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Commentary

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

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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 anti-cancer 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.

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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 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

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