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Commentary

Refining classification of malignant pleural mesothelioma reveals its Achilles' heel

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Malignant pleural mesothelioma (MPM) is a rare but deadly form of cancer originating from mesothelial cells lining the pleural. It occurs over a wide age range, typically presented with diffuse pleural thickening associated with an effusion and the diagnosis is based on tissue biopsy. According to 2015 WHO classification, MPM is divided to three morphological subtypes, namely, epitheliod which accounts for 60–80% of MPMs, sarcomatoid and biphasic when there is a combination of more than 10% of epitheliod and sarcomatoid pattern [1]. The presence of sarcomatoid component is a dismal prognostic feature highlighting the necessity for accurate diagnosis. However, the assessment of sarcomatoid pattern is challenging. In a recent study the interobserver agreement concerning the amount of sarcomatoid component even between expert pathologists was moderate [2]. Besides, MPM patients with identical histopathological evaluation have dramatically different clinical outcome and response to chemotherapy. Hence, it is necessary to refine the classic subtyping on the basis of similar clinical features. The latter urges for the deep understanding of molecular pathology. Within this frame a comprehensive transcriptomic analysis by Bueno, Stawiski and colleagues [3] employing a large cohort of MPMs revealed four distinct molecular subtypes: (a) sarcomatoid, (b) epithelioid, (c) biphasic-epithelioid and (d) biphasic-sarcomatoid. Another study by Hmeljak, Sanchez-Vega and co-authors [4], integrating genomic analysis recently demonstrated a novel subtype exhibiting female and younger age predominance with near haploidization along with *TP53* and *SETDB1* mutations. The clinical utility of this finding remains to be defined. Besides, in the same study the authors revealed strong expression on cancer cells of the negative checkpoint inhibitor VISTA that suppresses immune T cell response in epithelioid MPM [4]. Both studies, take into consideration the implicit aspect of discreteness in terms of histopathological subtyping or molecular clustering.

In an article in *EBioMedicine,* Alcala et al. [5] performed an unsupervised analysis based on Principal Component Analysis (PCA) without the assumption of discreteness, on transcriptomic data obtained from the above mentioned high-throughput studies [3,4]. By employing a continuous survival model that utilizes the first two principal components (PC) capturing 11% and 8% of gene expression variance respectively (7145 most variable genes), the authors managed to deliver a statistically significant prediction of survival based on gene expression profiles connected with specific characteristics. In particular, the first PC was related with the classic histopathological subtyping, whereas the second one that was described for the first time, it was independent of the morphological classification and independently associated with the survival. Of note the two-dimensional model, was superior in predicting survival than the models based on histopathological classification. Gene set enrichment analysis (GSEA) based on a collection of hallmark cancer genes [6] revealed that PC1 was significantly correlated with "inducing angiogenesis" and PC2 was related with "avoiding immune destruction" and "tumor-promoting inflammation" collectively reflecting the immune response. To this end the foremost finding was the identification of three novel molecular profiles with clinical significance, namely: (a) a "hot" profile characterized by rich T lymphocytic infiltration along with elevated expression of immune inhibitory molecules and high levels of pro-angiogenic genes; it was enriched for the non-epithelioid sybtypes and was associated with poor prognosis, (b) a "cold" profile defined by poor infiltration by effector cells along with high expression of pro-angiogenic molecules; it was highly correlated with the non-epithelioid sybtypes and was related with poor survival, (c) VEGFR2+/VISTA+ tumors exhibiting high levels of the major proangiogenic factor VEGFR2 and VISTA enriched for the epithelioid coming in line with the previous work [4]; these patients exhibited a favorable prognosis. To validate the RNA-seq data the authors examined the protein levels of 5 genes highly implicated in PCA dimension 1 and 2 and associated with angiogenesis and immune signaling (i.e. VEGFR3, VEGFR2, CD8, PD-L1, and VISTA). Importantly, the RNA-seq data obtained by the discovery series were validated in the replication series based on protein expression. Collectively the approach followed by the authors, proceeding without making any assumption of discreteness allowed the examination of the inherent continuity of the tumor profile of each patient revealing for the first time immune-vascular interaction as a potential hotspot with prognostic and therapeutic value.

