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Targeting Epigenetics in Drug Discovery

Antonello Mai*[a]

Epigenetics has gained ground in recent years within the drug discovery and medicinal chemistry research communities, as an increased understanding of the role of epigenetics in various diseases has emerged and epigenetic targets have been validated for therapy.

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This Special Issue of *ChemMedChem* on *Epigenetics and Drug Discovery* brings together a diverse group of papers on a range of topics from bromodomain inhibitors and long non-coding RNAs to classic agents targeting histone deacetylases (HDACs) and less typical HDAC inhibitors, such as the chimeric compounds designed by Greg Thatcher et al. and featured on the Front Cover of the issue that both target HDACs and act as selective estrogen receptor modulators (SERMs).

Epigenetics is related to but distinct from genetics. The classical definition of epigenetics involves the mitotically and/or meiotically heritable changes in gene activity that do not implicate alterations in DNA sequence. Today, this definition should be expanded to the study of regulation of gene activity that includes heritable and non-heritable alterations. Thus, epigenetic events also comprise of, for instance, reversible changes that can be induced by environmental factors at different points in life.

Epigenetics focuses on at least five series of events involving changes of chromatin at molecular levels: DNA modifications,

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histone modifications, histone variants, noncoding RNAs, and nucleosome remodeling. Epigenetic control of transcription is essential to drive cells towards their normal phenotype, and epigenetic deregulation can lead to initiation and progression of human diseases, including cancer, inflammation, cardiovascular and neurodegenerative diseases, and metabolic disorders.

DNA methylation is controlled by the DNA methyltransferases DNMT1, DNMT3A and DNMT3B, three enzymes that catalyze the transfer of a methyl group from the substrate *S*-adenosyl-L-methionine (AdoMet) to the C5-position of cytosine, predominantly in the CpG islands. DNA methylation is essential and plays a crucial role in cell development and many other physiological events, but aberrant DNA methylation can lead to genomic instability and silencing of tumor-suppressor genes with cancer onset and development. Even though DNMT was the first epigenetic target investigated for which inhibitors were identified, only two drugs (azacytidine and decitabine, both nucleoside inhibitors), used for the treatment of myelodysplasia, have been approved to date by the US Food and Drug Administration (FDA). Furthermore, only a small number of non-nucleoside DNMT inhibitors have been reported so far, and these have been typically characterized by low potency and/or chemical or metabolic instability. In the present Special Issue, two research articles address this topic: Medina-Franco et al. discuss the repositioning of olsalazine, a known anti-inflammatory drug, as a novel DNA hypomethylating agent, and Arimondo and Cantagrel describe a multifaceted medicinal chemistry study around SGI-1027, a valuable non-nucleoside DNMT inhibitor.

Chromatin remodeling mainly involves three types of proteins: writers, which add epigenetic marks such as acetyl or methyl groups to histones (and also to non-histone proteins) through covalent bonds; erasers, which remove these marks from the lysine residues of histones; and readers, which read and recognize the epigenetic marks on histone tails thus activating appropriate signaling pathways. Really, the concept of the acetylome should be extended to the "acylome", since we now know that acylations other than acetylation can constitute epigenetic marks at the lysine ε–amino groups; this concept of the expanding acylome is nicely covered in this Special Issue by Christian A. Olsen.

Among the writers, histone acetyltransferases (HATs) catalyze the transfer of acetyl groups from acetyl-CoA to the ε–amino groups of lysine residues in histones, as well non-histone proteins, and their aberrant activity can lead to leukemia and other cancers. Writers such as HATs and histone methyltransferases (HMTs) are the subject of intense research, and three Communications in the Special Issue aim at elucidating further their roles in disease through novel assays (A. Jeltsch), chemical probe development (J. Jin), and inhibitor design for p300 HAT (D. Rotili, A. Mai) and Tip60 HAT (Y. G. Zheng).

Histone deacetylases (HDACs) are without a doubt the most famous class of eraser enzymes, and two HDAC inhibitors (vorinostat and romidepsin) have been approved by the US FDA for the treatment of the refractory cutaneous T-cell lymphoma. After the boom over the last decade of research identifying HDAC inhibitors (HDACi) for cancer therapy, and in light of emerging skepticism on the therapeutic value of HDACis as single agents, the focus of this field is now turning towards different directions. In particular, hot topics within the HDACi field involve: 1) the dissection of their mechanisms of action (see papers from L. Zhang, W. Xu, and X. Li); 2) the targeting of the multi-protein- and multi-HDAC-containing complexes rather than the deacetylases themselves (see papers from M. W. Van Dyke, and H.-J. Kim, G. Han); 3) the identification of isoform-selective (see papers from T. Suzuki, N. Miyata, and F. Thaler, C. Mercurio) or non-hydroxamate (see the research paper from C. A. Olsen et al.) inhibitors; 4) the design of hybrids molecules with both HDAC inhibitory and another chemotherapeutic activity, such as estrogen receptor modulation (G. R. J. Thatcher); and 5) the design of HDACi for diseases beyond cancer, such as malaria (see the Full Paper from K. T. Andrews, T. Kurz et al.).

Another important class of erasers is the lysine demethylases (comprising the lysine-specific demethylases and the Jumonji-containing enzymes), for which aberrant activity or overexpression has been related to the onset and development of cancer, and the number of studies seeking to identify selective inhibitors of these enzymes has grown in recent years. In this Special Issue, Schofield and Kawamura report the improved potency and selectivity in cells of the *n*-octyl ester of IOX-1, a known Jmj-C inhibitor previously reported by the same group.

In the last few years, many studies have been devoted to the investigation of reader enzymes rather than the classic writers and erasers (epi-enzymes), with the aim to obtain a sharper and more selective modulation of cellular signaling pathways with respect to what has been achieved so far through epi-enzyme inhibition. Thus, a great deal of effort has been made to identify small molecules capable of interacting with bromodomains (for acetylation mark), and the progress to date is nicely summarized by Hilmar Weinmann and his colleagues from Bayer. Novel approaches are reported in this Special Issue directed towards molecular dynamics simulations (D. Huang, A. Caflisch) and towards the identification of novel inhibitors (O. Mirguet et al.). The state-of-art for readers for the methylation mark (methyl-lysine binding proteins) is overviewed by Manfred Jung and co-workers in their Review article.

Finally, an emerging topic in the field of epigenetic drug discovery is long noncoding RNAs (lncRNAs). These are gene tran-

scripts that never get translated into proteins and are reported to play crucial roles in the regulation of genomic integrity and imprinting, mRNA processing, and other cell functions, such as differentiation and development, through epigenetic mechanisms. The modes of action of lncRNAs (*cis*- or *trans*-acting) in epigenetics are summarized in this Special Issue by Irene Bozzoni et al., and given the critical roles of lncRNAs, it is likely their therapeutic potential will emerge in the near future.

Epigenetics is a diverse and expansive area of research with vast therapeutic potential, as can be seen from the topics covered in this Special Issue. The contributions herein go some way to exemplifying the diversity of the research currently underway in both industry and academia, and from the work described and reviewed, the future is certainly bright for epigenetics in drug discovery. I hope that the readers of *ChemMedChem* will appreciate and enjoy this Special Issue.

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