

Targeting genetic lesions in esophageal cancer

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As one of the most aggressive cancers, esophageal squamous cell carcinoma (ESCC) is the sixth leading cause of cancer deaths worldwide and particularly common in Asia.¹ Over the decades, the clinical management of ESCC patients has barely advanced; and the overall survival remains poor, largely because its molecular basis, especially the genomic abnormalities, is obscure, and no targeted therapy has been established.

Very recently, we and Song et al. have comprehensively characterized the genomic landscape of a total of approximately 300 ESCCs with whole-genome/exome sequencing, targeted sequencing, and copy number profiling, providing an important molecular foundation for understanding esophageal tumors and developing therapeutic targets.^{2,3} In addition to confirming those known ESCC-implicated driver genes (*TP53*, *CDKN2A*, *RBI*, *PTEN*, *NFE2L2*, *PIK3CA*, and *NOTCH1*), sequencing results unmasked a number of novel cancer genes that might play important roles in esophageal tumorigenesis, including *FAT1*, *FAT2*, *ZNF750*, *KMT2D*, *ADAM29*, and *FAM135B*. On the other hand, copy number analysis pinpointed previously unrecognized focal alterations such as loss of *RAF1* and *RASA1* and amplification of *FGFR1* and *MIR548K*. Integrated gene enrichment analysis of all copy number changes and somatic mutations highlighted several important pathways in ESCC, including chromatin modification, Wnt, cell cycle, Notch, and RTK–RAS–PI3K signaling.

Most importantly regarding clinical implications, both studies identified a number of potentially actionable genes and pathways in more than half of ESCC samples examined, such as receptor

tyrosine kinases (RTKs), GSK3B, XPO1, JAK2–STAT3, PI3K–AKT–MTOR pathways (Fig. 1).

Targeting aberrantly activated RTKs is a well-developed therapeutic approach with proven clinical success. FDA-approved targeted therapies have significantly transformed the clinical managements of certain groups of cancer patients, such as those with *ERBB2*-amplified breast cancers. RTKs including *FGFR1*, *EGFR*, *ERBB2*, *ERBB4*, *IL7R*, and *MET* were found to be amplified and/or have somatic mutations in ESCC^{2,3} (Fig. 1). Since many of these RTKs are well-characterized druggable proteins with FDA-approved regimen, the findings have the potential to rapidly facilitate the development of novel treatment strategies for ESCC patients. Of these RTKs, FGFR1 represents a very promising candidate. The FGFR family is composed of 4 kinases, FGFR1–4, which regulate a broad spectrum of signaling pathways and endocrinologic activities in both cell homeostasis and tissue development. The dysregulated FGFR pathway has been linked to diseases, especially malignancies. For example, somatic mutations of *FGFR1–4* occur in multiple types of tumors, including bladder, gastric, and endometrial cancers, as well as glioma. *FGFR1* and *FGFR2* are frequently amplified in lung, breast, and gastric cancers. In addition, genomic translocations that lead to fusion products constitutively activate FGFR1 and FGFR3 in myeloproliferative disorder and glioblastoma, respectively (reviewed in ref. 4). By multiple approaches, including fluorescence in situ hybridization, SNP array, array CGH, and immunohistochemistry, we found that *FGFR1* is amplified and overexpressed in 10–20% ESCCs. Recently,

Guagnano and colleagues unbiasedly profiled over 500 cancer cell lines, and showed that *FGFR1* amplification was the most significant predictor for the sensitivity of FGFR1 inhibition.⁵ Considering that multiple phase II clinical trials evaluating Dovitinib (small-molecule inhibitor against FGFR1) have shown satisfactory safety and efficacy, these results suggest that FGFR1 is a promising therapeutic target in ESCC.