So far, treatments strategies are largely based on a long-held assumption that cancers classified in the same histological subtype exhibit similar molecular patterns and share common clinical outcome. This approach has dictated oncological treatment for many years with success in many forms of can-

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cer, although for several common and rare cancers is ineffective. Hence an emerging question is how does the field make sense of the epitheliod-sarcomatoid-biphasic taxonomy to benefit MPM patient treatment? The present classification of MPM cannot predict the most effective therapeutic strategies. The study by Alcala et al. [5] brings to the fore the angiogenesis-immune interaction in MPM opening a window for new targeted therapeutic modalities. Besides, this study encourages the analysis of additional hallmarks of cancer [7] in this setting following the particular approach. For instance, taking into consideration the DNA damage response and immune signaling crosstalk [8,9], the "genome instability and mutation" hallmark warrants to be examined.

Refining MPM taxonomy taking into account along with the histopathological and imaging parameters the molecular and clinical profile will improve patient stratification towards personalized treatment. Living in the era of "omics", the integration of computational tools into effective models predicting treatment response as was recently demonstrated [10] can be of great value for MPM classification. Yet, implementation of "big data" without deep understanding of the underlying laws of nature can be misleading recalling the words of Isaac Asimov "The saddest aspect of life right now is that gather knowledge faster than society gathers wisdom".

Declaration of Competing Interest

The author declared no conflicts of interest.

References

[1] WHO classification of tumours of the lung, pleura, thymus and heart, 4th edition, 2015, Lyon.
[2] Galateau Salle F, Le Stang N, Nicholson AG, Pissaloux D, Churg A, Klebe S, et al. New insights on diagnostic reproducibility of biphasic mesotheliomas: a multi-institutional evaluation by the international mesothelioma panel from the mesopath reference center. J Thorac Oncol 2018;13(8):1189–203.
[3] Bueno R, Stawiski EW, Goldstein LD, Durinck S, De Rienzo A, Modrusan Z, et al. Comprehensive genomic analysis of malignant pleural mesothelioma identifies recurrent mutations, gene fusions and splicing alterations. Nat Genet 2016;48:407–16.
[4] Hmeljak J, Sanchez-Vega F, Hoadley KA, Shih J, Stewart C, Heiman D, et al. Integrative molecular characterization of malignant pleural mesothelioma. Cancer Discov 2018;8(12):1548–65.
[5] Alcala N, Mangiante L, et al. Redefining malignant pleural mesothelioma types as a continuum uncovers immune-vascular interactions. EBioMedicine 2019. https://www.ebiomedicine.com/article/S2352-3964(19)30610-2/fulltext.
[6] Kiefer J., Nasser S., Graf J., Kodira C., Ginty F., Newberg L., et al. Hallmarks of cancer gene set annotation. https://figshare.com/articles/Hallmarks_of_Cancer_Gene_Set_Annotation/4794025/1
[7] Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144(5):646–74.
[8] Pateras IS, Havaki S, Nikitopoulou X, Vougas K, Townsend PA, Panayiotidis MI, Georgakilas AG, Gorgoulis VG. The DNA damage response and immune signaling alliance: is it good or bad? Nature decides when and where. Pharmacol Ther 2015;154(Oct):36–56. doi:10.1016/j.pharmthera.2015.06.011.
[9] Grasso F, Frisan T . Bacterial Genotoxins: Merging the DNA Damage Response into Infection Biology. Biomolecules 2015 Aug 11;5(3):1762–82. doi:10.3390/biom5031762.
[10] Vougas K, Sakellaropoulos T, Kotsinas A, Foukas GP, Ntargaras A, Koinis F, Polyzos A, Myrianthopoulos V, Zhou H, Narang S, Georgoulias V, Alexopoulos L, Aifantis I, Townsend PA, Sfikakis P, Fitzgerald R, Thanos D, Bartek J, Petty R, Tsirigos A, Gorgoulis VG. Machine learning and data mining frameworks for predicting drug response in cancer: an overview and a novel in silico screening process based on association rule mining. Pharmacol Ther 2019(Jul):107395. doi:10.1016/j.pharmthera.2019.107395.