



Editorial

Epigenetics

Epigenetics comprises mechanisms that regulate gene expression without altering the DNA sequence [1,2]. Epigenetic changes are heritable from one cell to the other, and in some cases from parent to offspring. Importantly, epigenetic modifications integrate intrinsic and environmental stimuli and confer both lineage commitment as well as phenotypic plasticity [3]. Epigenetic mechanisms are thus involved in all biological processes and evidence on their important role in many diseases is emerging. In the present issue dedicated to EPIGENETICS we invited 14 contributions covering the topics of *Molecular Mechanisms, Diseases, Biomarkers, Chemical modifiers and Technologies*.

DNA methylation, histone modifications, nucleosome positioning and non-coding RNAs are the most studied epigenetic modifications. The steep decline in next generation sequencing costs and the development of bioinformatics tools has given access to genome-wide profiles of DNA methylation and histone modifications of many different cells types. This has led to the identification of new chromatin modifications and increased our comprehension of the *molecular mechanisms* of epigenetic regulation. Sawicka and Seiser describe the dynamics of histone H3 phosphorylation [4], while Auclair and Weber summarize the actual knowledge on DNA methylation and demethylation in a fundamental biological process such as development [5]. New epigenetic modifiers and readers have been identified and characterized. In this issue Kudithipudi et al. study the H4K20 lysine methyltransferase SET8, its targets and recognition motif [6].

Since epigenetic modifications are involved in gene regulation during differentiation and homeostasis with the ability to integrate environmental stimuli, it is not surprising that aberrant epigenetic patterns are found in many *diseases*. The role of epigenetic mechanisms in cancer is now well established and Hassler and Egger present an overview of the new concepts that are emerging thanks to epigenomic data [7]. Increasing data show that epigenetic regulation is also implicated in many other complex diseases. Kabesch and Adcock for example show how the environmental effects are integrated by epigenetic mechanisms leading to the development of respiratory diseases such as COPD and asthma [8]. Jimenez-Chillaron and co-workers illustrate how what we eat modifies our epigenetic marks and impacts on health [9].

Epigenetic modifications are reversible by *chemical modifiers* and have proven valuable as therapeutical targets. Seidel et al. review the recent advances in the development of chromatin modifying agents as anticancer therapy [10], while Gros et al. focus on DNA methylation inhibitors (DNMTi), the assays to identify them and analyze the expectations from the next generation of DNMTi

[11]. Then Hassler et al. describe how 5-aza-2'-deoxycytidine, an inhibitor of DNA methylation, induces the reactivation of tumor suppressor genes, senescence and apoptosis in a rare type of T cell lymphoma [12].

Additionally, Valente et al. describe the identification of highly selective histone methyltransferase inhibitors directed against PR-SET7 and EZH2 and their efficacy on the histiocytic lymphoma cell line U937 [13].

Epigenetics is a promising field for the development of new diagnostic, prognostic and predictive *biomarkers*. In addition, the increased access to epigenome-wide data facilitates the discovery of new biomarkers. In cancer patients, DNA methylation based markers are highly sensitive and can be detected in body fluids using minimal invasive procedures. As such the methylation status of Septin9 is used to detect colon cancer while the methylation status of MGMT is predictive of the response to temozolomide. How Kit et al. review the use, development and advantages of DNA methylation as biomarker for cancer, other diseases and prenatal diagnostics [14]. Kacevska and colleagues provide evidence for the epigenetic regulation by DNA methylation of the hepatic CYP3A4 gene, a major drug metabolizing enzyme in humans [15]. Their finding could explain interindividual differences in expression of this enzyme, which might have important implications for response or adverse effects of drugs in patients. Besides classic CpG methylation, non-CpG methylation has been detected in embryonic stem cells at high levels [16]. Pulverer et al. interrogated non-CpG (CCWGG) methylation in MCF7 breast cancer cells, childhood ALL and normal blood from healthy volunteers based on targeted microarrays. By testing 271 gene promoters, they could not detect non-CpG methylation, suggesting that only cytosines in the CpG context are methylated in tumor cells at detectable levels [16].

Sophisticated *technologies* are needed to follow chromatin states and dynamics to elucidate the functional aspects and origin of epigenetic marks. The advances in deep sequencing and the amount of collected data require good experimental design planning, quality control and bioinformatic analysis. Here Kaspi et al. discuss all these aspects for ChIP-seq approaches to map genome-wide histone modifications or protein-DNA interactions [17].

The development of new technological tools has dramatically increased our understanding of epigenetic regulation in recent years and we are now at the point of understanding that epigenetics not only impacts on certain phenomena such as imprinting, position effect variegation or X-chromosome inactivation, but is also essentially implicated in all cellular processes that are involved

in development, differentiation and homeostasis. Thus, a causative role of epigenetics is undisputable for cancer and other complex diseases. Epigenetic research has entered different fields and will help us to understand normal and pathological conditions. We expect in the near future to expand our current clinical standards for diagnosis, prognosis and therapy of different diseases, using novel epigenetic biomarkers and drugs, providing additional information to optimize and individualize patient management.

