against cancer, the promising features of agents acting on the immune system are now emerging in different tumor types. Here, Schotterl and colleagues review the current status of research dealing with the modulation of immune responses by HDACs. HDAC inhibitors are endowed with the capability to regulate the transcription of immunostimulating genes, the production of cytokines, the activity and function of macrophages and dendritic cells, as well as the activity of effector cells of the innate and adaptive immune system.

Overall, different aspects of the biology of HDACs are presented here, taking advantage of the contributions of different scientists working in the field.

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