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Commentary

Epigenetics in rhabdomyosarcoma: cues to new biomarkers and targeted therapies

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In this article of *EBioMedicine*, Chunxia Liu and colleagues [1] show that guanine nucleotide exchange factor T (GEFT) overexpression in rhabdomyosarcoma (RMS) cell lines and patients' biopsies is correlated to the methylation status of its promoter region, which is significantly lower in RMS tumours than in normal skeletal muscle, this strictly linking epigenetic aberrations to malignant phenotype. Indeed, epigenetically mediated upregulation of GEFT, a protein involved in Rho-GTPase activation [2], is shown to promote growth, progression and metastasis of RMS cells by controlling specific mediators of the epithelial-mesenchymal transition (EMT) and mesenchymal-epithelial transition (MET) processes, both *in vitro* and in xenograft mouse models. Specifically, the authors indicate that GEFT functions in RMS tumorigenicity are correlated with the aberrant modulation of the Rac1/Cdc42-PAK1 signalling pathway and its interrelated genes. Altogether, the reported findings are particularly interesting since they provide new insights into the molecular mechanisms involved in the metastatic capacity of RMS cancer cells. In addition to this, they have the translational potential for future personalised therapies, since they propose new possible targets for setting advanced therapeutic strategies against RMS tumours.

To better understand the relevance of the scientific data reported by Liu et al., [1] it is essential to underline the importance of epigenetic modifications in cancer progression, mainly in RMS dissemination.

RMS is the most frequently diagnosed malignant soft tissue sarcoma in children and adolescents [3]. The two main histological subtypes in childhood are alveolar RMS (ARMS) and embryonal RMS (ERMS), which are characterised by distinct clinicopathological features and outcomes [4]. RMS is particularly aggressive and patients with metastatic or recurrent disease have a poor clinical outcome with a 5-year overall survival of about 30%. Hence, the identification of innovative therapies against advanced RMS represents an urgent clinical need.

Tumours commonly share mutations in pivotal genes mainly implicated in cell proliferation and survival, but it is increasingly evident that epigenetic imbalance, due to alterations in DNA methylation, histone modifications and non-coding RNAs (ncRNAs), is a hallmark of many different malignancies. This is particularly true for RMS neoplasia, which is characterized by few specific genetic alterations, such as PAX3/7-FOXO1 translocations in ARMSs and RAS family-related mutations in ERMSs, being essentially defined by an aberrant epigenetic landscape. Indeed, altered expression of DNA methyltransferases and demethylases, enzymes involved in histone acetylation, methylation and phosphorylation as well as microRNAs, long non-coding and circular RNAs have been reported in RMS tumours [5–9]. In turn, due to the important impact in the regulation of gene expression at transcriptional and post-transcriptional levels, deregulation of epigenetic components alters a wide range of genes related to cell growth, differentiation, DNA replication, EMT/MET, migration, invasion and survival. So, epigenetic reprogramming appears to be a key challenge in the fight against RMS cancer and the identification of novel druggable targets represents the major goal for many biologists and clinicians. In recent years, several anticancer epigenetic drugs, the so called "epi-drugs", have been tested as single agents than in combination with conventional treatments, i.e. chemotherapy and radiotherapy, with the ambition to critically block cancer cell proliferation and reduce any mechanisms of tumour resistance [8,10]. Anyway, many epigenetic therapies, already approved by U.S. Food and Drug Administration, are represented by DNA demethylating agents and histone deacetylase inhibitors that may act on a broad range of coding and non-coding genes, potentially leading to unexpected side effects [10]. To this concern, the definition of specific epigenetically modified genes and precise molecular mechanisms playing role in their aberrant expression may represent a more focused solution that can help setting a novel generation of antitumoral molecules, designed to have maximal therapeutic efficacy and minimal toxicity with the final aim to improve safety and clinical outcomes of patients in near future. In their work, Liu et al. [1] underline the crucial role of epigenetic landscape in EMT/MET induction to sustain RMS tumour metastases and indicate that these processes are specifically associated with a marked DNA hypomethylation of the GEFT gene, which in turn influences the expression of EMT/MET-related factors by modulating the Rac1/Cdc42-PAK1 pathway. Indeed, the authors speculate that the epigenetic modification associated with the GEFT promoter region may have clinical applications by representing a potential biomarker for accurate RMS diagnostic evaluation, cancer staging and risk stratification. Accordingly, methylation levels at GEFT promoter region significantly correlated with RMS

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clinical pathological characteristics. Therefore, normalization of GEFT expression by a correct epigenetic reprogramming is suggested as a new therapeutic opportunity in the treatment of RMS patients, further outlining the importance to move epigenetic modifications from bench to bedside.

Declaration of Competing Interest

The author declares no conflict of interest.

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