EBioMedicine 68 (2021) 103393

Contents lists available at ScienceDirect

EBioMedicine

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

Commentary

DNA methylation in cancer: From mouse to human and back again

Manel Esteller[a,b,c,d]

[a] Josep Carreras Leukaemia Research Institute (IJC), Badalona, Barcelona, Catalonia, Spain
[b] Centro de Investigacion Biomedica en Red Cancer (CIBERONC), Madrid 28029, Spain
[c] Institucio Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, Catalonia, Spain
[d] Physiological Sciences Department, School of Medicine and Health Sciences, University of Barcelona (UB), Barcelona, Catalonia, Spain

ARTICLE INFO

Article History:
Received 26 April 2021
Accepted 28 April 2021
Available online 24 May 2021

Mouse models have been demonstrated as excellent tools to improve our understanding of tumour biology, particularly to dissect chemical carcinogenesis and as first proof-of-concept to test new anticancer drugs. Genetically engineered mice, (GEM) where the genetic disruption of an oncogene or tumour suppressor gene is achieved, are used to study the role of these genes in cancer biology. A disadvantage of GEM systems is that, except for familial cancer syndromes, they do not completely include the molecular heterogeneity that is a central feature of human neoplasms. The more real and rich landscape can be, however, mimicked by another class of murine system: externally cancer-induced models obtained by exposition to chemicals or radiation. The paradigm defining demonstration that ultraviolet radiation (UV) was associated with skin cancer was first found in mice, leading to the posterior advice to reduce UV exposure. Most importantly, the alteration of the epigenetic landscape, particularly DNA methylation, in murine cancer models is poorly described, with the exception of the transition from epithelial to spindle cell morphology in a mouse skin multistage carcinogenesis model [1]. In a recently published EBioMedicine article by Roth et al. [2], they combine both aims by studying the DNA methylation profiles of mouse cutaneous squamous cell carcinomas derived from a solar-simulated ultraviolet radiation model.

The discovery phase of the work involved the use of the reduced representation bisulphite sequencing (RRBS) technique that allows a comprehensive characterization of many CpG sites in the mouse genome at an affordable cost [3]. For DNA methylation screenings of few samples, the use of the Whole Genome Bisulphite Sequencing (WGBS) would be the best technique, but if we want to go deeper and obtain a relevant number of reads, the approach is expensive and applicable to a limited set of examples [3], thus RRBS represents a feasible option. An alternative would be the use of DNA methylation microarrays, where in humans the DNA Methylation Infinium EPIC BeadChip array includes more than 850,000 CpG sites [4], is the most popular source. However, until very recently, there was not a widely available equivalent platform to interrogate DNA methylation, and mostly custom-made approaches [5] have been used to assess the mouse DNA methylome. Interestingly, one of the main observations from the commented article is that many of the altered DNA methylation profiles in the murine cancer model were observed at distal regulatory sequences denominated enhancers. This finding replicates the observation in human cancer that regular enhancers [6] and super-enhancers involved in lineage commitment [7] are common targets of aberrant DNA methylation. In the article by Roth et al. [2] the authors identify hypermethylation of an intronic sequence of Filip1l that acts as an enhancer and drives the transcriptional silencing of the gene. Filip1l hypermethylation-associated silencing in human tumours have already been previously described [8], but here, the elucidation of its more specific mechanism and its presence in a murine cancer model provides additional value to the described article.

