EDORIUM Journals

Edorium J Pathol 2015;2:10–13.
www.edoriumjournalofpathology.com

EDITORIAL OPEN ACCESS

Potential etiologic of the epigenetic field defect in the diseases and in cancer

Giorgio Malpeli

Genome-wide association studies in diseases and cancer

The genomic era has brought to a great advance in our understanding of the molecular basis of diseases. Genome wide association studies (GWAS) has provided a comprehensive map of genetic susceptibility to some complex diseases [1, 2]. However, only a minority of diseases are associated with single nucleotide mutations, deletions, amplifications or polymorphisms. Recently, results of GWAS studies on many cancer types have been published and forthcoming, for example pancreas, gastric, prostate, breast, colon, and acute lymphoblastic leukemia [3-8].

Field defect concept

Different interpretations were proposed to explain the ineffectiveness of GWAS in many diseases, including untested rare variants, and gene-gene and gene–environment interactions [9]. One explanation was based on the epigenetic theory, which hypothesized that the epigenome is an interface between genome and environment to adjust the phenotype. The epigenetic code includes both methylation at cytosine in CpG site of DNA and covalent modifications of chromatin-associated proteins with regulatory properties on gene transcription [10]. In pathology, the theory of the field defect assumes that a local modification occurring in a tissue may anticipate the onset of a pathological condition, having potentially a causative role. The epigenetic marks meet the concept of field: they persist during the development of a cell type; if transmitted to offspring, they contribute to the generation of the wide range of different phenotypes and epigenomes with same genotype [11]. Epigenetic map can evolve during cell lifetime and influence the expression of the genome. Thus, the epigenetic changes transferred to daughter cells may potentially determine the inception of a silent field defect, even in the absence of cytological abnormalities.

Giorgio Malpeli[1,2]
Affiliations: [1]Department of Surgery and Oncology, the Hospital and University of Verona, Verona, Italy; [2]Department of Pathology, the Hospital and University of Verona, Verona, Italy.
Corresponding Author: Giorgio Malpeli, Department of Pathology and Diagnostics , PiastraOdontoiatrica, 2° piano, Piazzale L.A. Scuro, 10, Verona, Italy, 37134, Ph: +39 0458126727; Fax: +39 0458027136; Email: giorgio.malpeli@univr.it

Received: 11 July 2015
Published: 16 September 2015

Epigenome-wide association studies in diseases

Epigenome-wide association studies (EWAS) hold promise for the detection of new regulatory mechanisms that may be susceptible to modification by environmental and lifestyle factors affecting proneness to disease. One hundred and eleven different primary cells were profiled for histone modification patterns, DNA accessibility, DNA methylation and RNA expression, providing references resource for interpreting the molecular basis of human diseases [11]. Global epigenetic patterns were used to identify risk factor in exogenous factors as smoking, diet, medication, senescence, endogenous factors as senescence, and pathological factors as inflammation, arthritis, autoimmune diseases, chronic diseases and other types of diseases [12].

Interplay between genetics and epigenetics

The exogenous and endogenous agents able to induce epigenetic and genetic damages have been demonstrated to be major causes of diseases and cancer [13]. The epigenetic changes have gathered much attention as a pivotal player in aging, tissue atrophy, age-related neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, as well as in autoimmune diseases [14]. In this contexts, the epigenome could mediate interactions between genetic and environmental risk factors, or directly interact with pathological factors. Autoimmune diseases as systemic lupus erythematosus (SLE) and rheumatoid arthritis, unrelated to date with mutations in the DNA methylation

machinery, showed epigenetic disorder characterized by global hypomethylation and local hypermethylation in the promoter of some genes. The mechanism responsible for the widespread hypomethylation involved the loss of DNMT1 expression [15]. It is come to attention the role of genetic variability in determining epigenetic profiles [16, 17]. The interplay between genetics and epigenetic aspects is a key goal for the comprehension of aetiology of diseases.

