Editorial Commentary

Toward precision medicine based on the molecular landscape of carcinoma *in situ* of the bronchus: is it realistic for patients with pre-invasive lung disease?

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Early detection of cancer, particularly through screening of high-risk patients, is essential to decreasing the mortality due to cancer, notably lung cancer (1). Early detection is made possible by sampling of cytological and/or histological specimens that provide a diagnosis of the precancerous lesion. The diagnosis of precancerous lesions, in particular those of the lungs, is presently performed using a morphological approach. So, it is the pathologist who identifies and classifies through its microscope low, moderate or severe dysplastic lesions as well as carcinoma *in situ* of the respiratory epithelium (2-5). Moreover, the detection and clinical surveillance of suspicious macroscopic lesions can be performed using high resolution diagnostic techniques such as autofluorescence bronchoscopy (6-8).

Histological diagnosis of precancerous lesions is sometimes difficult and frontiers exist between a severe dysplastic epithelium and a carcinoma *in situ*, which on a morphological basis may give an uncertain classification and inter-observer variation. It is noteworthy that a certain number of these lesions (including carcinoma *in situ*) regress spontaneously while others inevitably develop into micro-invasive or invasive squamous cell carcinoma (9-11). However, morphological evaluation of *in situ* lung carcinoma alone does not allow prediction of a favorable or unfavorable outcome. In this context in recent years studies have aimed at identifying molecular biomarkers detected on the lung epithelium that may be associated with evolution toward an invasive squamous cell carcinoma (12-14). In fact, despite promising results, none of these studies have given conclusive results and have been adopted in the clinic for routine practice.

The possibility of predicting the evolution of a carcinoma *in situ* of the lung into an invasive squamous cell carcinoma should lead to administration of personalized therapy adopted to each patient and to more aggressive treatment in the case of certitude concerning cancerous transformation and future tumor invasion. In contrast, the absence of biomarkers predictive of transformation toward an invasive carcinoma, withholding therapy (especially in the absence of a surgical procedure) avoids excessive and ineffective treatment, which can be responsible for morbidity-mortality. It is in this context that the study by Teixeira *et al.* is particularly important (15). This study relies on a complex and multi-parametric molecular approach associated with a genomic, epigenetic and transcriptomic signature (15). Analysis of the different biomarkers was performed after laser capture micro-dissection of the lung epithelium showing notably lesions characteristic of carcinomas *in situ*. Frozen or formalin-fixed paraffin-embedded (FFPE) lung biopsies were used to extract out DNA and RNA (15). These nucleic acids were then analyzed using a high throughput technological approach (sequencing of the

whole genome, methylation on genes, and analysis of genes by sequencing on an Illumina or Affymetrix platform) (15). The molecular profile was then compared to progression of the carcinomas *in situ*, either toward an invasive squamous cell carcinoma, or regression of epithelial lesions toward low grade dysplasia or even toward normal lung epithelium (15). So, the authors of this study were able to obtain a molecular profile of carcinomas *in situ* predictive of either a good or bad outcome. This differential analysis of some gene expression was obtained with carcinomas *in situ* that either progressed into carcinomas or regressed (15). A certain number of genes showed significant variation between the two groups of lesions and showed chromosomic instability. Among these genes, five were strongly regulated, *ACTL6A*, *ELAVL1*, *MAD2L1 NEK2* and *OIP5* (15). It is noteworthy that these five genes alone were able to predict progression and tumor invasion. The expression of *NEK2* alone was also able to predict tumor progression (15). Analysis of genes showing hyper- or hypo-methylation gave a molecular signature that differentiated between carcinomas *in situ* progressing toward an invasive cancer and those regressing toward a low dysplasia or a normal epithelium. Several genes showed significant methylation in association with tumor progression, in particular those implicated in certain signaling pathways involving TGFb, WNT and Hedgehog molecules as well as the cell cycle (15).

Nonetheless, a couple of limitations can be expressed concerning this study. The authors, by combining laser capture microdissection of frozen or FFPE lung epithelium and then extraction of DNA and RNA and high throughput molecular analysis, performed a real "technological prowess" (15). In particular whole genome sequencing experiments were made from these laser capture microdissected epithelia. In this context, several analyses were not performed due to an insufficient amount of biological material and/or to degraded nucleic acids (15). Notably the RNA obtained from FFPE biopsies could be highly degraded. This study is then certainly difficult to perform in most institutions due to the complexity of the approach. The delay in obtaining results of these analyses is not yet adapted to the therapeutic care of patients. So, it remains a study identifying new potential therapeutic targets and cannot be envisaged for daily use currently. The cost of the technique is also not compatible, to date, for routine clinical practice. Another limitation of this study lies in fact that the lesions of the lung epithelium are often multifocal with alternating sites of variably severe, moderate and low dysplasia, of normal epithelia and of carcinoma *in situ* (2,5,10). So, it is probable that there exists, for the same patient, different lesions of carcinoma *in situ* with a signature characteristic of cancer progression or in contrast with a regressive or favorable outcome too. Moreover, since it is impossible to analyze the whole surface of the lung epithelium, even with autofluorescence-guided techniques, a certain number of false negative results (absence of detection of a molecular signature predictive of an invasive carcinoma) may exist. Currently, molecular therapeutics targeting one or several genomic alterations have not been developed for these precancerous lesions and their potential efficacy needs to be established in clinical trials. Some studies have questioned the interest in detection of precancerous lesions on the bronchial tree by bronchoscopy employing autofluorescence, in particular one question is to establish the real impact on improvement to patients' overall survival (16). Another limitation of this study is that the frequency and incidence of precancerous lesions in the proximal bronchial tree diminishes currently whereas more distal lesions that are not visible/available with the method of autofluorescence bronchoscopy increase. Thus, the contribution of such systematic approaches combined with lung biopsies and molecular analyses may be debatable in the future. From a mechanistic point of view this exploratory study does not explain or provide ideas or hypotheses concerning the cellular and molecular elements leading to spontaneous regression of the carcinoma *in situ* lesions toward a normal epithelium. In particular, the possible role of the immune system, of interactions with the cellular microenvironment or even of certain genetic polymorphisms was not discussed or studied (15).

Nonetheless, in the domain of oncology this study provides a proof-of-concept and shows that biological knowledge can inspire technological development, thus opening the way to mid- and long-term perspectives for personalized medicine targeting lesions at a very early stage of a cancer development. Finally, the identification of new molecular signatures of lung carcinomas *in situ* may lead one day to propose therapies targeting certain genomic alteration or even an immunotherapy (17).

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Footnote

Conflicts of Interest: P Hofman is a member of different industrial scientific advisory boards (Roche, AstraZeneca, Bristol-Myers Squibb, Pfizer, Novartis, Merck, MSD, Qiagen, Thermofischer, Biocartis) for which he receives honorarium.

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