Cutaneous squamous cell carcinomas are on the rise due to increased exposure to the sun, evolving lifestyles and increased life expectancy of humans. These allow for the accumulation of genetic and epigenetic effects that drive cellular transformation [9]. Localized lesions show an extremely high percentage of patients with very favourable prognosis, but for those with advanced or metastatic disease there are only a few possibilities in the therapeutical repertoire [9]. Human FILIP1L inhibits cancer cell invasion and metastasis through the inhibition of canonical WNT signalling [8], and thus, DNA methylation-associated silencing is selected in tumour evolution to promote neoplasm aggressiveness. Interestingly, if the normal activity of FILIP1L blocks downstream β-catenin transcriptional targets by WNT inhibition, the restoration of its expression in cutaneous squamous cell carcinomas could have therapeutic potential. In this regard, inhibitors of DNA methylation and histone modification that are approved for their use in certain subgroups of leukaemia's, lymphomas and sarcomas could also have a treatment niche in cutaneous squamous cell carcinomas, particularly since Roth et al. [2] also demonstrates the presence of FLIP1L hypermethylation in human high-risk cases.

The message to take home is diverse and involves many aspects of cancer research. First, mice models are still useful systems for preliminary tumour studies that end with a human sample as a final target. The simplicity of the murine platforms and its easy access are significant advantages. Second, many of the distorted DNA methylation events that contribute to tumorigenesis might not occur around the

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2021.103383.
E-mail address: mesteller@carrerasresearch.org

https://doi.org/10.1016/j.ebiom.2021.103393

minimal promoter of tumour suppressor genes and their associated CpG islands, but in faraway regulatory regions that in the three-dimensional context of a cell are really very close to the transcriptional start site [10]. And third and final, we can explore this knowledge not only to obtain more biomarkers for the disease, but also to design novel treatment strategies with the goal to recover a physiological epigenomic signature. Much work lies ahead, but the implementation of new user-friendly methodologies to assess DNA methylation in cancer models beyond humans and the development of more tumour-specific epigenetic compounds are promising avenues in the field.

Declaration of Competing Interest

Dr. Esteller reports grants from Ferrer International, personal fees from Quimatryx, outside the submitted work.

References

[1] Fraga MF, Herranz M, Espada J, Ballestar E, Paz MF, Ropero S, et al. A mouse skin multistage carcinogenesis model reflects the aberrant DNA methylation patterns of human tumors. Cancer Res 2004;64(16):5527–34.

[2] Roth K, Coussement L, Knatkoa EV, Higgins M, Steyaert S, Proby CM, et al. Clinically relevant aberrant filip1l DNA methylation detected in a murine model of cutaneous squamous cell carcinoma. EBioMedicine; 2021. doi: 10.1016/j.ebiom.2021.103383.

[3] BLUEPRINT consortium. Quantitative comparison of DNA methylation assays for biomarker development and clinical applications. Nat Biotechnol 2016;34(7):726–37.

[4] Moran S, Arribas C, Esteller M. Validation of a DNA methylation microarray for 850,000 CpG sites of the human genome enriched in enhancer sequences. Epigenomics 2016;8(3):389–99.

[5] Sanchez-Mut JV, Aso E, Panayotis N, Lott I, Dierssen M, Rabano A, et al. DNA methylation map of mouse and human brain identifies target genes in Alzheimer's disease. Brain 2013;136:3018–27 Pt 10.

[6] Vidal E, Sayols S, Moran S, Guillaumet-Adkins A, Schroeder MP, Royo R, et al. A DNA methylation map of human cancer at single base-pair resolution. Oncogene 2017;36(40):5648–57.

[7] Heyn H, Vidal E, Ferreira HJ, Vizoso M, Sayols S, Gomez A, et al. Epigenomic analysis detects aberrant super-enhancer DNA methylation in human cancer. Genome Biol 2016;17:11.

[8] Kwon M, Libutti SK. Filamin a interacting protein 1-like as a therapeutic target in cancer. Expert Opin Ther Targ 2014;18(12):1435–47.

[9] Ishitsuka Y, Hanaoka Y, Tanemura A, Fujimoto M. Cutaneous squamous cell carcinoma in the age of immunotherapy. Cancers 2021;13(5):1148. Basel.

[10] Murtha M, Esteller M. Extraordinary cancer epigenomics: thinking outside the classical coding and promoter box. Trends Cancer 2016;2(10):572–84.