References

- [1] A. Bird, Perceptions of epigenetics, *Nature* 447 (2007) 396–398.
- [2] S.L. Berger, T. Kouzarides, R. Shiekhattar, A. Shilatifard, An operational definition of epigenetics, *Genes Dev* 23 (2009) 781–783.
- [3] A.P. Feinberg, Phenotypic plasticity and the epigenetics of human disease, *Nature* 447 (2007) 433–440.
- [4] A. Sawicka, C. Seiser, Histone H3 phosphorylation – a versatile chromatin modification for different occasions, *Biochimie* 94 (11) (2012) 2193–2201.
- [5] G. Auclair, M. Weber, Mechanisms of DNA methylation and demethylation in mammals, *Biochimie* 94 (11) (2012) 2202–2211.
- [6] S. Kudithipudi, A. Dhayan, A.F. Kebede, A. Jeltsch, The SET8 H4K20 protein lysine methyltransferase has a long recognition sequence covering seven amino acid residues, *Biochimie* 94 (11) (2012) 2212–2218.
- [7] M.R. Hassler, G. Egger, Epigenomics of cancer – emerging new concepts, *Biochimie* 94 (11) (2012) 2219–2230.
- [8] M. Kabesch, I.M. Adcock, Epigenetics in asthma and COPD, *Biochimie* 94 (11) (2012) 2231–2241.
- [9] J.C. Jimenez-Chillaron, R. Diaz, D. Martinez, T. Pentinat, M. Ramon-Krauel, S. Ribo, T. Plosch, The role of nutrition on epigenetic modifications and their implications on health, *Biochimie* 94 (11) (2012) 2242–2263.
- [10] C. Seidel, C. Florean, M. Florean, M. Dicato, M. Diederich, Chromatin-modifying agents in anti-cancer therapy, *Biochimie* 94 (11) (2012) 2264–2279.
- [11] C. Gros, J. Fahy, L. Halby, I. Dufau, A. Erdmann, J. Gregoire, F. Ausseil, S. Vispé, P.B. Arimondo, DNA methylation inhibitors in cancer: recent and future approaches, *Biochimie* 94 (11) (2012) 2280–2296.
- [12] M.R. Hassler, A. Klisaroska, K. Kollmann, I. Steiner, M. Bilban, A.I. Schiefer, V. Sexl, G. Egger, Antineoplastic activity of the DNA methyltransferase inhibitor 5-aza-2'-deoxycytidine in anaplastic large cell lymphoma, *Biochimie* 94 (11) (2012) 2297–2307.
- [13] S. Valente, I. Lepore, C. Dell'aversana, M. Tardugno, S. Castellano, G. Sbardella, S. Tomassi, S. Di Maro, E. Novellino, R. Di Santo, R. Costi, L. Altucci, A. Mai, Identification of PR-SET7 and EZH2 selective inhibitors inducing cell death in human leukemia U937 cells, *Biochimie* 94 (11) (2012) 2308–2313.
- [14] A. How Kit, H.M. Nielsen, J. Tost, DNA methylation based biomarkers: practical considerations and applications, *Biochimie* 94 (11) (2012) 2314–2337.
- [15] M. Kacevska, M. Ivanov, A. Wyss, A. Rane, M. Ingelman-Sundberg, DNA methylation dynamics in the hepatic CYP3A4 gene promoter, *Biochimie* 94 (11) (2012) 2338–2344.
- [16] W. Pulverer, M. Wielscher, R. Panzer-Grumayer, T. Plessl, A. Kriegner, K. Vierlinger, A. Weinhausel, The stem cell signature of CHH/CHG methylation is not present in 271 cancer associated 5'UTR gene regions, *Biochimie* 94 (11) (2012) 2345–2352.
- [17] A. Kaspi, M. Ziemann, H. Rafehi, R. Lazarus, A. El-Osta, A pipeline for the identification and characterization of chromatin modifications derived from ChIP-Seq datasets, *Biochimie* 94 (11) (2012) 2353–2359.

Paola B. Arimondo*

ETaC USR n°3388, CNRS-Pierre Fabre, CRDPF, 3 avenue H. Curien,
31035 Toulouse Cedex 01, France

Gerda Egger¹

Department of Pathology, Medical University of Vienna, Währinger
Gürtel 18-20, 1090 Vienna, Austria

E-mail address: gerda.egger@meduniwien.ac.at (G. Egger)

Jorg Tost²

Centre National de Génotypage, CEA-Institut de Génomique Batiment
G2, 2 rue Gaston Crémieux, CP5721, 91057 Evry Cedex, France
E-mail address: tost@cng.fr

* Corresponding author. Tel.: +33 534506492; fax: +33
534503492.

E-mail address: paola.arimondo@etac.cnrs.fr (P.B. Arimondo)

Available online 11 September 2012

¹ Tel.: +43 1 40400 6389.

² Tel.: +33 (0)1 6087 8423; fax: +33 (0)1 6087 8485.