Editorial

Cyclin D1 expression in *KRAS* mutant non-small cell lung cancer—old wine into new skins

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Globally, lung cancer has the highest mortality rate among all cancers (1,2). Non-small cell lung cancer (NSCLC) comprises >80% of cases (3). Oncogene driver mutations in *EGFR*, *MET*, *KRAS*, *ALK*, *BRAF* are commonly described in NSCLC (4). The prevalence of KRAS mutation is higher in Western population (~30%) compared to Asian population (~10%) (4,5). This is attributed to the varying prevalence of smoking in the different populations and early role of *KRAS* in carcinogenesis among smokers (6). *KRAS* encodes a cytoplasmic GTPase that shuttles between the active GTP-bound form and the inactive GDP-bound form, regulated by GEFs and GAPs. In the active form, KRAS transduces signal from cell surface receptors to downstream effectors, regulating key cellular processes such as proliferation and survival (7). In *KRAS* mutant NSCLC, activating missense mutations involving codons 12, 13 and 61 lock the KRAS GTPase in a constitutive active form, initiating downstream signaling and promoting uncontrolled cell proliferation and survival in the absence of ligand stimulation. A downstream effector of KRAS is Cyclin D1/CCND1, which controls cell division by regulating CDK4/6 activity during G1-S transition of the cell cycle. Cyclin D1 is frequently upregulated in many cancer types (8). In NSCLC, *CCND1* gene amplification was observed in up to 32% of cases but cyclin D1 overexpression was found in up to 76% of cases (9), indicating additional signaling mechanisms exist to induce cyclin D1 overexpression but these mechanisms are not fully elucidated yet.

Despite being an oncogenic driver, targeted therapies against KRAS have been slow in development due to the lack of suitable "pockets" for small molecule binding (4). However, KRAS G12C mutant-specific small molecule inhibitors such as AMG510, MRTX849, JNJ-74699157 (10-12) have gained traction in the last year and an inhibitor of the SOS1:KRAS protein-protein interaction, BI3406, with wide KRAS inhibitory activity have been reported (13). Nevertheless, treatment strategies for *KRAS* mutant NSCLC remain limited and chemotherapy remains as the standard of care (4). As such, prognosis for NSCLC remains poor especially in patients with advanced disease (14). Numerous clinical studies have investigated the prognostic value of *KRAS* mutations in NSCLC but the results were variable due to differences in patient populations and endpoints (15). Therefore, there is a need for new prognostic markers in *KRAS* mutant NSCLC patients to improve disease control and selection of the best treatment strategy.

In an effort to identify potential prognostic markers in *KRAS* mutant NSCLC, Luangdilok *et al.* (in 2019) evaluated the expression of cyclin D1 protein on the overall survival in a Thai population of NSCLC patients with mutant *KRAS* versus wild type *KRAS* (16). The authors enrolled 95 NSCLC patients with wild type *EGFR* and studied the clinical characteristics, prevalence of the *KRAS* mutation and expression of cyclin D1. Most patients were in the advanced stage IV (73.7%) of the disease and most cases were adenocarcinoma (90.5%). 28 of them (29.5%) carried *KRAS* mutation while the remaining 67 (70.5%) were wild

type for *KRAS*. Among the clinical characteristics, not surprisingly, smoking history (P=0.001) and male gender (P<0.001) associated significantly with the presence of the *KRAS* mutation. Furthermore, NSCLC patients with *KRAS* mutation (n=28) had significantly shorter overall survival compared to patients with wild type *KRAS* (n=67) (median survival of 5.2 *vs*. 13.2 months). Interestingly, the authors demonstrated that NSCLC tumors with *KRAS* mutation (n=24) had a significantly higher expression of cyclin D1 protein than NSCLC tumors with wild type *KRAS* (n=36).

Luangdilok *et al.* (in 2019) go on to suggest that mutant KRAS protein may induce cyclin D1 overexpression through constitutive activation of the RAS-MEK-ERK pathway. Within the group of NSCLC patients with *KRAS* mutation, those with high cyclin D1 expression (n=14) had markedly shorter overall survival compared to those with low cyclin D1 expression (n=4) (median survival of 3.5 *vs*. 41.7 months). The association of poor prognosis with CCND1 overexpression and *KRAS* mutation status has been similarly suggested in early stage NSCLC by Dragoj *et al.* (in 2015) in a previous paper (17). In addition, Halilovic *et al.* (in 2010) suggested in *KRAS* mutant cancer cell lines that cyclin D1 expression was dependent on *PIK3CA* mutations and MEK/ERK inhibition as well (18). Hence, the definitive mechanistic links in *KRAS* mutant NSCLC have not been fully established, and future work will need to address if co-targeting KRAS mutant protein, and others such as PIK3CA and MEK/ERK will be potentially synergistic and beneficial for this disease. Studies using candidate gene approaches with small sample sizes as adopted by Luangdilok *et al.* (in 2019) remain hypothesis-generating. The roles of other genes such as *PIK3CA* in the regulation of cyclin D1 expression were not studied. The sample size is small and thus the findings may not be representative in a larger dataset. Future studies should be performed in larger cohorts and incorporate coexistent *PIK3CA* mutations and MEK/ERK pathway activation in the analysis to validate the prognostic role of cyclin D1 in *KRAS* mutant NSCLC.

Recently, the field of study into *KRAS* mutant NSCLC has taken on new directions, and there is renewed interest in this previously "undruggable" target. This study among others should provide further impetus to develop "new" understanding and treatments for this "old" target.

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