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Biomedical Journal

journal homepage: www.elsevier.com/locate/bj

Highlights

On the road to epigenetic therapy



Emma L. Walton

Staff Writer at the Biomedical Journal, 56 Dronningens Gate, 7012 Trondheim, Norway

ABSTRACT

Keywords:

Epigenetics
Epimedicine
Cancer
Osteoporosis
Fall risk

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

E-mail address: ewalton86@gmail.com.

Peer review under responsibility of Chang Gung University.

<http://dx.doi.org/10.1016/j.bj.2016.08.005>

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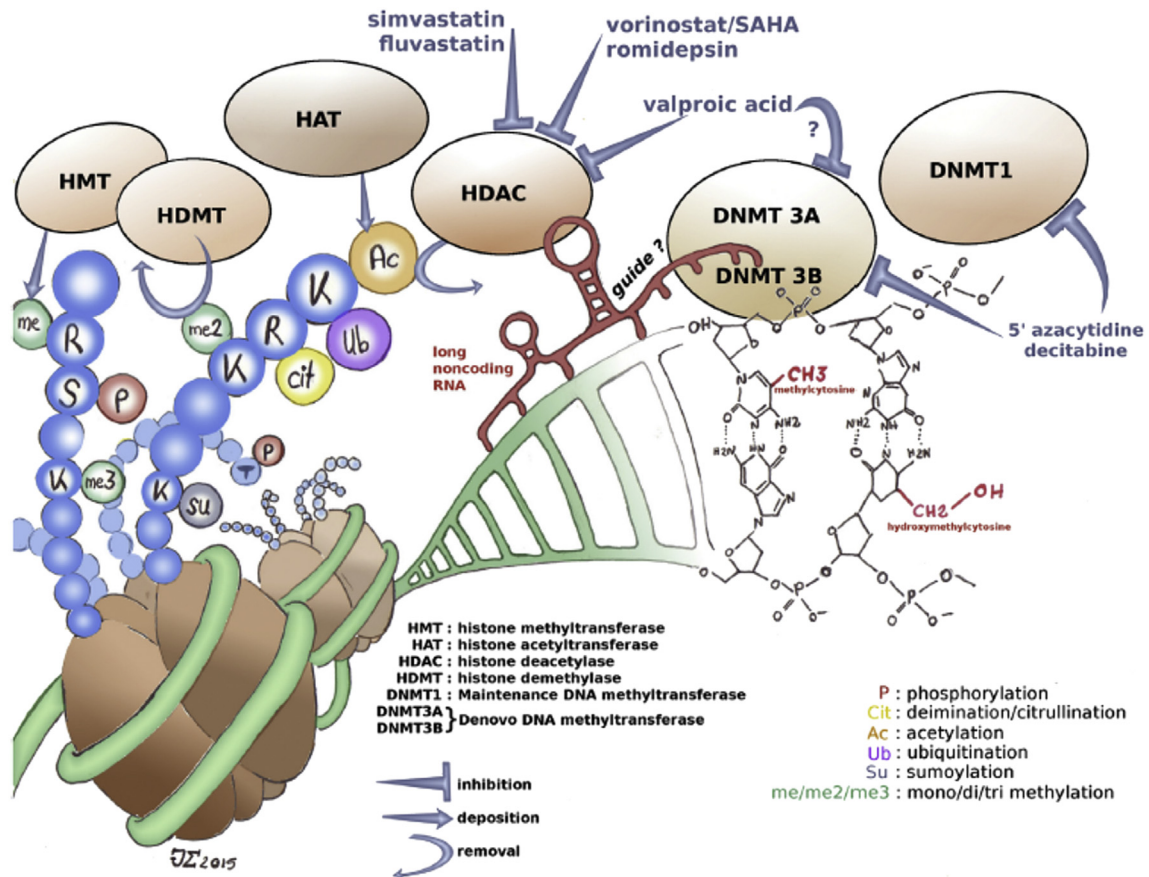


Fig. 1 – Epigenetic modifications and currently available treatments acting on them. Kindly provided by Häfner et al. [1], see main article for more details.

detected in a whole host of diseases, from neurodevelopmental 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

consumption [10]. Now, in the first prospective study of its kind to be conducted in Taiwan, Lin et al. [11] potentially add a new superpower to the effects of high vegetable consumption: protection against osteoporotic fractures.

Osteoporosis causes bones to become brittle and weak, such that a simple fall or even mild stress may lead to a fracture. Postmenopausal women are at highest risk, with nearly one third of such women in Europe, the US and Taiwan developing the condition [12,13]. Modifiable risk factors have been linked to bone health including exercise [14] although some studies do not support the link between milk consumption and good bone health [15]). Some studies have found a positive association between bone mineral density and vegetable consumption [16,17], although few prospective or longitudinal studies, particularly in Asian countries where diets are very different from the Western norm, have examined this link.

In this context, Lin et al. set out to investigate prospectively the relationship between lifestyle factors and the incidence of fall-related fractures in postmenopausal Taiwanese women. They recruited female volunteers from a community health clinic and performed blood samples, body measurements and questionnaires inquiring about lifestyle factors such as weekly diet. In total 953 women recruited responded to telephone interviews in the 2 and ½ years following this initial analysis. During this period, falls were reported by 183 women, 25 of whom incurred fractures. Among women who reported a fall, vegetable consumption was significantly lower in women incurring a fracture, with the cut-off (i.e. the point at which this effect was the strongest) being vegetable consumption <6 times a week. Other variables including milk consumption, BMI and exercise had no obvious association with fracture risk.

