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CORRESPONDENCE

MUC6 distribution in the spectrum of pulmonary mucinous adenocarcinoma

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TO THE EDITOR:

We read with great interest the insightful and investigative paper by Kishikawa et al. recently published in the Journal[1], which delt with the distribution of membrane-bound (MUC1, MUC4) and secretory (MUC2, MUC5AC, MUC6) mucins in a consecutive series of 70 pulmonary invasive mucinous adenocarcinoma (IMA). We congratulate Authors for the sake of clarity and scientific sound of their paper, whose main conclusions, well reflected in the title, are that MUC6 expression is likely to define a distinct subset of tumors with their own specific clinicopathologic traits and genetic alterations[1]. The article is worth mentioning not only for its inherent scientific value of well-conducted piece of research, but also because it confirms our previously reported observations dating back to 2017 on the same subject, where we reappraised under a similar experimental design the spectrum of pulmonary adenocarcinomas with mucin production, including 12 IMA and 15 invasive colloid adenocarcinomas, as basket categories deriving from distinct domains of stem/progenitor cells or local influence areas along bronchioles according to different mucin (MUC1, MUC2, MUC5AC, MUC6) and nuclear transcription factor (CDX-2, TTF1, HNF4-alpha) immunohistochemistry, clinical and demography traits, and common genetic traits[2]. Our original splitting approach[2], which is different from the lumper interpretation provided by the World Health Classifications[3,4], has been confirmed by this commendable study on pulmonary IMA[1], just because it unravels diverse phenotypic-genotypic events linked to the inherent heterogeneity of cell differentiation lineages and, potentially, offers strategies of therapy[5]. The respectful statement by the Authors that "this is the first study cohort to assess the association between mucin expression and various clinicopathological and molecular parameters in IMA"[1] is however partial, although results of either study[1,2] converge on the same conclusion that there is a clinicopathological relevance to this investigative approach in mucin-laden pulmonary adenocarcinomas.

In their paper, Kishikawa et al. exhaustively described a subset of pulmonary IMA with diffuse expression of MUC6 (a marker of gastric differentiation of antral/mucopeptic cell type) exhibiting *KRAS-WT*, small tumor size and female patient prevalence, but without significant correlation with TTF1 or CDX2 expression[1]. MUC6 was particularly abundant in *CD74-NRG1*-rearranged IMA, but the prevalence of this fusion gene was low (2.9% of analyzed tumors). Looking at Figs. 2 and 3 of the paper, it appears clear that IMA featured lepidic-looking and tuft-like growth pattern with columnar cells filled by apical mucin, basally located nuclei and negligible extracellular mucin extravasation. Interestingly, the lower the MUC6 expression, the higher the probability of KRAS mutation, while the higher expression of MUC6, the higher the likelihood of KRAS-WT[1], probably for the mutually exclusive character of some molecular alterations (synchronous *KRAS* mutation and *TTF1* repression is known to cause IMA in the lung)[6]. In our previous paper[2], by means of clustering analysis, we first identified an IMA subset we called subcluster S3 or cellular mucinous adenocarcinoma (cellular phase of IMA), which was hallmarked by the same antral gland/foveolar cell gastric differentiation as that reported by Kishikawa et al.[1], with MUC6+, MUC1+ membrane and TTF1−/CDX2− profile[2]. This phenotype was under the regulatory control of HNF4-alfa and MUC5AC and was thought to derive from the distal terminal bronchiole[2]. Mitoses and apoptotic bodies were negligible, suggesting apoptosis blockage in their development[2]. Accordingly, we devised a six IHC biomarker-based operative flowchart (MUC1, MUC5AC, MUC6, TTF1, CDX2, HNF4-alpha) to trace back the position of this subset of IMA from putative different stem/reserve cell niches distributed along the terminal and respiratory bronchioles up to alveolar cells[2]. Of note, the visceral endoderm *HNF4-alpha* master gene in the presence of TTF1-downregulating tumors induced MUC5AC and MUC6 transactivation with eventual mucinous gastric differentiation[2]. On histologic grounds (Fig. 1A–D), this S3 subcluster was characterized by pure IMA appearance with multiple microscopic neoplastic foci of well-differentiated mucin-laden cells showing MUC1 membrane-related cell detachment, lepidic growth, tufting, labyrinthine invasion, preserved mucin secretion polarity, basophilic mucin, negligible mucin extravasation (no secretion phase[2]) and uncommon freely floating elements. Pathologic to molecular correlation evidenced I to III tumor stage, 50% female prevalence and 50% *KRAS* mutation in this S3 subcluster of IMA. Disappearance of *TTF1* function upon mutation[7] or haploinsufficiency[6] and lack of *CDX2*-mediated secretory activity[8] are likely to play a role in shifting bronchiolar to gastric-mucin epithelium, thereby leading to the development of this spectacular subset of IMA where mucin extravasation is negligible and MUC1 expression is typically membrane-bound (not cytoplasmic as seen in alveolar type 2-differentiated cells)[2]. Metastatic IMA exclusion from the gastro-enteropancreatic (GEP) tract may be challenging and needs clinical integration because of its prototypical character on histologic and IHC grounds, with a role for *KRAS G12C* mutation in the diagnostic work-up (one of the least frequent mutations in pulmonary IMA compared with GEP carcinomas)[1,9,10]. We feel our paper's observations[2], which agree upon the Kishikawa et al.'s[1] study, may actually contribute to reappraise this subset of tumors,