Field defect in cancer

Epigenome-wide association studies (EWAS) were performed in various cancer types mainly by comparing cancer tissues with adjacent tumor-free tissue [18]. However, cancerous organs may exhibit epigenetic changes even in regions with histologically normal tissue, making organ tissue from healthy control subjects a preferable choice for epigenetic studies [19, 20]. A frequent early alteration found in normal tissue adjacent to cancer is the expression deficiency of proteins involved in DNA repair (mutator phenotype). This type of abnormality is a prototypical field defect, as it predisposes normal cells to accumulate secondary genetic and epigenetic changes and finally to become genetically unstable. For example, methylation of MGMT, a gatekeeper DNA repair enzyme that removes mutagenic and cytotoxic adducts from the O6-guanine in DNA, was found in several sporadic cancer types and also in normal tissues adjacent and far to cancer sites in the same tissues [21, 22].

Epigenetic mechanisms promote the switch among transcriptional variants expressed at gene loci [23–26]. The expression switch from isoform M1 of the PKM2 (pyruvate kinase) gene to the isoform M2 in glioblastoma, a mediator of the Warburg effect in tumor, correlated with hypomethylation of M2 promoter [23].

Epigenetic origins of the field defect in cancer

The actual models of cancer onset predict that pro-tumorigenic mutations unable to produce morphological change can predispose to cancer formation. It is thought that genome wide hypomethylation and local hypermethylation in the CpG islands of specific gene promoters precede the cell transformation process towards a neoplasia and accumulation of genetic alterations [27, 28].

Several studies have identified genetic and epigenetic alterations in apparently normal mucosa of colorectal cancer patients [20, 27, 29]. The synchronous colorectal carcinomas provide a model to study the contribution of epigenetic mechanisms to field cancerization [30]. LINE-1 hypomethylation in non-cancerous colonic mucosa demonstrated to be an epigenetic predictive biomarker for multiple colorectal cancer risk. Later, it was demonstrated that at least a proportion of sporadic colorectal cancers displays a CpG island methylator phenotype (CIMP) [31]. However, this unique methylation phenotype plays a role in different cancer types. CIMP-positive tumors exhibit common molecular and clinicopathological characteristics, suggesting that CIMP represents a distinct cross-cancer carcinogenic pathway [32].

External signals and the microenvironment can perturb cell homeostasis by inducing epigenome changes and a field defect predisposing to diseases. Ultraviolet light exposure demonstrated to be etiopathological agent of premalignant and malignant skin cancer formation. UVA light exposure induces radical oxygen species and the activation of several signal cascades, as increased AP-1 and matrix metalloproteinase expression, impaired TGF-beta signaling, enhanced collagen degradation, and decreased collagen synthesis [33]. In addition, oxidative damages lead to recruitment of DNMT1 and DNMT3B protein to damaged sites and hypermethylation of selected CG-rich promoters [34, 35] A significant advance in the comprehension of skin cancerization was provided by studies on an animal model lacking the CSL gene, a component of the Notch signaling pathway, in mesenchymal cells [36]. In this model, dermal atrophy and inflammation were precursor lesions anticipating cell transformation to skin cancer activated by UVA treatment. In human fibroblasts, the loss of Notch2 due to hypermethylation at atrophic and inflamed skin areas duplicated the phenotype CSL-null [36]. These data suggest that a field of cancerization can emerge by defects of the cell-to-cell interactions mediated by epigenetic changes which alter the Notch signaling pathway.

Epigenetic complexity and perspectives

The results of the work of Kaz et al. 2014 [27] and Subramaniam et al. 2014 [20] on colon cancer open further levels of complexity for the definition of epigenetic field defect. In fact, the spread of methylation varied according with the anatomical location of the sampling and the distance from cancer location. These evidences suggest that a more precise comprehension of the pathogenetic role of epigenetic mechanisms in cancer onset requires longitudinal studies able to depict step by step the cancerization of specific districts of a tissue.

A field defect mediated by epigenetic changes can arise in any cell type, promoting degeneration and cancerization. We are in the phase of learning how aberrant placement of the epigenetic marks and alterations of the epigenetic machinery are involved in diseases. A comprehensive understanding of epigenetic mechanisms, their interactions, and the interplay of epigenetic and genetic studies, in health and disease represent a priority in the biomedical research.

