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Commentary

The biology of uveal melanoma – next challenges

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Uveal melanoma (UM), a rare cancer of the eye, has been deeply characterized for its molecular lesions in terms of chromosomal copy number alterations (CNAs), gene expression, somatic mutations and DNA methylation (for reviews see [1, 2]). It shows a very limited number of somatic mutations, very few of which are recurrent [3] (probable initiator mutations in GNAQ [4], GNA11 [5], CYSLTR2 [6] and PLCB4 [7], all acting in the same G-protein coupled receptor signaling pathway, mutations in BAP1 [8] and SF3B1 [9] that drive metastasis and mutations in EIF1AX [10] that apparently are involved in tumor formation but not progression). A few CNAs (monosomy of chromosome 3 [11] chr8q gain [12] and chr6p gain [13]), global gene expression profiles or an expression analysis of a number of genes that have been included in a prognostic signature [14] as well as whole genome DNA methylation similarly distinguish two to four classes of UM [15]. It is possible to predict the propension to develop metastases based on each of these molecular domains. Approaches to fuse these data in order to develop a combined molecular predictor have not significantly improved prognostic assessment [16].

Our present knowledge on the mutational landscape of UM indicates that a single mutation in one of the four known "initiator" genes (GNAQ, GNA11, CYSLTR2, and PLCB4) is enough to form a tumor and a single further mutation in either BAP1 [8] or SF3B1 [9] is enough to drive metastasis. These mutations are almost perfectly segregated from the classes defined by gene expression profiling or by CNA. All these approaches yield two clearly distinct classes with each two subclasses with different metastatic potential. This clear distinction can be taken for evidence of non-continuous risk distribution, yet a recent single cell transcriptomics-based analysis hints at a mixture of class-1 low risk and class-2 high risk cells within a single tumor whereby the proportion of these two cell types finally determines the real risk of metastasis [17]. It is not clear how this cell admixture model can explain the clearly distinct risk-associated molecular classes and further research is needed to clear that point.

The few driver mutations, even if assisted by secondary drivers [18], are best compatible with a linear tumor evolution model, but recent evidence introduced the punctuated equilibrium model (or the big bang model) to UM [19]. This model postulates a phase of high genomic instability followed by the outgrowth of stabilized clones into a heterogenous tumor [20, 21]. Tumor heterogeneity has not systematically been addressed for UM. Given the paucity of mutations, heterogeneous subpopulations are unlikely to be traceable by exome sequencing but CNA analyses might help. A recent large-scale analysis of CNA revealed much more cytogenetic events with a discrete frequency than heretofore believed [22].

Still we do not know the deletions of which genes on chromosome 3 except for BAP1 are important for UM metastasis. Early work trying to define the minimal critical interval could not single out specific genes [23]. Chr3 monosomy can come about in a single step by losing one copy during mitosis due to non-disjunction although cases with partial deletion of one copy of chr3 have been reported [24]. Alternatively, several genes including non-coding genes on chr3 can cooperate in determining the metastatic risk.

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For chr8q, ASAP1 (DDEF1) has been proposed as a cause for the impact of this CNA on metastatic risk [25] and MYC can be excluded since it does not change expression as a consequence of CNA [26]. Yet ASAP1 might not explain all of the strong effect on metastatic risk conveyed by chr8q gain.

Chr6p gain is inversely associated with metastatic risk and we still do not know why. Higher expression of the HLA genes located on chr6p would be expected to guarantee better neoantigen presentation, but overexpression of HLA might determine escape from natural killer cell-mediated tumor control [27]. A recent paper showing that the incorporation of the four-class discriminator developed by Robertson and colleagues further improves prognostic assessment [28], might indicate that there is still room for improvement.

There is a continuous flow of publications addressing gene expression signatures often focusing on specific, functional defined gene ensembles, yet most of these approaches consist in bioinformatic exercises that generate neither biological insight nor clinical (prognostic) applications. Reviewers of such papers should insist on a rigorous two-stage design (training set-validation set) and comparison to existing prognostic classifiers.

DNA methylation has not fully been exploited so far. In a recent paper, we show that DNA methylation contains a wealth of prognostic information. Even the genes differentially methylated in GNAQ versus GNA11 mutated cases show a clear association with the outcome that might depend on the interaction of the gene TET2 encoding a demethylating enzyme [29]. Non-coding RNAs have so far shown only a limited association with clinical features and follow-up for UM [30], and more research is needed.

The main unmet need in UM is therapy [31, 32]. Despite the relative success of Tebentafusp, a bispecific gp100 peptide-HLA-directed CD3 T cell engager, for HLA-A*02:01-positive adult patients with unresectable or metastatic UM [33], there is still a need for innovative therapy. Given the limited success of anti-CTLA-4 and anti-PD-1/PDL-1 antibodies, additional checkpoints such as LAG3 and TIGIT must be evaluated as targets and preclinical data are needed.

Inhibitors of YAP have shown activity in preclinical studies [34-36], and the search for more suitable and eventually more active analogs is still going on. Drug repurposing might meet with success in the midterm before new drugs have completed clinical testing, especially if the drugs to be repurposed have already completed toxicity profiles. Yet only drugs or drug combinations able to silence contemporaneously the MAP-kinase and YAP/TAZ pathways are likely to work in the clinic.

Given the fact that 90% of UM metastasize to the liver, our understanding of this tropism, the liver (immuno-) niche, and the liver tumor microenvironment should also be deepened [37].

Taken together, we need still more insight into UM tumor evolution, the drivers and their mechanisms that explain the effects of important CNAs. We need to better understand the metastatic niche in the liver and the related tropism of UM cells, and most important, we need drugs for metastatic UM and for adjuvant therapy. Unless (if ever) we find the one drug that works, any drug that has some effect on tumor progression and metastasis is welcome. Yet the path of discovery in the field of UM justifies some optimism regarding future therapy of this disease.

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