Editorial

A novel prognostic marker of non-small cell lung cancer: chromosome 9 open reading frame 86 (*C9orf86*)

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Predicting the prognosis of individual patients is often as important as predicting individual disease susceptibility in the clinical practice (1). To date, we are able to utilize a number of prognostic indicators using human genome information and molecular technologies that: range from classical histopathological classification to somatic genetic changes (mutations, amplification, translocations and deletions) (2-4). Recently, Peng and colleagues have suggested a novel prognostic marker in patients with non-small cell lung cancer (NSCLC): overexpression of the chromosome 9 open reading frame 86 (*C9orf86*) gene (5). They evaluated C9orf86 protein expression in 180 NSCLC specimens and discovered that its expression is associated with poor prognosis. Although *C9orf86* might be only another prognostic marker which might have occurred coincidentally with other influential genetic changes, but this observation is worthy of remark because of several reasons that will be discussed.

The Ras super family, which are made up of small GTPases, modulate a number of diverse cellular functions including cell signaling and thus cell proliferation, differentiation and survival (6). Among the most studied in the Ras subfamily, *K-ras* is known to be a vital oncogene for the progression of lung cancer. Although various trials focusing on important downstream signaling have attempted, effective treatments on *K-ras* mutations have yet to be established (7). Another member of the Ras subfamily protein, Rab-like protein 1 (*RBEL1*), the alias of *C96orf86* and located at 9q34.3, has been known to be an important player in several cancers including breast, colon, and pancreatic cancer (8-10).

The study by Peng and colleagues aimed to explore the association between C9orf86 expression and prognosis among patients with NSCLC. *In vitro* studies using several cancer cell-lines have reported that upon si-RNA mediated *C9orf86* knockdown, cancer cells presented significant growth suppression and apoptosis (11). In a study assessing 180 breast cancer specimens, patients who demonstrated high levels of C9orf86 expression in tumor tissues had significantly worse survival than those with low levels of C9orf86 expression (8). Similarly in a study evaluating 73 pancreatic cancer specimens, patients with tumors expressing C9orf86 [the authors uses another alias in the paper: *RABL6A* (RAS oncogene family-like protein 6 isoform A, which is encoded by *RBEL1*)] had a worse prognosis compared with those who did not express C9orf86 (9). Peng and colleagues firstly explored whether the expression of C9orf86 had the same prognostic significance for NSCLC patients (5). They found that four (SPC-A-1, H460, H520, and H1975) out of six lung cancer cell-lines expressed C9orf86 significantly higher than the control cell-line 16HBE. Seventy four out of 180 (41.11%) NSCLC samples expressed C9orf86 via immunohistochemistry. Analyses comparing clinico-pathological status and C9orf86 expression highlighted both lymph node metastasis (N stage) and clinical stage to be significantly associated with C9orf86 positivity. Other clinical parameters including age, gender, T stage and histology were not associated with C9orf86 expression. A multivariate cox regression analysis verified that *C9orf86* is an independent prognostic factor. This association between C9orf86 positivity and prognosis varied depending on the histological type of lung cancer. Although the association

of C9orf86 positivity and prognosis was found to be statistically significant among patients with adenocarcinoma, the same was not seen among patients with squamous cell carcinoma (SCC). However, patients with SCC tend to also have a worse prognosis. This discrepancy may be due to variability in histology between adenocarcinoma and SCC. We cannot definitively conclude that C9orf86 positive patients have a worse prognosis in NSCLC. Interestingly their sub-analysis showed administration of adjuvant chemotherapy among C9orf86-negative patients resulted in prolong survival, whereas the same result was not seen among those who were C9orf86 positive. We cannot immediately accept the importance of *C9orf86* in chemotherapy sensitivity because there might be biases in administering adjuvant chemotherapy or not according to individual patient status. However, this observation is in line with the previous results that *C9orf86* depletion in pancreatic cancer selectively sensitized the cells to oxaliplatin-induced cell arrest and apoptosis (9). Moreover over-expression of Rab6c, another RAB subfamily protein, induces the intracellular accumulation of several anticancer drugs (12). Thus, the status of *C9orf86* in cancer cells might influence the sensitivity to anticancer agents, for which stratification of patients according to C9orf86 expression status might be required. Clinical utilization of *C9orf86* seems too optimistic because the oncogenic mechanism of *C9orf86* has not been fully elucidated.

TP53 and Alternative Reading Frame protein (ARF) are well-known tumor suppressor genes that are shown to interact with *C9orf86* (13,14). *C9orf86* inhibits p53 through interfering p53 oligomerization with MDM2 (14,15). Knockdown or overexpression of C9orf86 led to the increase or decrease of p53 expression, respectively (15). However, these experiments used ARF absent cell lines, MCF-7 and SK-BR-3 (8), and other mechanisms independent on the ARF/p53 pathway could also exist.

Contrary to the aforementioned oncogenic roles, *C9orf86* has a role as a tumor suppressor. Zhang and colleagues reported that depletion of *C9orf86* via short hairpin RNAs in primary mouse embryo cells resulted in centrosome amplification and aneuploidy (16). They concluded that the *C9orf86* controls chromosome stability and centrosome regulation. Proper centrosome stability is essential to the prevention of tumorigenesis (3). Although this particular function of *C9orf86* was not discussed in the article and may differ among cell types, further investigation is needed in order to explain these conflicting roles of *C9orf86* as both an oncogene and a tumor suppressor gene.

Peng and colleague have attempted to highlight the clinical relevance of *C9orf86* in NSCLC using immmunohistochemistry in a relatively small cohort. There are obstacles in utilizing *C9orf86* as a treatment target or a clinical marker, also *in vitro* or *in vivo* analysis is required in order to elucidate the close interacting partners of *C9orf86*. Future studies may clarify the precise role of *C9orf86* and its association with other molecules in NSCLC.

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Footnote

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

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