These findings support the findings of previous (although not all) studies that vegetable consumption decreases the risk of fractures in postmenopausal women [18,19], although the exact mechanism behind this effect is unclear. After dairy products, vegetables are the second largest source of dietary calcium in the Taiwanese population [20]. Reports in the lay – often alternative health section – of the press argue that vegetables are a superior source of calcium and even go as far as renouncing milk as bone-weakening with claims that its acid-producing properties raise blood pH leading to the dissolution of bone. However, diet has little effect on systemic pH [21], which is effectively managed by the kidneys. Thus, the key to healthy bones probably lies in sufficient calcium (and vitamin D) intake, regardless of source. Although these findings await replication in a larger study, Lin et al. conclude by recommending that individuals consume vegetables at least twice per day for better bone health.

Also in this issue:

Review articles

The central role of the neurosurgeon in epilepsy treatment

Epilepsy that does not respond to pharmacological treatment can be effectively and safely treatment by surgery [22]. In this review, Son and Kim [23] highlight the importance of the early

and central involvement of the neurosurgeon in the management of such patients for optimal treatment.

The inflammasome: it's not all in the name

The inflammasome, as its name suggests, strongly initiates a pro-inflammatory response when it senses pathogens and cellular damage in innate immune cells. In this review however, Martel et al. [24] discuss some of the lesser known roles of the inflammasome in autophagy, metabolism, eicosanoids production and phagosome maturation, and suggest that it is about time that this “complex” complex was re-baptized.

Original articles

New algorithm may predict benefits of weight loss in diabetics

Overweight and obesity account for a major proportion of cases of diabetes mellitus (DM). Although the health benefits of shedding excess pounds are clear, weight loss does not enable all patients to reduce their dose of antidiabetic medication. In this retrospective study of 121 obese or overweight patients with DM, Shantha et al. [25] devise the “WIG” scoring system based on weight loss in the first 3 months of lifestyle intervention, and markers of insulin resistance and blood sugar control. The WIG system predicted with moderate accuracy those patients able to achieve dose reductions following weight loss and thus may prove a useful tool if validated in a larger weight loss trial.

Risk factors and incidence of post-stroke depression in Taiwan

Post-stroke depression (PSD) is a serious complication that occurs in around one third of stroke patients [26]. PSD strongly impairs recovery after stroke, yet only a minority of patients are diagnosed and treated in clinical practice [27]. Tsai et al. [28] investigate the incidence of and risk factors associated with PSD in stroke patients followed up for one year in a Taiwanese hospital. Their findings highlight again that the development of PSD is not only restricted to the initial months after stroke, and identify female gender and high depressive score at baseline as risk factors for the condition.

Cataloguing osteoarthritic changes of the jaw

Osteoarthritis (OA) is an age-related common chronic condition of the joints resulting from the breakdown of cartilage and underlying bone. OA can manifest in any joint, although it primarily affects weight-bearing joints such as the knee and hip. Mani et al. [29] use computer tomographic imaging to investigate OA-related changes in elderly patients with temporomandibular joint dysfunction and determine whether they resemble changes seen in generalized OA. They find that joint involvement, in particular condylar changes, was very common in such patients and that most patients were affected by early OA, hence advocating treatment at an early stage to prevent disease progression.

Toothache is a major cause of emergency pediatric dental visits in Taiwan

Little is known about the prevalence and cause of emergency pediatric dental visits in Taiwan. To address this issue, Jung et al. [30] search medical records from the largest hospital in

Taiwan Pediatric dental emergencies over a two year period. Although the most common cause for visits was orodental trauma, 30% of visits were related to toothache, suggesting that raising awareness about proper at-home care could reduce the number of emergency visits.

Correspondence

Psychobiotics: the dawn of bacterial-based mood enhancers?

Perhaps the road to happiness lies in ingesting the right bacteria? In this correspondence, Kali [31] discusses the emerging field of psychobiotics, defined as living organisms that produce a health benefit in patients with psychiatric disorders when ingested in adequate amounts.

Letter

Should we revise or simply forget Impact Factor?

Recent issues of the *Biomedical Journal* included an article [32] and its subsequent letter [33] relating to the problems with Impact Factor. Mention of this publication metric stirs strong emotions within the scientific community, exemplified perhaps in three contrasting opinions about the use of Impact Factor published as letters in this issue. Many suggestions have been proposed to improve the metric in the past. Shanbag [34] argues that banning self-citation and restricting the total number of citations does not make sense because imposing such rules could limit the citation of good quality articles. Padubidri and Shetty [35] on the other hand argue that self-citation is a source of great bias, and that a correction factor could be introduced to limit the number of self-citations in a particular journal. Finally, Kanchan and Krishan [36] think instead that trying to quantify quality is an almost futile exercise. In their view, the problem with Impact Factor lies not in the index itself but in its inappropriate use. Impact Factor, they conclude, has been taken out of context and should be used judiciously when deciding on grant allocations and career promotion.

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