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Highlights

On the road to epigenetic therapy

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ABSTRACT

In this issue of the *Biomedical Journal*, we examine how far the explosion of epigenetic studies in recent years has translated to benefits for patients in the clinic, and we highlight an original study suggesting that increased vegetable intake protects against osteoporotic fractures. We also hear several opinions on the use, or perhaps misuse, of Impact Factor and what the future should hold for this publication metric.

Spotlight on reviews

On the road to epigenetic therapy

The sequencing of the human genome at the turn of this century heralded the exciting possibility that all complex diseases could be understood by looking at DNA. This excitement turned quickly into disappointment as genome-wide association studies by and far failed to fulfil this ambitious promise. Attention turned instead to the idea that the mechanisms by which the book of DNA is read, and not the book itself, might hold the answers. Recent years have seen an explosion in studies investigating the role of such "epigenetic" mechanisms in health and disease, but how far has this work translated into benefits for patients? In this issue of the *Biomedical Journal*, Häfner and Lund [1] explore this question and conclude that the road ahead is still a long and winding one.

Although initially coined in the 1940s by the embryologist Conrad Waddington to describe the processes by which genotype brings about phenotype [2], the term epigenetics has received a facelift in the modern era to encompass mechanisms leading to functionally relevant changes in gene expression that are not due to modifications in DNA sequence. As Häfner and Lund point out though, a consensus definition of epigenetics is difficult to pin down, in particular with regard to how stable such changes in gene expression must be and the exact nature of the molecules involved. All sources agree however that chemical modifications of DNA and histones constitute epigenetic mechanisms [Fig. 1]. The histone proteins that surround and compact our DNA are decorated with post-translational modifications, such as acetylation and methylation, which may recruit activating or repressive complexes and determine the accessibility of underlying DNA. Likewise the methylation of cytosine residues in DNA may lead to transcriptional silencing at some genes and prevents troublesome transposons from wreaking havoc on our DNA. Ultimately, it is these mechanisms that enable the 200 different cell types of the human body to be produced from the same genome.

Given their fundamental role in determining what genes are expressed (and how much), it comes as no surprise that alterations to these epigenetic modifications have been

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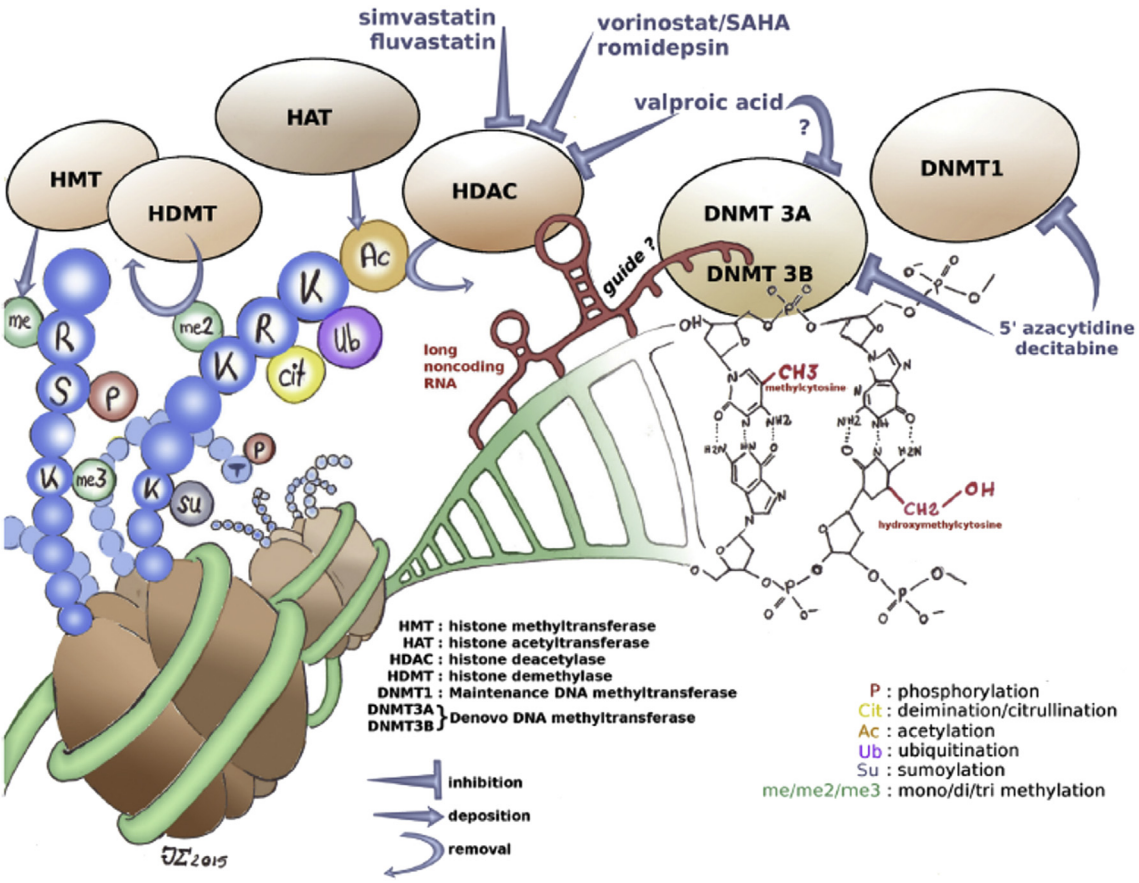

