Commentary

Savior or not: ADAM17 inhibitors overcome radiotherapy-resistance in non-small cell lung cancer

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According to WHO cancer report in 2015, lung cancer is the most leading cause of cancer-associated death and accounts for approximately 20% of whole cancer-related death. The 5-year survival rate is less than 30% and the average of other types of cancer such as colon, breast, and prostate cancer in stage II and more advanced stages. Therefore, lung cancer is recognized as a poor prognostic cancer and needs an establishment of efficient therapy. Anti-EGFR drugs dramatically reduce tumor growth for non-small cell lung cancer (NSCLC) with EGFR mutations but the clinical outcome has been still disappointing because of against treatment by genetic alterations emerged as clinical problems (1). Moreover, it was reported that a combination therapy by using anti-EGFR drugs and ionizing radiation (IR) has provided no additive beneficial outcome in those patients (2). Accordingly, targeting other EGF signaling-related molecules would be breakthrough for anti-EGFR therapy-resistant NSCLC and is highly demanded.

A disintegrin and metalloproteinases (ADAMs) have implicated roles in remodeling of extracellular matrix and ectodomain shedding of membrane-bound proteins including growth factors and receptors via their proteolytic activity. Evidence is accumulating that ADAMs are involved not only in development but also in various diseases including inflammation, neurodegeneration, and especially in cancer. Downregulation of ADAMs attenuates tumor growth and metastasis in mouse models, suggesting that ADAMs contribute to tumor progression and metastasis. Analysis of clinical samples has demonstrated that overexpression of ADAMs is often observed in various tumors and positively correlated with aggressive phenotypes and poor prognosis (3). Therefore, ADAMs are thought to be a potential therapeutic target for cancer. Eventually, many inhibitors against ADAMs or matrix metalloproteinases (MMPs) have been developed so far as described in elsewhere (4). However, none of them is clinically available because of poor efficacy or side effects. ADAM17 is the most well-characterized ADAM proteinase and alternatively called as tumor necrosis factor-α converting enzyme (TACE). Overexpression of ADAM17 was found in breast, brain, colon, kidney, liver, lung, ovary, pancreas, prostate, and renal cancer (5). Depletion of ADAM17 expression in myeloid cells resulted in a significant reduction of lethality in an LPS-triggered septic shock mouse model by preventing TNFα secretion (6). Therefore, ADAM17 is a promising therapeutic target for inflammation-related diseases and cancer. Overexpression of ADAM17 is strongly associated with aggressive phenotypes and poor prognosis in NSCLC (3). Sharma and colleagues focused on the ADAM17 function as a sheddase for EGF ligands including EGF, HB-EGF, neuregulins, and amphiregulin and demonstrated that ADAM17 contributed to resistance against radiotherapy in NSCLC (7). They found that the expression of Furin protease was upregulated by IR in a dose-dependent manner. Furin cleaves a pro-domain of ADAM17 that covers the catalytic domain, and then ADAM17 is ready to cleave its substrates. Increased Furin expression led to an enhancement of ADAM17-mediated secretion of not only EGF ligands but also activated leukocyte cell adhesion molecule (ALCAM). Anti-EGFR monoclonal antibody, cetuximab, had no anti-proliferative effect on IR therapy-resistant lung carcinoma cell, A549. Pretreatment with anti-ADAM17 siRNAs or a metalloproteinase inhibitor, TMI-

005 (apratastat), in A549 cells sensitized them to IR and downregulated phosphorylation levels of EGFR. Moreover, a combination of anti-ADAM17 reagents (anti-ADAM17 siRNA or TMI-005) with IR therapy prolonged survival compared with mice taking Cetuximab and IR therapy (7). EGFR shares its downstream signaling molecules such as MAPK and PI3K/Akt with other EGFR family members, ErbB2 (Her2), ErbB3 (Her3), and ErbB4 (8). Cetuximab cannot inhibit signalings derived from ErbB3- or ErbB4-dimerized receptor. Taken together, ADAM17-mediated secretion of EGF ligands induces ErbB3- and/or ErbB4-mediated common EGFR downstream pathways and shows resistance to anti-EGFR therapy. The authors did not examine whether pharmacological or genetic inhibition of ADAM17-cleaved substrates, amphiregulin and ALCAM sensitizes the resistant tumors to IR. Nor did they check whether proteinase activity of ADAM17 is required for the acquisition of IR therapy resistance. Expression of not all ADAM17-cleaved substrates including HB-EGF were increased by irradiation in the paper, and they did not figure out these points (7). Collectively, precise mechanisms of ADAM17-mediated IR therapy resistance still remain to be elucidated by further analysis.

