



KDM4B under hypoxia: a new targetable pathway for epithelial ovarian cancer?

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Ovarian cancer is one of the most fatal gynecological malignancies in women. In 2012, global statistics ranked ovarian cancer as the seventh most common cancer and the eighth most common cause of cancer-related death in women worldwide (1). The lethality is mainly attributed to late presentation of the disease, rapid and widespread metastases in the peritoneal cavity, and high occurrence of disease relapse due to chemoresistance (2). The most common form of ovarian cancer, epithelial ovarian cancer (EOC), is divided into type I and II. The latter comprises the most commonly diagnosed subtype—high-grade serous adenocarcinoma, which is usually genetically unstable and highly metastatic.

Targeting tumor metastasis has been an attractive but challenging therapeutic goal in EOC treatment. Attempts made in recent years include the development of anti-angiogenic drug bevacizumab, which improves the progression-free survival of advanced ovarian cancer patients when used in combination with chemotherapy (3). Angiogenesis is induced by hypoxia—a feature that arises when perfusion or diffusion of oxygen is limited due to disorganized tumor growth. Besides angiogenesis, hypoxia promotes tumor metastasis and chemoresistance in many cancers, including EOC, via many different pathways that have yet to be drugged (4). These hypoxic response pathways mostly converge on a master transcriptional regulator, the hypoxia-inducible factor-1 (HIF-1), consisting of a heterodimer (a α -subunit and a β -subunit)

that regulates a myriad of hypoxia-induced genes (5). Increasing findings are suggesting that HIF-1 α directly activates a number of Jumonji domain-containing histone demethylases, including KDM3A, KDM4B and KDM4C that are known to demethylates tri- and di-methylated lysine 9 of histone H3 (H3K9me3/me2), two important histone marks associated with repressed transcription (6,7). Therefore, HIF-1 regulates many genes not only through direct transactivation, but also via indirect or secondary pathways such as epigenetic homeostasis, in response to changes in oxygen tension.

Studies on hypoxia-regulated pathways in EOC are emerging. A recent work by Wilson *et al.* tested the expression level of KDM4B in EOC and validated that KDM4B expression correlates with hypoxic condition (indicated by the marker carbonic anhydrase 9), especially in the metastatic tumors (8). The authors showed that KDM4B is upregulated significantly in several EOC cell lines, but marginally in a normal ovarian surface epithelial cell line, when treated with hypoxic condition. Given the recent theory that EOC could also arise from the fimbriae epithelium of the fallopian tube (9), it remains to be examined whether the hypoxia-induced KDM4B upregulation is true (if yes, to what extent) in the fimbriae cells of the fallopian tube. By performing KDM4B knockdown experiments, Wilson *et al.* further showed that KDM4B activates different sets of genes when the EOC cells are in different oxygen conditions. Intriguingly, the

number of genes regulated by KDM4B is two-fold higher in normoxia than in hypoxia, even though the expression level of KDM4B shows the opposite trend. Consistent with a previous study by another group (6), the knockdown of KDM4B increases H3K9me3 at the promoters of its target genes but not at the global level. These findings suggest that the expression of KDM4B is required for its function as a histone demethylase but the extent of its demethylating activity is unlikely to depend on its level of expression (beyond an unknown threshold). Therefore, the mechanisms that determine the functional specificity of KDM4B and its interplay with other histone demethylases, in the presence or absence of hypoxia, remain to be elucidated.

Importantly, the study by Wilson *et al.* showed that the loss of KDM4B significantly reduces the metastatic potential of EOC cells in both *in vitro* and *in vivo* models. In their intraperitoneal xenograft mouse models, the most striking reduction in peritoneal dissemination of EOC affected by KDM4B knockdown was seen in the omentum, which is typically the main site of EOC metastasis. Based on the “seed and soil” theory of metastasis, the “soil” for secondary EOC tumors in this context refers to a layer of peritoneal mesothelium and the omental tissues beneath. Since the early step of peritoneal metastasis requires the attachment and invasion of EOC cells onto the barrier of human peritoneal mesothelial cells (HPMCs), it would be interesting to investigate the role of KDM4B on the interaction between EOC cells and HPMCs, using 2D or 3D co-culture methods (10). In addition, the homing of disseminated EOC cells to the omentum, which consists mainly of adipocytes, has been suggested to involve lipid transport and metabolic adaptations that allow EOC cells to utilize lipids from the adipocytes for proliferation (11). Therefore, the effects of KDM4B knockdown on lipid metabolism in EOC may also worth to be investigated in future studies.

Considering that KDM4B has more than hundreds of target genes, it could be difficult to identify which are the exact downstream effectors responsible for KDM4B-mediated metastasis. By selecting several candidate genes that are previously proven to be key contributors to tumor progression and metastasis, Wilson *et al.* demonstrated that KDM4B positively regulates platelet-derived growth factor- β (PDGFB), lipocalin 2 (LCN2), lysyl oxidase (LOX) and lysyl oxidase-like 2 (LOXL2), especially in hypoxic condition. However, the study lacks a rescue model to show whether ectopic expression of any of these metastatic-driving genes could compensate the loss of KDM4B in the metastasis of EOC. The effect of KDM4B overexpression

on the regulation of these genes has also yet to be explored. Among the validated KDM4B target genes, LOX has been shown to promote metastasis in EOC (12,13). It is also a compelling target for anti-metastatic therapeutics in breast cancer, but only limited to patients with negative expression of estrogen receptor (ER) (14,15). On the other hand, KDM4B overexpression is more prominent in the ER+ luminal breast cancer subtype (16). This raises the question whether LOX is indeed relevant in the KDM4B-mediated metastatic pathway and thus demands further elucidation. Given that EOC tumors are mostly ER+, it may be necessary to validate whether the expression of ER would be useful for patient stratification in targeting KDM4B-mediated EOC metastasis.

Overall, the study by Wilson *et al.* revealed KDM4B as a functional link between hypoxia and EOC metastasis. The results are encouraging and provide opportunities for the development of anti-metastatic drug, albeit with challenges. Due to cross-reactivity and compensatory pathways, it remains difficult to inhibit the specific activity of the KDM4 subfamily (17). However, recent studies have identified a novel small molecule NCDM-32B that potently inhibits the activity of KDM4 subfamily, especially with high selectivity for KDM4C (18). In addition, the NCDM-32B inhibitor has been shown to impair proliferation and anchorage-independent growth in several breast cancer cell lines, possibly through the suppression of met proto-oncogene (MET) (16). Therefore, based on these findings, the KDM4 inhibitor NCDM-32B appears to be a potential anti-metastatic drug in EOC. As KDM4B may have overlapped or distinct functions with/from KDM4A and KDM4C, potential side effects of KDM4 inhibitor should be taken into consideration in future drug development.

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