BRMS1 expression in resected lung adenocarcinoma

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The identification of prognostic markers for surgical resected cancers is a current issue for several malignancies (1,2). As regard lung adenocarcinoma (LUAD), despite curative-intent surgical resection, tumor recurrence and spread remain the primary causes of cancer-related death among patients with early stage. A precise prediction of the risk of tumor recurrence at the time of surgery could spare patients the toxicity of adjuvant chemotherapy, and target other patients for increased therapy and surveillance (3).

Differently from advanced stages, risk factors to identify patient with surgically resectable LUAD who have high risk of recurrence are poorly defined. TNM stage, tumor size, lympho-vascular invasion, and visceral pleural invasion are the main prognostic factors for resected LUAD (4). Moreover, others risk factors are now under investigation, such as architectural grade, carcinogenembryonic antigen (CEA) levels, standardized uptake value (SUV) of positron emission tomography (PET), thyroid transcription factor (TTF)-1 expression levels, mutations in KRAS gene, tumor protein p53 gene, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha, single nucleotide polymorphisms, and microRNA (4-8).

Selected metastasis suppressor genes are also other potential prognostic factors for resect LUAD. For example, decreased levels of CD82 molecule gene (KAI1) and KISS-1 metastasis-suppressor gene (KISS1) have been associated with poor prognosis in a small series of lung cancers (9,10). Among selected metastasis suppressor genes, the breast cancer metastasis suppressor 1 (BRMS1) gene is one of the most promising as prognostic factors in LUAD. BRMS1 maps to chromosome 11q13.1-13.2 and contains a helix-turn-helix DNA binding domain and coiled-coiled domains, suggesting that it may be part of a transcription complex (11).

BRMS1 has been shown to function as a corepressor to inhibit NF-kB transactivation by deacetylation of the RelA/p65 subunit at K310. It also regulates angiogenesis, phosphoinositide signalling, expression of microRNA, and p300 histone acetyltransferase levels. Moreover, the loss of endogenous BRMS1 significantly promotes basal and TGF-Beta-induced epithelial to mesenchymal transition (EMT) in lung cancer cells (12).

A reduced BRMS1 expression has been identified as a predictive factor of poor prognosis in breast cancer (13), nasopharyngeal carcinoma (14), gallbladder adenocarcinoma (15), and melanoma (16).

Smith and co-workers first reported that BRMS1 expression was reduced in NSCLC cells and human tumor tissue correlating with worse overall survival (OS) (17). Loss of BRMS1expression is related to promoter methylation by RelA/p65-DNA methyltransferase and to phosphorylation on serine 30 by CK2α resulting in 14-3-3 mediated nuclear exportation of BRMS1 and following proteasome-mediated ubiquitination and degradation. Interestingly, methylation of BRSM1 promoter correlate with smoking history and poor survival (18).

More recently, the same research group has been investigated the BRMS1 expression in 1,030 patients who underwent complete resection for LUAD (19). This large cohort, included patients from stage I to stage IIIA with a prevalence of stage I patients (85%), median follow-up was 5-years. BRMS1 expression was evaluated on the basis of intensity of nuclear immunostaining, with 0+ indicating no staging and 1+, 2+,3+ indicating weak, moderate, and strong staging respectively. The low
BRMS1 expression was defined as an intensity score of 0 to 2 and the high expression as a score of 3. Low BRMS1 expression was associated with greater tumor size, higher pathologic stage, and greater lymphatic and vascular invasion. Furthermore, BRMS1 expression had also a strong correlation with LUAD histologic subtype and architectural grade. In particular, micropapillary and solid predominant LUAD had low BRMS1 expression, on the other hand lepidic predominant subtype were more common in the BRMS1 high-expression group. In accord with the determinations in previous small series, Bucciarelli et al. confirmed that low BRMS1 expression was associated to poor prognosis, resulting as an independent predictor of worse OS [hazard ratio (HR) =1.35, 95% confidence interval: 1.10–1.65, P=0.004] and disease-free survival (DFS) (HR=1.27, 95% confidence interval: 1.05–1.54, P=0.012).

Despite the study elegantly examined the role of BRMS1 in a very large cohort of resected LUAD, the contribution of this single biomarker in a multivariate model including standard clinicopathologic features as age, sex, surgery type, pathologic stage, tumor size, lymphovascular invasion, and histologic subtype seems small. Even if, the study cohort is characterized for 85% by stage I patients, the presence of patients with pathological stages other than I, in particular about 7% of stage IIIA, could be mystifying. As regards, a retrospective subgroup analysis, evaluating the prognostic role of BRMS1 levels for different stage could be performed. Interesting, in addition to BRMS1 immunohistochemical analysis, Bucciarelli and co-workers showed in two independent cohorts of stage I LUAD without nodal metastasis, namely Nagoya cohort (n=79) and University of Michigan cohort (n=128), that low BRMS1 mRNA transcript levels significantly correlated with decreased OS. According to this, immunohistochemical and mRNA BRMS1 expression could be evaluated focusing pathologic stages that are borderline for adjuvant chemotherapy such as T2a-b without nodal metastasis, evaluating thus a potential predictive role of this biomarker.

Analogous to the paper of Bucciarelli and colleagues, in the last ten years, several studies identified immunohistochemical expression of single protein as potential prognostic factor for resected lung cancer, such as AAA+ nuclear coregulator cancer associated (ANCCA) (20), phosphatase and tensin homolog (PTEN) (21), baculoviral inhibitors of apoptosis proteins repeat-containing 6 (BIRC6) protein (22), transcriptional coactivator with PDZ-binding motif (TAZ) (23), mammalian target of rapamycin (mTOR) (24), disintegrin (25), metalloproteinase-9 (ADAM9) (25), and others. Unfortunately, nowadays none of these potential prognostic factors is entered in clinical practice, both difficulties to reproducibility and implementation, as well as a low representativeness of all pathways implicated in tumor progression by a single biomarker, have prevented the widespread use of these biomarkers in the clinic.

Probably, the combinatory analysis of BRMS1 expression with the expression levels of other factors implicated in tumor growth, angiogenesis, and tumor progression could results in a more effective prognostic tool. As it happens for other malignancies, for example about hormone positive resected breast cancer with the Food and Drug Administration (FDA) approved gene expression profiling, namely Oncotype DX and MammaPrint (1) or about gastric cancer with tool under clinical investigation, as the use of The Cancer Genome Atlas (TCGA) project and the Asian Cancer Research Group (ACRG) molecular classifications (2).

Be that as it may, Bucciarelli and co-workers, are to be congratulated on their contribution about the study of resected LUAD prognosis, using a very large cohort of resect LUAD with predominant stage I patients. They have identified a new potential biomarker that can be validated in new under development approaches combining both transcriptomic and proteomic data related to tumor progression pathways.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References
