

### Editor's Note:

In the era of personalized medicine, a critical appraisal new developments and controversies are essential in order to derived tailored approaches. In addition to its educative aspect, we expect these discussions to help younger researchers to refine their own research strategies.

## Controversies on Lung Cancer: Pros and Cons

# Rebuttal from Professor Helmut H. Popper

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I would like to thank Dr. Dacic for her article defending the present classification of mucinous adenocarcinomas.

I will not comment on enteric adenocarcinoma as this entity usually does not produce mucin and in addition is characterized by an apical brush border composed of long microvilli, which are even seen in H&E stained sections under high power magnification. Also the statement of Dr. Dacic is clear and does not need any comment.

However, some other statements need some comments and critical remarks:

“An alternative approach to lung adenocarcinoma, classifies mucinous adenocarcinomas as the non-terminal respiratory unit (TRU)-type because of their origin from the bronchial epithelium or submucosal glands and a gastric mucin phenotype”.

Centrally located adenocarcinomas are in general rare, and some of them resemble bronchial glands, but in my experience they usually present with an acinar morphology and show a mixture of cells differentiated towards goblet as well as serous cells. In contrast the majority of invasive as well as non-invasive mucinous adenocarcinomas present with a lepidic pattern, which is a classic pattern of peripheral type adenocarcinomas, starting at the bronchioalveolar junction zone.

What drives a mucinous differentiation is not understood completely. Normally goblet cells and secretory columnar

cells are seen in larger bronchioles but are almost absent in terminal bronchioles where Clara cell is the major cellular component. Under certain circumstances goblet and secretory cells can be formed out of regenerating peripheral stem cells at the bronchioalveolar junction zone. In an attempt to create a model for asthma, goblet cell hyperplasia was created by expressing IL13 or inhalation of toxic gases causing a neutrophil dominated inflammation in laboratory animals (1,2); MUC5AC expression was seen in these cells. In ovalbumin sensitized animals expression of TGF $\alpha$  induced MUC5AC and via EGFR stabilized goblet cell hyperplasia (3). An inflammatory condition seems to be important for goblet cell hyperplasia, most likely a prerequisite for a mucinous adenocarcinoma. In cystic pulmonary adenomatous malformation types 1–3 a goblet cell proliferation can be seen and again IL13/ILR4 $\alpha$  and MUC2 expression was demonstrated (4). In genetically engineered mice the expression of mutated KRAS does induce non-mucinous adenocarcinoma *in situ* —a co-expression of MUC2/5AC can induce a mucinous phenotype (5) (and unpublished personal data).

“Mucinous adenocarcinomas in addition to cytokeratin 7, typically co-express cytokeratin 20. TTF-1 and napsin A are usually negative”.

“Colloid adenocarcinoma may show focal and weak expression of cytokeratin 7 and TTF-1. Furthermore, they

tend to show expression of intestinal markers such as CDX2 and MUC2”.

In our series of IMAC TTF1 was positive in the majority of cases. Furthermore also colloid AC usually expressed TTF1. In a minority of cases we found co-expression of TTF1 and CDX2 within the tumor, confined to different subsets of the tumor. Co-expression of cytokeratin 7 and 20 we also have seen (6).

In the study of Zhang TTF1 negativity was associated with males, heavy smokers, larger tumor size, and more advanced disease stage. TTF1-negativity was more common in solid and invasive mucinous-predominant carcinomas, whereas TTF1+ tumors were common in AIS, MIA, and lepidic-predominant adenocarcinomas (7).

Skoulidis identified three major subgroups of KRAS-mutant lung adenocarcinoma with distinct biology defined by co-occurring genetic alterations of either LKB1, TP53, or CDKN2A/B, and the latter coupled with low TTF1 expression (8).

An explanation for the discrepant reports on TTF1 positivity/negativity in IMAC might be found in the study by Winslow: Nkx2-1/TTF1 downregulation or loss is related to loss of differentiation and increased metastatic capacity. Thus, the oncogenic and suppressive functions of Nkx2-1 in the same tumor type substantiate its role as a dual function lineage factor (9). As we had investigated predominantly well differentiated mucinous adenocarcinomas, this could be an explanation for TTF1 positivity in the majority.

“73% of primary lung mucinous adenocarcinoma show G12D and G12V KRAS mutations, that are frequently observed in mucinous colorectal and pancreatobiliary adenocarcinoma. This is in contrast to non-mucinous lung adenocarcinoma that more often show G12C KRAS mutation”.

In our series of IMAC we have seen a similar high percentage of KRAS mutations. Although mutations in codon 12 were the most common ones, there were a substantial number of mutations in codon 13, and there were also codon 61 mutations. Even within codon 12 we found different variants. Only colloid adenocarcinomas were all KRAS mutated (6).

“Mucinous lung adenocarcinomas have been associated with poor overall survival and progression-free survival when compared to other subtypes of lung adenocarcinomas. They tend to present at advanced stage of disease that cannot be surgically treated”.

This cannot be proven by our study: we compared

IMAC versus NMAC by tumor stage and could not find a significant difference. In our study all cases were compared in a multivariate analysis and the cases were stratified by stage. One explanation to the conflicting results might be, that we analyzed only stages IA to IIIA, which all were surgically removed.

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## Footnote

*Conflicts of Interest:* The author has no conflicts of interest to declare.

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