Fig. 1 – Epigenetic modifications and currently available treatments acting on them. Kindly provided by Häfner et al. [1], see main article for more details.

detected in a whole host of diseases, from neuro-developmental disorders, cardiovascular disease and cancer [3], with the latter being by far the best studied example. Cancer cells typically show low levels of DNA methylation coupled with pockets of hypermethylation at promoter regions that may lead to the silencing of tumor suppressor genes [4]. New sequencing technologies have recently identified driver mutations in enzymes and proteins that establish, erase or read epigenetic marks. The fact that epigenetic modifications are reversible makes them highly promising drug targets. A handful of epigenetic agents have been approved by the US Food and Drug Administration, including the DNA methylation inhibitor 5-azacytidine (Vidaza®) and histone deacetylase inhibitors. These inhibitors have shown some success in treating hematological malignancies [5,6], but suffer from the same drawbacks as many other chemotherapeutic agents in that they act as a sledgehammer targeting both cancerous and normal cells.

Enter the next generation of epigenetic inhibitors with greater selectivity, which generally target reader, writer and eraser proteins. Most are still in preclinical or early clinical testing, and their optimal use will depend strongly on knowledge of how exactly epigenetic pathways are disrupted in cancer cells. For example, the histone lysine methylase EZH2 is often overexpressed in cancer and is associated with poor prognosis [7]. DNA sequencing has revealed a specific mutation in EZH2 in up to 22% of germinal center origin of diffuse large B-cell lymphoma (DLBCL) [8]. In cellular assays, the EZH2 inhibitor GSK126 strongly limits the growth of EZH2 mutant DLBCL cells but not EZH2 wild-type cells [9].

With the increasing accessibility of sequencing technologies and global efforts to catalogue epigenomes (take the Human Epigenome Project for example), the possibility that drugs can be developed to target particular epigenetic mechanisms gone haywire specifically in cancer cells becomes foreseeable in the near future. Yet, as Häfner and Lund conclude, such therapies are meant to be complementary to and not replace existing treatments, and with an ever-changing disease like cancer, "having more than one string to one's bow won't be amiss".

Spotlight on original articles

Vegetables intake may protect against osteoporosis

We are all well aware of the health benefits of the mighty vegetable. Both fruits and vegetables are rich sources of vitamins, minerals, dietary fiber and antioxidants. Low consumption is linked to increased risk of non-communicable diseases, with WHO estimating that 5.2 million deaths worldwide in 2013 were attributable to inadequate fruit and vegetable