Editorial

Unraveling the etiology of primary malignant melanoma of the esophagus

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Recent next generation sequencing (NGS) screens have led to a refined understanding the molecular classification of cancer, uncovering both distinct as well as shared mutations across organ systems. Of special interest are shared mutations, as they allow for cross-cancer use of approved therapies, such as vemurafenib, initially approved for melanomas, on other tumors with BRAF mutations. While major recurrent oncogenes have been identified, the search for lower frequency mutations is key for moving targeted therapy forward. For example, while BRAF mutations are the dominant aberration in sun-exposed melanomas, other melanomas exhibit subtype-specific mutations. The last few years have seen several whole genome (WGS) or whole exome sequencing (WES) studies across rarer melanoma subtypes, uncovering specific gene drivers in desmoplastic, spitzoid, ocular, acral and mucosal melanomas. The latter two are of particular interest, as they arise in sun-shielded body parts with low or absent UV exposure. Mutational profiling may be helpful in identifying the etiology of these cancers: while some acral melanomas show a weak preference for C>T mutation, hinting at some UV exposure (1), anal and vulvar mucosal melanomas show a non-descript profile indicating absence of any major carcinogen and spontaneous carcinogenesis (2). Surprisingly, mucosal melanomas of the oral cavity show a preference of C>A mutations normally seen in lung cancer and may hint at smoking as an etiological factor (3). Li *et al.* now present a WES study of a patient with primary malignant melanoma of the esophagus (PMME) that also exhibits a predominant C>A signature in a non-smoker patient (4). The fact that these melanomas have a distinct non-UV signature is of great interest and may hint at a common mechanism that affects melanocytes in the oral cavity and esophagus. Interestingly, the reported somatic mutations affect genes previously linked to melanoma, including *BRAF*, *CDKN2A* and *PTEN*, mirroring earlier findings of a wide range of driver mutations in PMME (5). Of particular interest are observed mitogen-activated protein kinase (MAPK) pathway mutations in this PMME patient, particularly $NF1^{L626I}$, $KRAS^{G13D}$ and $BRAF^{H574Q}$, which are different from the mutations typically seen in melanoma (i.e., $BRAF^{V600E}$, $NRAS^{Q61L/R}$). The reported *NF1* mutation may provide some clues about the significance of these variants. Melanomas with *NF1* mutations have recently been recognized as an important third melanoma subclass, and have been found to occur in older patients, to exhibit elevated number of somatic coding mutations, and to be partly sensitive to MEK inhibition (6). A common characteristic of *NF1*-mutant melanomas are concurrent mutations in other MAPK pathway genes (6,7). In the PMME case discussed by Li *et al.*, the other MAPK mutations of interest are in *KRAS* and *BRAF*. Given the triple MAPK pathway hit (*NF1*, *KRAS*, *BRAF*), it would be interesting to known whether the patient responded to extracellular signal-regulated kinase (ERK) or MEK inhibition, two genes that lie downstream of the MAPK pathway.

Li *et al.* also provide impressive evidence of intratumor heterogeneity across several samples from within the primary lesions, as well as across lymph node samples. For example, Li *et al.* show that a $PIK3CA^{E545E}$ mutation is limited to a distinct metastatic clade only. This mutation is most probably activating and may be treatable with a PI3K/AKT/mTOR

inhibitor (8), illustrating that heterogeneity may hamper treatment with a single agent only.

While this paper by Li *et al.* is thoroughly enlightening, there are remaining questions that need to be answered by follow-up PMME WES studies. As the authors acknowledge, the study is across a single patient only. As such, more studies are needed to paint a complete picture of the molecular landscape of PMME. The study also does not fully address the fundamental difficulty in distinguishing PMME from metastases of other primary tumors and esophageal malignancies (9). In this particular case, can we exclude the possibility that the patient from Li *et al.* suffered from a regional metastasis of an adenocarcinoma of the lung, which show frequent *KRAS* mutations and a mutational profile with predominant C>A mutations? While unlikely, it would have been nice if the authors discussed this possibility.

Other than these issues, the study by Li *et al.* represents an important contribution to our growing molecular understanding of melanoma. The study raises the possibility that mucosal melanomas of the esophagus, possibly together with melanomas of the oral cavity, may need special attention and may be molecularly distinct from other primary mucosal melanomas. Studies such as the one by Li *et al.* are an important building block in our ability to understand the molecular underpinnings of melanoma and will be invaluable in ushering in the era of melanoma precision medicine.

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References

1. Liang WS, Hendricks W, Kiefer J, et al. Integrated genomic analyses reveal frequent TERT aberrations in acral melanoma. Genome Res 2017;27:524-32.
2. Hintzsche JD, Gorden NT, Amato CM, et al. Whole-exome sequencing identifies recurrent SF3B1 R625 mutation and comutation of NF1 and KIT in mucosal melanoma. Melanoma Res 2017;27:189-99.
3. Lyu J, Song Z, Chen J, et al. Whole-exome sequencing of oral mucosal melanoma reveals mutational profile and therapeutic targets. J Pathol 2018;244:358-66.
4. Li J, Yan S, Liu Z, et al. Multiregional Sequencing Reveals Genomic Alterations and Clonal Dynamics in Primary Malignant Melanoma of the Esophagus. Cancer Res 2018;78:338-47.
5. Langer R, Becker K, Feith M, et al. Genetic aberrations in primary esophageal melanomas: molecular analysis of c-KIT, PDGFR, KRAS, NRAS and BRAF in a series of 10 cases. Mod Pathol 2011;24:495-501.
6. Krauthammer M, Kong Y, Bacchiocchi A, et al. Exome sequencing identifies recurrent mutations in NF1 and RASopathy genes in sun-exposed melanomas. Nat Genet 2015;47:996-1002.
7. Halaban R, Krauthammer M. RASopathy Gene Mutations in Melanoma. J Invest Dermatol 2016;136:1755-9.
8. Janku F, Wheler JJ, Naing A, et al. PIK3CA mutations in advanced cancers: characteristics and outcomes. Oncotarget 2012;3:1566-75.
9. Sim Y, Teo JS, Iqbal J, et al. Primary melanoma of the esophagus, a diagnostic challenge. Asian J Surg 2015;38:236-8.