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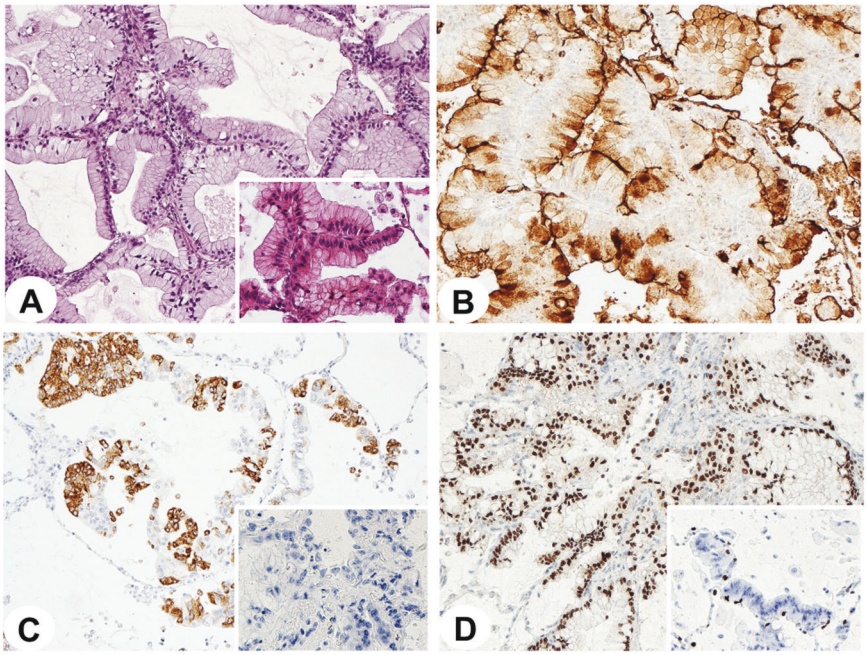

Fig. 1 Representative pictures from the S3 subcluster in a case of invasive mucinous adenocarcinoma. This pulmonary invasive mucinous adenocarcinoma shows a labyrinthine pattern of growth with lepidic growth (**A**) and is hallmarked by mucin-laden columnar cells with basal nuclei, absence of mitoses or apoptotic bodies and uniform histologic appearance with tufting (**A**, inset). Tumor cells are diffusely positive for MUC1 on cell membrane (**B**), and show cytoplasmic decoration for MUC6 along with CDX2 negativity (**C**, inset). Nuclear decoration for HNF4-alpha is accompanied by complete lack of TTF1 labeling (**D**, inset).

which however does not account alone for the complexity of pulmonary IMA[2].

Giuseppe Pelosi [1,2]✉ and Angelica Sonzogni[3]
[1]*Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy.* [2]*Inter-Hospital Pathology Division, Istituto di Ricovero e Cura a Carattere Scentifico—IRCCS MultiMedica, Milan, Italy.* [3]*Department of Pathology and Laboratory Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy.*
✉*email: giuseppe.pelosi@unimi.it*

REFERENCES

1. Kishikawa S, Hayashi T, Saito T, et al. Diffuse expression of MUC6 defines a distinct clinicopathological subset of pulmonary invasive mucinous adenocarcinoma. Mod Pathol 2021;34:786–97.
2. Sonzogni A, Bianchi F, Fabbri A, et al. Pulmonary adenocarcinoma with mucin production modulates phenotype according to common genetic traits: a reappraisal of mucinous adenocarcinoma and colloid adenocarcinoma. J Pathol Clin Res 2017;3:139–52.
3. Editorial Board: Borczuk C, Cooper W, Dacic S, et al. Thoracic tumours. Vol 5. 5th ed. International Agency for Research on Cancer - Lyon (France): 2021.
4. Travis WD, Brambilla E, Nicholson AG, et al. The 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical and Radiologic Advances Since the 2004 Classification. J Thorac Oncol 2015;10:1243–60.
5. Cha YJ, Shim HS. Biology of invasive mucinous adenocarcinoma of the lung. Transl Lung Cancer Res 2017;6:508–12.
6. Maeda Y, Tsuchiya T, Hao H, et al. Kras(G12D) and Nkx2-1 haploinsufficiency induce mucinous adenocarcinoma of the lung. J Clin Invest 2012;122:4388–400.
7. Hwang DH, Sholl LM, Rojas-Rudilla V, et al. KRAS and NKX2-1 Mutations in Invasive Mucinous Adenocarcinoma of the Lung. J Thorac Oncol 2016; 11:496–503.
8. Saandi T, Baraille F, Derbal-Wolfrom L, et al. Regulation of the tumor suppressor homeogene Cdx2 by HNF4alpha in intestinal cancer. Oncogene 2013;32:3782-8.
9. Nakaoku T, Tsuta K, Ichikawa H, et al. Druggable oncogene fusions in invasive mucinous lung adenocarcinoma. Clin Cancer Res 2014;20:3087–93.
10. Chang JC, Offin M, Falcon C, et al. Comprehensive Molecular and Clinicopathologic Analysis of 200 Pulmonary Invasive Mucinous Adenocarcinomas Identifies Distinct Characteristics of Molecular Subtypes. Clin Cancer Res 2021;27:4066–76.

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AUTHOR CONTRIBUTIONS

GP and AS: conceptualization, methodology, original draft preparation, review, editing, and manuscript finalization.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Giuseppe Pelosi.

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