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Editorial

Cancer, epigenetics and the Nobel Prizes

1. Editorial

The Nobel Prize in Physiology or Medicine 2012 have been awarded jointly to Sir John B. Gurdon and Shinya Yamanaka "for the discovery that mature cells can be reprogrammed to become pluripotent" as it is described in the Nobel Prize web site. Professors Gurdon and Yamanaka have all the merits to be bestowed with such a prestigious award for their seminal discoveries in the area. However, we can also consider this annual prize as a recognition to Epigenetics, similarly to the Nobel Prize of 2006 for Andrew Z. Fire and Craig C. Mello for their of RNA interference - gene silencing by double-stranded RNA. Reprogramming requires changing the epigenome of the cells and non-coding RNAs are critical elements in the establishment of epigenetic patterns.

One definition of Epigenetics is "the transmitted inherited genome activity that does not depend on the naked DNA sequence". Epigenetics explains how the same genotype can produce different phenotypes as it occurs in monozygotic twins or cloned animals. There are several chemical modifications affecting DNA, RNA, and proteins that constitute the epigenetic setting, such as DNA methylation, histone modifications, chromatin remodeling factors associated, nucleosome positioning and non-coding RNA activity. Although the disruption of epigenetic patterns might be behind the occurence of many human disease, it is in cancer were major changes have been described and studied in detail. Human tumors undergo a global DNA hypomethylation, which takes place mostly at endoparasitic sequences and DNA-repetitive regions, and a promoter CpG island hypermethylation of selected tumor suppressor transcripts of coding genes (i.e. hMLH1, BRCA1 and p16Ink4a) and microRNAs (i.e. miR-124a, miR-34B/c and miR-200 family) (Heyn and Esteller, 2012). The accompanying reviews from Jansson and Lund, 2012; Suzuki et al., 2012 dwell in the contribution of microRNAs disruption to carcinogenesis and the understanding of the impact of DNA methylation in microRNA transcriptional silencing in human tumors, respectively.

From a translational standpoint, DNA methylation has provided useful biomarkers for the correct diagnosis, prognosis and prediction of chemosensitivity of malignancies (Heyn and Esteller, 2012). For example, the initial finding of the predictor effect of MGMT hypermethylation in chemosensitivity for alkylating drugs, the specificity of GSTP1 hypermethylation for the screening of prostate carcinoma and the observation that DNA hypermethylation changes were detectable in biological fluids have generated many confirmatory follow-up studies energized the biotech companies and driven several clinical trials. The article by Nogueira da Costa and Herceg (2012) describe the advantages and pitfalls of the epigenetic biomarkers. Among the most promising applications, it is important to note the use of DNA methylation profiles in the accurate diagnosis of Cancer of Unknown Primary (Fernandez et al., 2012), a clinical oncology problem of growing relevance.

DNA methylation does not act alone and it is associated with other epigenetic marks such as histone modifications. Histone proteins are not only good-for packaging elements for DNA, but also important to determine gene expression. It is a more complicated scenario than DNA methylation because histone have several isoforms, different aminoacid positions to modify, and several chemical groups (acetylation, methylation, phosphorylation, sumoylation, ubiquitination, etc.). Human tumors display massive disruptions of the histone modification landscape such as a reduction of monoacetylated lysine 16 and trimethylated lysine 20 of histone H4, among others. In addition, histone modifiers are also target of mutation/amplification/deletion in cancer: histone methyltransferases, demethylases, deacetylases, acetyltransferases, etc. Barneda-Zahonero and Parra, 2012 comment the particular involvement of histone deacetylases in tumor formation and progression. DNA methyltransferases, TET proteins and microRNA processing machinery enzymes are also targets of genetic disruption in carcinogenesis. Furthermore, chromatin-remodeling proteins are also imbalanced and defective in cancer cells, and the article of Dr. Kumar, 2012 will be an eye-opener to realize about the contribution of these last factors to cellular transformation.

Interestingly, pathological epigenetic marks are erasable and we can externally intervene to change the landscape of the epigenome: epigenetic proteins and marks are good targets for the development of new anticancer drugs. The approval of DNA demethylating agents and histone deacetylase inhibitors for the treatment of leukemia and lymphoma patients was an awakening call for "Big Pharma" that has placed epigenetics drugs in the crossroad of many

industry-based projects. So far, most of these drugs are not specific and with limited success in solid epithelial tumors, but the picture is fastly changing. In addition to an improved molecular selection of sensitive patients for each type of drug, new targets and compounds are appearing such as inhibitors for histone methyltransferases, histone demethylase, sirtuins, histone kinases, bromodomains or drugs that target microRNAs. The manuscript by Nebiosso et al. (2012) explain in detail the "state-of-the-art" in epigenetic clinical trials and Hoffmann et al., 2012 whilst La Thangue, 2012 and Hoffmann et al., 2012 focused in histone deacetlyase and histone demethylases inhibitors, respectively.

Many questions remain open in cancer epigenetics and new discoveries are made every week in this young and vigorous field: the role of 5-hydroxymethylcytosine, the contribution of non-coding RNAs beyond microRNAs such as antisense RNAs (Guil et al., 2012), the function of long non-coding RNAs such lincRNAs, the understanding of completed whole genome bisulfite sequencing samples, the relation between aging and epigenetic marks (Heyn et al., 2012), the analyses of single cells using epigenomics…Stay tuned and enjoy the ride.

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