Editorial

Role of enhancer activation in pancreatic cancer metastasis

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Aberrancies in chromatin conformation can lead to altered gene expression thus promoting cancer development. Chromatin is the substratum for transcription factors (TF) to bind DNA and the degree of chromatin compaction determines TF accessibility to their target cis-regulatory elements including promoters and enhancers. Results comparing chromatin profiles between primary tumors and matched non-malignant tissues evidence a profound dynamic throughout the carcinogenic process (1-4). This dynamic effectively reprograms the enhancer landscape toward the activation of oncogenes such as *MYC* (1,2). Supporting findings in a variety of tumors of different lineages suggest that the aberrant enhancer reprogramming is a general mechanism involved in carcinogenesis (1-4). However, the role that this mechanism could have in the metastatic process remains vastly unexplored.

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal human malignancies due to absence of methods for early diagnosis and chemoresistance of advanced disease. *KRAS* is mutated in 95% of PDACs and is a well-validated driver of PDAC initiation and growth (5,6). However, the biology involved in the advance to metastasis is less understood. In a recent article, Roe *et al.* (7) tested the hypothesis that enhancer reprogramming could be a mechanism promoting PDAC progression. To that aim, the authors performed a genome-wide analysis of histone H3 lysine 27 acetylation (H3K27ac) in cultured organoids from a well-established mouse model of PDAC progression (8). The analysis included organoids derived from pancreatic ducts (N organoids), Pancreatic Intraepithelial lesions (P organoids) and pairs of Primary tumor (T) and Metastasis (M organoids) providing a complete picture of the enhancer landscape across the disease.

The results show a significant divergence in the enhancer landscape only observed for the M organoids as compared to all the earlier stages that show highly correlated H3K27ac profiles (7). The lack of an evident enhancer reprogramming already for T organoids is somehow unexpected in view of previous H3K27ac results in primary tumors (1-4,9). For colorectal and gastric cancer, also sharing with PDAC the gastrointestinal origin, H3K27ac landscape shows significant differences already in the primary tumor as compared to matched normal tissue, with a high number of newly activated *GAIN* enhancers nearby oncogenes (1,2). The delayed enhancer reprogramming observed in PDAC derived organoids could be a tumor-type specific characteristic or could result from differences between the mouse model and the primary human tissues. Mouse models are induced systems that share features of human cancer, although they represent a simplified version of a more complex disease. Therefore, direct analysis of human PDAC will be required to assess the relevancy of enhancer reprogramming in real patients.

To further investigate the involvement of this epigenetic mechanism in metastasis promotion, Roe *et al.* (7) focused on the *GAIN* enhancers in the transition between the T and the M organoids that may be hypothesized as being directly involved in metastasis promotion. Interestingly, those H3K27ac *GAIN* enhancers in M organoids already show accessible chromatin in the T organoids, by ATAC-seq analysis. This result suggests that enhancers may be in a predetermined but "poised" stage already in the primary tumor that could be switched on later to promote the metastatic process. The *GAIN* enhancers are close to genes for developmental pathways and show enrichment in

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binding motifs for Forkhead families (FOX) TFs. FOXA1 is overexpressed in M organoids and ChIP-seq analysis confirmed elevated occupancy of FOXA1 at the *GAIN* enhancers. FOXA1 is a pioneer TF that could potentially activate the H3K27ac *GAIN* enhancers during transition from T to M organoids. To assess that hypothesis, Roe *et al.* performed FOXA1 perturbation of expression in 2-dimensional (2D) organoid cultures. FOXA1 overexpression in T organoids resulted in the activation of a subset of the H3K27ac *GAIN* regions observed in M organoids. This effect was enhanced by combined overexpression of FOXA1 and GATA5 in T organoids which coordinately resulted in a better recapitulation of the *GAIN* enhancers in M organoids. The activation of the *GAIN* enhancers was also accompanied by an increase in expression of the corresponding genes revealing the functionality of enhancer reprogramming. FOXA1 expression also resulted in an acquisition of a significant metastatic phenotype as shown by an enhanced anchorage-independent growth and enhanced ability of the 2D culture to colonize the lung parenchyma when injected via tail vein into recipient mice.

All together, the results from Roe *et al.* (7) highlight the crucial role that chromatin remodeling has on the PDAC metastatic process, implicating FOXA1 as the driver of enhancer reprogramming. Oncogenic alterations in the enhancer landscape could confer a fitness advantage to tumor cells leading to an increased metastatic behavior as a result of transcriptional mechanisms compatible with dedifferentiation and increased proliferation. The findings could have clinical implications for cancer therapy since new drugs that act on chromatin remodelers are currently in clinical trials and may benefit PDAC patients.

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