ADAMs might be thought to be undruggable targets. All developed ADAM inhibitors failed clinical trials because of poor efficacy or side effects. The ADAM family comprises large family (>20 in mammals) and shares their substrates among them and MMPs. For instance, in case of pro-TNFα conversion, ADAM10, ADAM19, and MMP-3 work as TACE (6), indicating ADAMs or MMPs is a multi-enzyme multi-substrate system. In addition to the points as described above, the structure of catalytic domain is very similar among ADAMs and MMPs. These points render us hard to develop the specific inhibitors. These problems indicate that sole inhibition of a specific ADAM may not provide good clinical outcomes due to cross-reactivity among ADAMs, and also broad-spectrum inhibitors against ADAMs and MMPs are not useful in clinic because of side effects. Consequently, development of specific ADAM inhibitors is highly challenging. TMI-005 that was effective in the treatment for IR-resistant NSCLC is a non-selective and a broad-spectrum metalloproteinase inhibitor for ADAMs and MMPs. TMI-005 had made an entry to the phase 2 clinical trial in 2005 but it was terminated in 2006 because of lack of efficacy on rheumatoid arthritis (RA) (9). ADAM17 knockout mice are embryonic lethal because of epithelial abnormalities (10) whereas ADAM17$^{ex/ex}$ mice that have dramatically reduced but still retained ADAM17 expression in all tissues are viable. Although TMI-005 is orally bioavailable and did not show severe side effects in over 300 RA patients (9), ADAM17$^{ex/ex}$, which is considered as ADAM17 inhibitor-taking mice, showed an increased susceptibility to inflammation in the intestine challenged by dextran sulfate sodium and breakdown of intestinal barrier as compared with unchallenged mice (11). This suggests that inhibition of ADAM17 could cause severe epidermal defects in patients with inflammation. ADAMs also provide cell adhesion properties to tumor cells via their disintegrin or cysteine rich domain (12). ADAM12 enhances TGF-β signaling involved in epithelial-mesenchymal transition (13), and tumor growth in a catalytic activity-independent manner (14), suggesting that catalytic activity is dispensable for tumor growth and TGF-β signaling. Sole inhibition of catalytic activity of ADAMs may be insufficient for an inhibition of tumor growth. Recent studies reported that anti-ADAM17 D1(A12) monoclonal antibody, the first specific inhibitor for ADAM17, showed anti-tumor effect *in vitro* and *in vivo* (15,16). This monoclonal antibody simultaneously binds to catalytic and disintegrin domains. Consequently, the monoclonal antibody might be useful for ADAM17-targeting therapy.

A number of anti-ADAM inhibitor were developed and challenged to clinical trials so far. All of them failed to be used in clinic because of side effects and/or lack of efficacy so far. However, given the accumulating evidence that metalloproteinase ADAMs and MMPs are involved in tumorigenesis and poor prognosis they are still promising therapeutic targets. Computer-based drug development and optimization by using information of crystal structures such as in silico screening have become a strong method. However, there are only two available crystal structures of human ADAMs (17,18). Noberini *et al*. developed some specific inhibitors against ligand binding domain of the Eph receptors based on their crystal structures (19) although the receptor cross-reacts with multiple ligands among the family as in the case of the ADAM-substrate recognition system (20). Full investigation of ADAM functions in cancer and determination their crystal structures are necessary to develop specific inhibitors of ADAMs. Also, decoy reagents by using substrate recognition sequences to abolish protease activity might be suitable for their specific inhibition. A combination therapy using specific inhibitors against a given ADAM(s) that specifically mediates progression of the disease of interest (called order-made medicine) would be the best therapy for ADAM-related diseases.

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Footnote

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