Keywords: Epigenetic field defect, Cancer, Genetic damages, Autoimmune diseases

How to cite this article

Malpeli G. Potential etiologic of the epigenetic field defect in the diseases and in cancer. Edorium J Pathol 2015;1:10–13.

Article ID: 100004P03GM2015

****

doi:10.5348/P03-2015-4-ED-3

****

Author Contributions

Giorgio Malpeli – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

Copyright

REFERENCES

1. Blair DR, Lyttle CS, Mortensen JM, et al. A nondegenerate code of deleterious variants in Mendelian loci contributes to complex disease risk. Cell 2013 Sep 26;155(1):70–80.
2. Hindorff LA, Sethupathy P, Junkins HA, et al. Potential etiologic and functional implications of genome-wide association loci for human diseases and traits. Proc Natl Acad Sci U S A 2009 Jun 9;106(23):9362–7.
3. Childs EJ, Mocci E, Campa D et al. Common variation at 2p13.3, 3q29, 7p13 and 17q25.1 associated with susceptibility to pancreatic cancer. Nat Genet. 2015 Aug;47(8):911–6.
4. Darabi H, McCue K, Beesley J, et al. Polymorphisms in a Putative Enhancer at the 10q21.2 Breast Cancer Risk Locus Regulate NRBF2 Expression. Am J Hum Genet 2015 Jul 2;97(1):22–34.
5. Helgason H, Rafnar T, Olafsdottir HS, et al. Loss-of-function variants in ATM confer risk of gastric cancer. Nat Genet 2015 Aug;47(8):906–10.
6. Hoffmann TJ, Van Den Eeden SK, Sakoda LC, et al. A Large Multiethnic Genome-Wide Association Study of Prostate Cancer Identifies Novel Risk Variants and Substantial Ethnic Differences. Cancer Discov 2015 Aug;5(8):878–91.
7. Khalili H, Gong J, Brenner H, et al. Identification of a common variant with potential pleiotropic effect on risk of inflammatory bowel disease and colorectal cancer. Carcinogenesis 2015 Jun 12. pii: bgv086.
8. Xu H, Zhang H, Yang W, et al. Inherited coding variants at the CDKN2A locus influence susceptibility to acute lymphoblastic leukaemia in children. Nat Commun 2015 Jun 24;6:7553.
9. Stranger BE, Stahl EA, Raj T. Progress and promise of genome-wide association studies for human complex trait genetics. Genetics 2011 Feb;187(2):367–83.
10. Portela A, Esteller M. Epigenetic modifications and human disease. Nat Biotechnol 2010 Oct;28(10):1057–68.
11. Roadmap Epigenomics Consortium, Kundaje A, Meuleman W, et al. Integrative analysis of 111 reference human epigenomes. Nature 2015 Feb 19;518(7539):317–30.
12. Paul DS, Beck S. Advances in epigenome-wide association studies for common diseases. Trends Mol Med 2014 Oct;20(10):541–3.
13. Bernstein C, Nfonsam V, Prasad AR, Bernstein H. Epigenetic field defects in progression to cancer. World J Gastrointest Oncol 2013 Mar 15;5(3):43–9.
14. Zhang Z, Zhang R. Epigenetics in autoimmune diseases: Pathogenesis and prospects for therapy. Autoimmun Rev 2015 May 27. pii: S1568-9972(15)00116–0.
15. Zhao M, Wang Z, Yung S, Lu Q. Epigenetic dynamics in immunity and autoimmunity. Int J Biochem Cell Biol 2015 May 27. pii: S1357-2725(15)00143–0.
16. Kerkel K, Spadola A, Yuan E. Genomic surveys by methylation-sensitive SNP analysis identify sequence-dependent allele-specific DNA methylation. Nat Genet 2008 Jul;40(7):904–8.
17. Lemire M, Zaidi SH, Ban M, et al. Long-range epigenetic regulation is conferred by genetic variation located at thousands of independent loci. Nat Commun 2015 Feb 26;6:6326.
18. Verma M. Epigenome-Wide Association Studies (EWAS) in Cancer. Curr Genomics 2012 Jun;13(4):308–13.
19. Kuan JC, Wu CC, Sun CA, et al. DNA methylation combinations in adjacent normal colon tissue predict cancer recurrence: evidence from a clinical cohort study. PLoS One 2015 Mar 27;10(3):e0123396.
20. Subramaniam MM, Loh M, Chan JY, et al. The topography of DNA methylation in the non-neoplastic colonic mucosa surrounding colorectal cancers. Mol Carcinog 2014 Feb;53(2):98–108.
21. Shen L, Kondo Y, Rosner GL, et al. MGMT promoter methylation and field defect in sporadic colorectal cancer. J Natl Cancer Inst 2005 Sep 21;97(18):1330–8.