Another notable drug candidate in ESCC is XPO1, a nuclear exporting protein, which is essential for nuclear export of numerous molecules including a number of key tumor suppressors, such as p53, p27, FOXO1, IκB, BRCA1, and APC. XPO1 expression levels are upregulated in multiple solid tumors and hematological malignancies (reviewed in ref. 6). The increase in XPO1 levels leads to mislocalization of tumor suppressors and cell cycle regulators, which, in turn, results in their inactivation. Indeed, overexpression of XPO1 is associated with a poor prognosis in many types of tumors,⁶ and inhibition of XPO1 was, therefore, proposed as an attractive anti-neoplastic therapeutic strategy. We have discovered that XPO1 is mutated and overexpressed in ESCC, and that KPT330, a novel small molecule targeting XPO1, exerts strong anti-tumor activity in ESCC cells.² Importantly, phase I clinical trials of KPT-330 in hematologic malignancies (NCT01607892) and solid tumors (NCT01607905, NCT01896505) have shown promising results. In addition to being considered as a direct therapeutic target, XPO1 overexpression was also reported to cause resistance to chemotherapeutic drugs, which might be partly explained by the fact that some of the proteins exported by XPO1, for example

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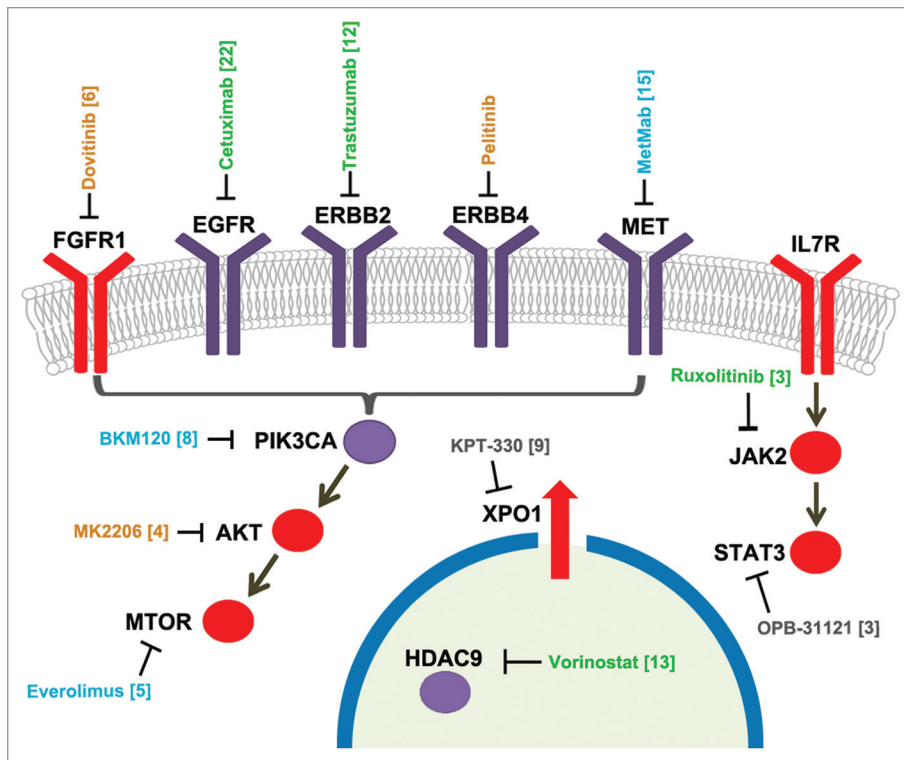


Figure 1. Druggable genetic lesions in ESCC. Targets harboring gene amplification or protein over-expression are marked in red and somatic mutations in purple. Representative therapeutic agents currently in Phase I clinical trials are marked in gray, phase II in brown, phase III in blue, and FDA-approved in green. Due to space limitations, the total number of agents for each target is shown in brackets.

topoisomerase I/II α and BCR-ABL, are themselves drug targets. Blocking XPO1 nuclear export activity by either siRNA or XPO1 inhibitors restored sensitivity to chemotherapeutic drugs such as doxorubicin, etoposide, cisplatin, and Imatinib (reviewed in refs. 6 and 7). Since poor response to traditional chemotherapeutic drugs (e.g., doxorubicin, etoposide, and cisplatin) is a major hurdle in the clinical management of ESCC, inhibiting XPO1 in those ESCC patients with XPO1 over-expression might be particularly helpful in enhancing the efficacy of chemotherapies. These observations form the rationale that KPT-330, either as a single agent or in combination with current chemotherapeutic drugs, might offer tangible benefits for ESCC patients.

In summary, recent genomic studies indicate potential therapeutic merit of the newly identified genetic lesions, which may ultimately help to develop effective targeted approaches for ESCC.

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