NRG1: a cinderella fusion in lung cancer?

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“Since *NRG1* fusions act through the activation of the ERBB receptor, blocking the activity of the NRG1–ERBB–PI3K–AKT pathway might be the best strategy for the treatment of *NRG1*-fused tumors.”

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The amazing bridge between gene fusions and lung cancer has been greatly consolidated during the last decades. The identification of *ALK* and *ROS1* rearrangements gives the great opportunity to rewrite the standard-of-care for a portion of advanced non-small-cell lung cancer (NSCLC) patients. Despite their very low incidence, these well-known genomic rearrangements share common features strictly associated to specific phenotypes of lung adenocarcinoma. This makes them ideal for diagnostic procedures, patients' stratification and therapies [1,2]. In this scenario, the finding of further intriguing targetable gene fusions, despite with a low incidence (1–2%) in NSCLC, is now increasing and it is watched with attention by the clinical community [3].

Recently, the *NRG1* gene has been described as a new molecular feature of NSCLC [4]. The *NRG1* gene is located at the long arm of chromosome 10 (10q23.1 region) and encodes for the neuregulin 1, a growth factor belonging to the complex family of proteins also called heregulins. These proteins are structurally related to the stimulation of ERBB receptors tyrosine kinase activity and EGF signals. Specifically, the NRG1-receptor binding induces the phosphorylation of the intrinsic kinase domains of ERBB3 and stimulates its dimerization with ERBB2 receptor and the activation of the downstream PI3K–AKT and MAPK pathways [5].

The neuronal isoform NRG1 III-β3 is generally not expressed in normal lung tissue, but it was found to be ectopically activated in lung tumor cells by *NRG1* genomic rearrangements involving mainly *CD74* and *SLC3A2* genes [6]. It is the first fusion associated with the mucinous subtype of lung adenocarcinoma with an occurrence ranging from 8 to 27%. By contrast, *NRG1*-gene fusions occur in 1–2% of NSCLC and occasionally reported in other solid tumors [7]. It has been more extensively investigated in Asian than Caucasian lung cancer patients in whom it has been not yet fully elucidated and remains only partially understood [6].

ERBB signaling is one of the most deregulated lung cancer cascades. ERBB3 is not frequently affected by mutations or amplifications in lung cancer. Furthermore, *MET* or *HER2* amplifications, which represent additional mechanisms of ERBB3 activation in lung tumors, rarely occur. Thus, the overproduction of NRG1 ligands could represent one of the leading mechanisms by which lung cancer cells aberrantly activate ERBB3-related receptor tyrosine kinase signaling.

The first suggestion of a real clinical utility of *NRG1* fusion comes by analyzing a large sample of mucinous lung adenocarcinoma in Asians for the *NRG1* breaks. In fact, patients with stage I disease harboring tumors with *NRG1* fusions showed an inferior overall survival and a trend toward a shorter disease-free survival compared with those without *NRG1* fusions [8]. The powerfulness of this fusion has been highlighted *in vitro*. In fact, the expression of *CD74*–*NRG1* fusion gene is able to promote cancer stem cell properties and it is involved in stem cell function of several types of cancers, including lung cancer. These data imply the existence of a mechanism by which the activated ERBB receptors contribute to the acquisition of cancer stem cell-like characteristics together with the ability of cancer cells to develop a resistance to chemotherapy [9]. Moreover, in the absence of RAS pathway

mutations, NRG1 overexpression can play a major role in the primary cetuximab resistance in colon cancer cells and in primary resistance to trastuzumab in *HER2* overexpressing breast cancer cells [10,11].

Of interest, *NRG1* fusions have been proved to be coexistent with *ALK* fusion or *RAS* mutation in NSCLC patients, both in primary and in metastatic sites of lung tumors [12–14]. Moreover, it has been recently considered as a potential mechanism of resistance after treatment with tyrosine kinase inhibitors in *ALK*-rearranged NSCLC cell lines. In fact, by using primary cultures of cancer cells from pleural effusion of an *ALK*-positive lung cancer patient, the increase of the NRG1 ligand levels and the consequent activation of ERBB3 pathway has been directly related to resistance to crizotinib treatment [15]. This assumption has been further confirmed showing that, under treatment with second-generation *ALK* inhibitors, NSCLC cells activated the EGFR family pathways directly through the NRG1–ERBB3–EGFR activation axis [16]. In support to these *in vitro* reports, the onset of the *SLC3A2*–*NRG1* gene fusion during the natural history of two invasive mucinous lung adenocarcinoma in Asiatic patients has been described. These heavily pretreated patients received the combination of lumretuzumab, a monoclonal anti-ERBB3 antibody, plus erlotinib, an anti-EGFR small molecule, showing tumor shrinkage [17]. Furthermore, the use of afatinib, a pan-ERBB-family kinase inhibitor, in *NRG1*-positive samples resulted in a surprisingly durable response in patients with lung adenocarcinoma and cholangiocarcinoma [7,18].

ERBB3 overexpression actually represents one of the targets of greater interest for the current pharmacological studies. In fact, its activation through phosphorylation has been detected in various cancers including metastatic lung carcinoma in presence of acquired resistance to other ERBB family inhibitors [19]. Moreover, due to its inactive tyrosine kinase domain, ERBB3 has been reported to have a critical role in the dimerization process in the context of acquired *de novo* resistance to ERBB3 targeted therapies. However, despite the well-tested efficacy of EGFR and *HER2* inhibitors, ERBB3 specific upregulation has not been yet targeted with clear clinical efficacy. Of all the anti-ERBB3 agents, patritumab is in advanced clinical development, being currently investigated in a Phase III trial for treatment of NSCLC (JapicCTI-101262) [20]. Additional trials are investigating neratinib, alone and in combination with temsirolimus (NCT01827267) and trastuzumab emtansine (T-DM1; NCT02289833), in *HER2* molecular profiled advanced NSCLC. Of great interest is MM-121. An ongoing open-label trial is investigating MM-121, a fully human monoclonal antibody targeting specifically ERBB3, in combination with docetaxel or pemetrexed compared with docetaxel or pemetrexed alone, in patients with heregulin-positive, advanced NSCLC with primary end point overall survival (NCT02387216).

Overall, *NRG1* fusions could represent new potential molecular alterations able to predict the therapy activity in a specific lung adenocarcinoma subtype. Since *NRG1* fusions act through the activation of the ERBB receptor, blocking the activity of the NRG1–ERBB–PI3K–AKT pathway might be the best strategy for the treatment of *NRG1*-fused tumors.

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