Editorial

Specific copy number changes as potential predictive markers for adjuvant chemotherapy in non-small cell lung cancer

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Structural and numerical changes in cancer genome have been extensively investigated because of their fundamental contribution to initiation and development of human cancer. In the past, conventional karyotypic analysis of tumor samples led to identification of several oncogenes and tumor suppressor genes, such as the *MYC* and *RB* (1,2). Over the past two decades, gene copy analysis technology has progressed remarkably, enabling the identification of regions recurrently gained or lost, with a size small enough to narrow down to genes that are potentially relevant for the malignant properties of tumor cells. For example, *TITF1*, and *SOX2* have been identified as novel oncogenes through the integrative analysis of genome-wide copy number and gene function (3,4). Such genes may serve as therapeutic targets, thereby directly contributing to clinical practice. Another way to translate copy number data into the clinic is to utilize them as prognostic and predictive markers. In particular, developing predictive markers for certain treatments is vital because they make it possible to maximize the therapeutic benefits to patients.

Adjuvant chemotherapy (ACT) for patients with non-small cell lung cancer (NSCLC) underdoing complete resection has become the standard treatment based on several independent large-scale randomized studies (5). The studies reproducibly showed that platinum doublet treatments produce approximately 4–15% survival benefit. This benefit is very meaningful because it may directly contribute to cure of the disease. However, the treatments are inevitably associated with adverse events, which causes approximately 1% of deaths. Thus, establishing reliable biomarkers for ACT is very important. Both ERCC1 and RRM1 emerged as promising biomarkers for ACT (6,7); however, their usefulness has not yet been demonstrated by a phase III trial (8). Therefore, predictive biomarkers for ACT that can readily be used in the clinical settings are currently lacking (9).

Recently, Rotolo *et al.* have reported a comprehensive study in *Translational Lung Cancer Research* evaluating copy number changes using samples from the Lung Adjuvant Cisplatin Evaluation Biomarker (LACE-Bio) project, which was launched to identify promising biomarkers for ACT in a large cohort of patients participating in the ACT trials; the IALT, ANITA, JBR10, and CALGB9633 (10). The authors analyzed copy number alterations in 976 formalin-fixed paraffin-embedded (FFPE) samples with over 200 thousand single nucleotide polymorphism (SNP) probes. This resulted in the identification of recurrently amplified or lost regions with high resolution, followed by the correlation between those regions and the clinical outcome with a median follow-up duration of 5.2 years. The authors have confirmed several recurrently gained or lost regions, defined as 2-fold higher or lower copy number. For instance, approximately 40% of the samples exhibited loss of *CDKN2A* and *CDKN2B* residing adjacently in 9p21.3. *CDKN2A* is alternatively transcribed, encoding two critical tumor suppressor proteins: p16INK4 and p14ARF (11). *CDKN2B* encodes p15, another cell cycle inhibitor (12). Many studies have shown that alterations in these genes, including copy number loss, are associated with a poor prognosis in NSCLC patients (13,14). In addition, the authors found that *LKB1* (also known as serine/

threonine kinase 11; *STK11*) is prognostic. *LKB1* functions as a multifunctional tumor suppressor gene that regulates cell polarity, metabolism, proliferation, and migration and is frequently mutated, particularly in lung adenocarcinoma (15). Its loss is associated with poor prognosis in various types of human cancer (16), demonstrating its role in tumor suppression. Thus, Rotolo *et al.* successfully confirmed the prognostic relevance of these regions.

In addition to these previously reported genes, the study found several novel candidates as predictors for prognosis. Nevertheless, prognostic values of some of them seem contradictory to previously reported findings. For example, the guanine nucleotide exchange factor gene *VAV1* in 19p13.3-2, initially identified as a proto-oncogene through NIH3T3 cell screen, was conversely reported to be not amplified but lost in the study, correlating with worse prognosis. A recently study demonstrated the oncogenic functions of *VAV1*, showing that three somatic gene mutations occurring in human lung adenocarcinoma exhibit transformation ability, as measured by anchorage independent growth and tumor formation in immunodeficient mice (17). In addition, the lost region in 19p13.3-2 contains another oncogenic gene, *TCF3* (18). Therefore, further studies are needed to evaluate prognostic potential of genes in this region.

The strength of that study is that the samples were obtained from a randomized study evaluating the impact of ACT. This allowed exploration of altered regions that are potential predictive markers for ACT efficacy. The authors identified three regions that correlated with survival benefit in patients receiving ACT. Among them, an amplified region in 20q11.21 is interesting because it includes multiple genes potentially involved in oncogenesis and chemotherapy response. A previous study found that this region was amplified in NSCLC (19). Among these genes, *TPX2*, a cofactor of Aurora Kinase A (AURKA), plays a pivotal role in regulating microtubule assembly during mitosis (20), thereby potentially affecting the efficacy of microtubule-targeted drugs, such as vinorelbine and paclitaxel. Because most ACT-treated patients participating in the LACE-Bio project received vinorelbine or paclitaxel-containing platinum doublets, it is speculated that an increased copy number of *TPX2* are associated with ACT efficacy. Recently, Orth *et al.* demonstrated that TPX2 expression is involved in the radiosensitizing effect of paclitaxel *in vitro* (21). The study also reported that in The Cancer Genome Atlas (TCGA) cohort treated with taxane-based radiochemotherapy, AURKA and TPX2 levels were associated with better overall survival in lung adenocarcinoma. Nevertheless, the results of Orth *et al.* contradict those of Rotolo *et al.* because they found that a high TPX2 expression correlates with better survival in taxane-based radiochemotherapy and patients with an increased copy number of *TPX2* had worse benefits from ATC. However, both studies differ significantly in terms of treatment settings (ACT *vs.* radiochemotherapy). Thus, the status of targeted tumors cells differed significantly; ACT mostly targeted micrometastatic lesions with many dormant tumor cells whereas radiochemotherapy mostly targeted massive primary lesion with many actively proliferating tumor cells. For this reason, it is possible that an increased *TPX2* expression affected the benefits of each treatment in different ways. Therefore, further validation of these results is required.

The amplified region of 20q11.21 contains other genes with oncogenic properties including *BCL2L1* and *PDRG1*. Multiple coamplified genes may exhibit oncogenic properties synergistically (22). It is therefore possible that two or more gens co-amplified in 20q11.21 synergistically contribute to tumor development and/or affect sensitivity to chemotherapy. To investigate these hypotheses, further studies are needed to evaluate the effects of the introduction of putative target genes in 20q11.21 alone or in combination on oncogenic transformation or chemosensitivity using a normal lung epithelial model. An HBEC model developed by our group could be one of the ideal models because it has been extensively used to evaluate the effect of introducing or silencing of multiple genes on oncogenic properties or chemosensitivity (23-25).

In conclusion, the study by Rotolo *et al.* suggests several specific gained or lost regions in NSCLC samples, which could potentially serve as prognostic biomarkers and/or predictors for ACT. Further evaluation of their usefulness in different sets of cohorts as well as biological analyses are needed to proceed to prospective phase III studies investigating the prognostic value and predictive roles in ACT of specific copy number changes.

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Footnote

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declare.

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