

RESEARCH HIGHLIGHTS

Epigenetics in disease and well-being

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Abstract

The research education seminar ‘Epigenetics in disease and well-being’ organized by and held at Linköping University, Linköping, Sweden earlier this year, aimed to discuss the interaction between environmental factors and epigenetic modifications and its consequences for human and animal health. A selection of presented papers is hereby presented which highlighted the mechanisms by which environmental stressors challenge homeostasis to such an extent that the effects can become transgenerational but also proposed the development of epigenomic-based pre-emptive medicine.

Key words: research seminar; environment; stress; epigenetic misregulation; disease and well-being; Linköping University

Many diseases and dysfunctions of non-microbiological origin have substantially increased over the past 40–50 years. Common for many of these is the metabolic syndrome a series of metabolic risk factors that increase the predisposition of an individual to atherosclerotic vascular disease, hypertension and type-2 diabetes. Alongside, there is increasing evidence that environmental factors, including exposure to pharmaceutical and toxic chemicals act without direct damage to the genome but, by modifying gene expression they ultimately lead to dysfunction. Likewise, pre-conception, intra-uterine or even post-natal stress is able to increase allostatic load and prevent re-establishment of homeostasis, also ultimately leading to dysfunction via positive or negative modifications in the epigenome. Such epigenetic modifications can have long-lasting effects on development, metabolism and health even at later age, evidencing profound alterations of the epigenetic profile of an individual, animal or human, that could well be passed over generations. On the other hand, if a phenotype is caused by epigenetic modifications (as DNA-methylation, histone modifications of the action of non-coding RNAs) some of these pathways could be chemically reversed. The latter opens for the

development of eventual therapeutics of epigenetics, to modulate/reverse unfavorable processes.

A 2-day research education seminar, supported by the Japan Society for the Promotion of Science, brought together researchers from different backgrounds to a common focus: to understand the interaction between environmental factors and epigenetic modifications and its consequences for disease and well-being in humans and animals. The goal of the seminar was to provide a broad spectrum of research and current knowledge on trans-generational effects for graduate students, junior researchers and clinicians with the hope of stimulating future research projects and the improvement of personalized medicine. The meeting, organized by and held at Linköping University, Linköping, Sweden earlier this year, covered different aspects of comparative epigenetics, from basic research to epidemiological, animal and human cohort studies, bridging animal models with clinical human medicine. The program included topics on trans-generational effects of paternal- and maternal (mal)nutrition, on trans-generational epigenetic effects of stress on human health as well as on animal welfare including the role of retrotransposons and of glucocorticoids, the effect of

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adverse birth characteristics and of assisted reproduction techniques on male (in)fertility and epigenetics, and the linkage of past environmental exposures to current disease trends.

This and the following issues of *Environmental Epigenetics* shall include a selection of representative mini-review papers of held presentations. In this current issue, the paper by Laura Michele Hack and coworkers from the Max-Planck-Institute of Psychiatry at Munich, Germany, entitled 'Epigenetic mechanisms involved in the effects of stress exposure: Focus on DNA hydroxymethylation' [1], summarizes research on the use of 5-hydroxymethylcytosine (5 hmC) as epigenetic mark to monitor the development of stress-related disorders. Their paper highlights aspects of the dynamic regulation of 5hmC upon fear-related learning and memory providing evidence-derived from animal model-studies- of the importance of the hydroxymethylome on stress-related psychopathology.

Local contributors from Linköping University, Sweden highlighted further aspects of the effects of stress onto the epimodulation of neuropeptides. Annika Thorsell and Daniel Nätt summarize in their article 'Maternal stress and diet may influence affective behavior and stress-response in offspring via epigenetic regulation of central peptidergic function' [2], recent findings on the effects of gene-regulation following maternal malnutrition in model rodents with a focus on epigenetic regulation of peptidergic activity, particularly corticotropin-releasing hormone and the least studied neuropeptide Y (NPY), both involved in regulation of endocrine function, energy homeostasis, as well as affective health. The authors make other additions to research in stress-load. In their mini-review 'Stress-induced transposons reactivation—a mediator or an estimator of allostatic load?' [3], Dr Nätt and Dr Thorsell summarize available knowledge on allostatic load, and introduce the (re)activation of the endogenous virus-like elements retrotransposons as a major component for increasing allostatic load in mammals after stress-induction. The authors propose that monitoring retrotransposon activity would offer a more accurate measure between allostatic load with aging and disease compared to the current neuroendocrine-, immune-, metabolic-, clinical- and anthropometric health biomarkers currently used.

In a most comprehensive and elegant contribution, Prof Takeo Kubota from the Department of Epigenetic Medicine, University of Yamanashi, Japan covered in his article 'Epigenetic alterations induced by environmental stress associated with metabolic and neurodevelopmental disorders'

(T. Kubota, in preparation), thoroughly summarizes current knowledge—including that derived from own studies—on congenital and acquired disorders caused by epigenetic misregulation. Most importantly, embracing the concept of epigenomic reversibility, he proposes the development of epigenomic-based pre-emptive medicine based on the application of early medical intervention, taking advantage of epigenomic signatures to early detect the developmental origin of disease. In the forthcoming issue of *Environmental Epigenetics*, the paper by Alonso-Magdalena et al., 'Bisphenol-A and metabolic diseases: Epigenetic, developmental and transgenerational basis' (P. Alonso-Magdalena, in preparation) summarizes the developmental effects of endocrine disruptors related to metabolic diseases. The authors focus on the metabolic effects of gestational exposure to Bisphenol-A (BPA) and the eventual reprogrammatic effect of this disruptor on stem cells. The extension of the epigenetic effects caused by BPA are difficult to foresee, but are part of our incipient knowledge of the transgenerational impact of obesity.

In sum, the articles presented hereby and the nextcoming issue of *Environmental Epigenetics* largely mirror the core of the meeting on Epigenetics in disease and well-being held at Linköping University, Sweden earlier this year. Environmental stressors, either as classical experimental diet- or fear- challenge, or ambient exposure to chemical disruptors challenge homeostasis to such an extent that the effects can become transgenerational. Mechanisms of action were hereby discussed, particularly searching for best methods to monitor allostatic load. Last, but not least, the meeting encouraged interventional strategies to revert, whenever possible, the extent of these epigenetic effects on health and well-being.

References

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