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Perspective

Modulation of Epigenetic Mechanisms for Anti-Cancer Intervention–New Challenges and Perspectives

Schnekenburger M[1]* and Diederich M[2]

[1]Laboratoire de Biologie Moléculaire et Cellulaire du Cancer, Hôpital Kirchberg, Luxembourg, Luxembourg

[2]College of Pharmacy, Seoul National University, Seoul, Korea

***Corresponding author:** Schnekenburger M. Laboratoire de Biologie Moléculaire et Cellulaire du Cancer, Hôpital Kirchberg, 9, rue Edward Steichen, L-2540 Luxembourg, Luxembourg

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Text Description

For long years genetic mutations were considered as the only driver of the accumulation of successive transformational events associated with carcinogenesis. Nowadays, a large body of evidence clearly established that, besides genetic lesions, massive deregulation of the epigenetic machinery including DNA methylation, histone modifications and non-coding RNAs contributes to all major cancer hallmarks. These aberrations disturb the physiological regulation of gene expression and protein functions involved in the control of essential processes including cell cycle and metabolism, DNA repair, cell growth, differentiation and apoptosis leading to a disruption of cellular homeostasis and subsequent cancer development [1-6].

Since epigenetic alterations are potentially reversible and involved in the earliest steps of malignant transformation, they are considered as promising targets for anti-cancer interventions using epigenetically active compounds [1-4,7,8]. Conversely, over the past years, many agents have been reported; however, only four molecules [*i.e.* two DNA methyltransferase (DNMT) inhibitors and two histone deacetylase (HDAC) inhibitors obtained clinical approval as epigenetic anti-neoplastic drugs and a relatively small number are in advanced clinical trials [4,8-10]. Although we are convinced that targeting epigenetic mechanisms is of considerable interest for effective chemopreventive and chemotherapeutic purposes, inevitably, a number of challenges remain prior to any epigenetic intervention against cancer.

A first challenge consists in the detailed characterization of genome-wide epigenetic signatures in healthy cells as well as a better understanding of their dynamic evolution due to environmental exposure including dietary behavior and lifestyle. Moreover, carcinogenic alterations of these signatures largely remain to be investigated. Data sets obtained by genome-wide high throughput analyses of the DNA methylation landscape associated to histone modification profiles and non-coding RNA expression patters will be investigated by rapidly developing bioinformatics tools [11]. Massive data sets will then further be integrated by multi- and inter-disciplinary approaches in order to ultimately generate an individualized "epigenetic identity card" as a basis for a true personalized medicine. Collectively, identification of epigenetic signatures of any cell provides valuable information about its state (identity, developmental potential, health…) and should lead to novel biomarkers for diagnostic purposes, to predict the need of epigenetic interventions by chemopreventive or chemotherapeutic approaches depending on the stage of the disease, to monitor the efficiency of such interventions and potentially measure their adverse health effects. One example of such a marker corresponds to the progressive DNA hypermethylation-mediated glutathione *S*-transferase pi (GSTP1) gene silencing associated with prostate cancer progression [12-14].

A better understanding of epigenetic mechanisms in health and disease will also allow the identification of novel epigenetic alterations specifically associated to certain disease states and thus representing potential new therapeutic targets. Indeed, up to date, most epigenetic drugs are targeting DNA methylation by blocking or inhibiting the activity of DNMTs or histone post-translational modifications, mainly lysine acetylation, by targeting HDAC activities [4,9,10,15]. In comparison, a rather limited number of molecules have been reported to target the activity of histone acetyl transferases (HATs) or additional histone modifiers such as isoenzymes of the histone methyltransferase (HMT) and histone demethylase (HDM) families, which are involved in the regulation of the status of methylation of lysine and arginine residues [4,6,16]. Furthermore, most HDAC modulators act as pan-non-sirtuin-HDAC inhibitors or are selective against some structurally related HDAC isoenzymes and only very few potent *in vivo* sirtuin modulators are reported. Nevertheless, the use of new *in silico* predictive tools and improved drug discovery pipelines should lead in a near future to the development of new molecular scaffolds displaying more selective inhibitory activity profiles against HDAC activities (class- or isoenzyme-specific inhibitors), histone methylation modifiers, and probably against "writers" and "erasers" of other histone post-translational modifications. Furthermore, based on the identification of active DNA demethylation pathways involving the removal of 5-methylcytosine *via* the sequential modification of cytosine bases that have been converted by ten-elven (TET) enzyme-mediated oxidation [17], we can assume that a tightly controlled activation of these pathways may represent an efficient alternative to DNMT inhibitors to achieve therapeutic DNA demethylation. These new agents would represent valuable tools for mechanistic studies as well as future anti-cancer therapy, which might be more beneficial to patients by targeting more the pathways that are specifically altered in certain cancer subtypes.

A next important point relates to the multiple epigenetic cofactors for which the availability is tightly linked to the redox and metabolic status of the cell and consequently to nutrition [18,19]. Here, we are just starting to apprehend how metabolic reprogramming is affecting our epigenome and those of cancer cells. Further investigations should allow the identification of potentially new "druggable" targets

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to prevent or treat cancer but also to inform us about the potential beneficial impact of nutritional interventions for healthy ageing and on age-related diseases.

Beside "erasers" and "writers" of epigenetic code, epigenetic "readers" represent an important family of proteins, which translate the epigenetic code into biological functions. These regulators "understand" different methylation and oxidation states cytosines [20,21] as well as of histone marks [22]. Targeting these epigenetic effectors or modulating specific protein-protein interactions within chromatin remodeling complexes will certainly unravel new mechanistic insights into chromatin regulation and indicate new opportunities for anti-cancer interventions.

Finally, both frightening but most likely also of considerable potential, are the first insights into trans- or intergenerational epigenetic effects [23]. Indeed, it becomes clearer that alterations of the epigenetic makeup of our ancestors could potentially leave a trace in our own epigenome and could affect health and disease of future generations. Authors clearly state that "different nutritional cues during infancy and childhood can have adverse effects during adult life, and exposure to pollutants, alcohol, and tobacco can affect fetal programming". Even though highly controversial, future investigations will clarify to what extend epigenetic changes could contribute to "developmental origins of health and disease".

In conclusion, epigenetics is currently one of the most rapidly growing areas of biological research; it has changed our view of the "transmission and manipulation" of DNA-encoded information and it could now even lead to change social behaviors. Without any doubt, major breakthroughs in cancer management will emerge from this exciting field.

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