22. Svrcek M, Buhard O, Colas C, et al. Methylation tolerance due to an O6-methylguanine DNA methyltransferase (MGMT) field defect in the colonic mucosa: an initiating step in the development of mismatch repair-deficient colorectal cancers. Gut 2010 Nov;59(11):1516–26.
23. Desai S, Ding M, Wang B, et al. Tissue-specific isoform switch and DNA hypomethylation of the pyruvate kinase PKM gene in human cancers. Oncotarget 2014 Sep 30;5(18):8202–10.
24. Guo W, Cui L, Wang C, et al. Decreased expression of RASSF1A and up-regulation of RASSF1C is associated with esophageal squamous cell carcinoma. Clin Exp Metastasis 2014 Jun;31(5):521–33.
25. Lev Maor G, Yearim A, Ast G. The alternative role of DNA methylation in splicing regulation. Trends Genet 2015 May;31(5):274–80.
26. Malpeli G, Amato E, Dandrea M, et al. Methylation-associated down-regulation of RASSF1A and up-regulation of RASSF1C in pancreatic endocrine tumors. BMC Cancer 2011 Aug 12;11:351.
27. Kaz AM, Wong CJ, Dzieciatkowski S, et al. Patterns of DNA methylation in the normal colon vary by anatomical location, gender, and age. Epigenetics 2014 Apr;9(4):492–502.
28. Yang B, Bhusari S, Kueck J, et al. Methylation profiling defines an extensive field defect in histologically normal prostate tissues associated with prostate cancer. Neoplasia 2013 Apr;15(4):399–408.
29. Alonso S, Dai Y, Yamashita K, et al. Methylation of MGMT and ADAMTS14 in normal colon MUCOSA: biomarkers of a field defect for cancerization preferentially targeting elder African-Americans. Oncotarget 2015 Feb 20;6(5):3420–31.
30. Yamada A, Minamiguchi S, Sakai Y, et al. Colorectal advanced neoplasms occur through dual carcinogenesis pathways in individuals with coexisting serrated polyps. PLoS One 2014 May 21;9(5):e98059.
31. Gonzalo V, Lozano JJ, Alonso-Espinaco V, et al. Multiple sporadic colorectal cancers display a unique methylation phenotype. PLoS One 2014 Mar 18;9(3):e91033.
32. Kaneda A, Matsusaka K, Sakai E, Funata S. DNA methylation accumulation and its predetermination of future cancer phenotypes. J Biochem 2014 Aug;156(2):63–72.
33. Rittié L, Fisher GJ. UV-light-induced signal cascades and skin aging. Ageing Res Rev 2002 Sep;1(4):705–20.
34. Molognoni F, Cruz AT, Meliso FM, et al. Epigenetic reprogramming as a key contributor to melanocyte malignant transformation. Epigenetics 2011 Apr;6(4):450–64.
35. O'Hagan HM, Wang W, Sen S, et al. Oxidative damage targets complexes containing DNA methyltransferases, SIRT1, and polycomb members to promoter CpG Islands. Cancer Cell 2011 Nov 15;20(5):606-19.
36. Hu B, Castillo E, Harewood L, et al. Multifocal epithelial tumors and field cancerization from loss of mesenchymal CSL signaling. Cell 2012 Jun 8;149(6):1207–20.