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Editorial

Protein Acetylation and the Physiological Role of HDACs

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It was in 1964 that V. G. Allfrey and colleagues first reported the isolation of acetylated histones and speculated—well ahead of their time—about their possible role in RNA synthesis [1]. About ten years later, the nucleosome was defined as the basic unit of chromatin [2] and soon thereafter DNAseI hypersensitivity analysis of isolated HeLa cells nuclei demonstrated that histone acetylation impacts on chromatin structure [3].

Since then, the importance of acetylation for the regulation of chromatin and gene activity has been demonstrated by numerous studies and this posttranslational modification is now rivaling phosphorylation in its importance. The field benefitted enormously from the early identification of molecules, such as Trichostatin A, which inhibit the enzymes removing acetyl groups—histone deacetylases (HDACs)—and thus lead to hyperacetylation of histones and chromatin [4]. These HDAC inhibitors (HDACis) turned out to have very interesting biological effects, such as induction of differentiation in cellular model systems. In addition, it had been realized that HDACis show antiproliferative potential when applied to cultures of transformed cells [5] and this sparked an enormous interest in their potential use for therapeutic purposes. A variety of substances, coming from natural or synthetic sources, have been tested in cancer models, and also in other pathologies, such as neurodegeneration, autoimmunity, or inflammation: in many cases target they were found to be beneficial. These inhibitors usually all or most of the HDACs—there are eleven of them—and therefore it is not clear yet which HDAC(s) are implicated in which pathology. The last ten years have witnessed a wealth of clinical trials, primarily in cancer, and also more recently in other settings, and today two inhibitors—SAHA and romidepsin—have been approved for clinical treatment of cutaneous T cell lymphoma. In parallel to this, genetic analysis of HDACs has progressed, in particular in the mouse, where all HDACs have now been ablated. This analysis revealed that some HDACs, such as HDAC1 or 3, are essential genes [6, 7], while others are dispensable for development, but show specific phenotypes when ablated, for example, organism-wide increased tubulin acetylation in the case of HDAC6 knockout mice [8]. In addition, conditional alleles of these and other HDACs have been generated allowing to test their function in specific organs or in combinations, by using appropriate Cre-expressing mice lines. These studies identified important roles for HDACs, for example, in the nervous system, in the heart, or in lymphocytes [9–11].

This special issue deals with "protein acetylation and the physiological role of HDACs." As should be evident from the important short introduction above, this is an exciting topic which has implications for basic research and a demonstrated increasing medical relevance.

Several reviews address the general role or regulation of HDACs (T. Hayakawa and J. I. Nakayama; C. Segre and S. M. Chiocca; A. Peserico and C. Simone). A number of reviews cover our recent understanding of the role of HDACs in cancer and various models are discussed, such as—among others—leukemia (C. Biagi et al.; L. Bagella and M. Federico), pancreatic cancer (A. Ouaissi et al.; C. Bevan and D. Lavery), breast cancer (A. Linares et al.), or the link between autophagy, apoptosis, and HDAC inhibition in cancer cells (H. Rikiishi). Also, several reviews address important aspects of HDAC function on nonhistone proteins (e.g., on interferon regulatory factor, A. Masumi) and in particular their role in the cytoplasm (S. Khochbin et al.; W.-M. Yang and

Y.-L. Yao; C. Creppe and M. Buschbeck). The importance of HDACs on cardiac development and function or in hypoxia is also addressed (H. Kook and H. J. Kee; N. Sang and S. Chen) and a number of additional topics are touched upon by dedicated reviews or a few primary data papers.

In summary, this special issue gives an excellent overview of the current status of research on HDACs and should be a valuable source of reference material for students or researchers.

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