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Editorial

Epigenetic drug discovery special issue

After deciphering the human genome it was recognized that additional levels of information are required to govern the function of an organism and that these are not solely based on the information encoded in the base sequence of the DNA. This layer of information beyond genetics has become known as Epigenetics. It describes inheritable changes of gene expression and, hence, the alteration of the phenotype of a cell or organism without a change in the genetic code.[1,2] The basic concepts of epigenetics were already recognized and the term was introduced over 60 years ago. Nevertheless, it took until the mid-90s to identify and characterize histone modifying enzymes as defined biochemical entities with a role in transcriptional regulation and in the pathogenesis of, for example, cancer. Today, we know that small non-coding RNA, DNA methylation and hydroxymethylation as well as post-translational modifications of histones such as acetylation or methylation constitute the biochemical basis of epigenetics.[3] Influences of the environment such as toxic chemicals, nutrition or even stress can alter gene expression and may persist through epigenetic mechanisms. Prominent examples are, for example, the epigenetic marks in identical twins that diverge increasingly with age[4] or the development of bee larvae to working bees respectively the queen bee. The development of one of the possible bee phenotypes is depending on whether they have been nurtured with pollen or gelee royale. The latter has been shown to contain an HDAC inhibitor, (*E*)-10-hydroxy-2-decenoic acid.[5] RNAi mediated silencing of the DNA methyltransferase DNMT3 leads to a queen phenotype.[6] An important example for human disease is the silencing of genetically intact tumor suppressor genes as a hallmark of carcinogenesis. Especially regarding drug discovery we are still in the infancy of epigenetics but already the first epigenetic drugs are approved for human use and promising candidates are in clinical trials.[7]

The large effort in epigenetic research has also been accompanied by a wealth of structural data on the respective targets in an attempt to understand the underlying mechanisms on a molecular level. A major contribution in that field was the crystallographic analysis of the nucleosome that showed not only how the DNA is wrapped around the histone octamer, but also how histone tails, the main targets of histone modifying enzymes, interact with DNA.[8] In addition, three-dimensional structures of epigenetic effector proteins have been obtained, either in a free state or complexed with cofactors, inhibitors or peptide substrates. Most of the structural work has been carried out on individual histone modifying enzymes or protein binding sites responsible for the specific recognition of epigenetic marks. The available structural data led to crucial molecular insight into the architecture that underlies epigenetic target recognition and will be helpful in the future development of small molecule modulators for epigenetic targets.[9]

In this issue, we present three review articles and nine original papers that deal with progress in the Medicinal Chemistry of Epigenetics, mainly on histone modifications. Firstly, we review the impact of protein structures and computer based approaches on epigenetic inhibitor development. Then, Huber et al. report the fascinating story of the NAD-dependent histone deacetylases (sirtuins), especially with light to their role in neurodegeneration and the conflicting evidence about sirtuin activators. Finally, Clausen et al. review on histone demethylases that are considered an upcoming class of anticancer targets with great promise. The series of original papers is started by de Lera et al. who present structure–activity studies on analogues of the natural product inhibitor psammaplin A that act as inhibitors of histone deacetylases (HDACs). The group of Ganesan presents also analogues and a total synthesis of natural products, specifically the highly potent HDAC inhibitor largazole. The sirtuins are then represented by two papers on synthetic inhibitors, namely coumarins and pyrimidines with a thiourea structure from the Mai group and thioureas with a benzimidazole scaffold by Link et al. The histone acetyltransferases (HATs) are covered by Sippl et al. with pyridoisothiazolone inhibitors and by Sbardella et al. who present alkylidene malonates with a mixed inhibition/activation profile. Lysine demethylases are covered by the papers of Ganesan and Miyata that both have developed novel analogues of the LSD1 inhibitor tranylcypromine. Finally, Jung et al. present arginine methyltransferase (PRMT) inhibitors that suppress androgen dependent gene activation. Thus, this set of papers at the forefront of Epigenetic Medicinal Chemistry covers a whole range of important epigenetic targets and shows promising directions for further research.

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