ADAM-17: A Target to Increase Chemotherapeutic Efficacy in Colorectal Cancer?

Adam M. Lee and Robert B. Diasio

Chemotherapy-induced activation of ADAM-17 results in increased growth factor shedding and activation of growth factor receptor-mediated pro-survival response. Enhanced ADAM-17 activity and HER ligand shedding results in resistance to chemotherapy in CRC. Therapies that decrease ADAM-17 activity in conjunction with current treatments may enhance response rates in advanced CRC patients. Clin Cancer Res; 16(13): 3319–21. ©2010 AACR.

In this issue of Clinical Cancer Research, Kyula and colleagues provide striking evidence that colorectal cancer (CRC) shows an acute response to chemotherapy by activating ADAM-17, and that enhanced ADAM-17 activity accompanied by increased human epidermal receptor (HER1) ligand shedding results in resistance to chemotherapy in CRC (1).

CRC is the third most common cause of cancer death in the United States primarily due to metastases that are resistant to conventional therapy (2). CRC cells are genetically unstable, which lead to biologic heterogeneity among many phenotypes, including the heterogenous expression of different growth factors and growth factor receptors involved in carcinogenesis, angiogenesis, and metastasis (3, 4). Transforming growth factor-α (TGF-α) and epidermal growth factor (EGF) bind to the EGF receptor (EGFR). The resulting phosphorylation of EGFR stimulates the signaling pathways to promote cell proliferation, cell survival, invasion and metastasis, and tumor-induced neoangiogenesis (Fig. 1A; ref. 3). Previous studies have also shown that exposure to chemotherapy or ionizing radiation can activate EGFR prosurvival response pathways in tumor cells, and that co-expression of EGFR (HER1) and TGF-α correlates with aggressive disease and poor prognosis in several types of tumors including CRC (1).

These findings led Kyula and colleagues to investigate the mechanisms that activate the HER-mediated survival response to chemotherapy in CRC cells. Initial studies focused on the cleavage of TGF-α and other HER ligands following exposure to 5-fluorouracil (5-FU). These studies showed statistically significant increases in human TGF-α, amphiregulin (AREG), and heregulin shedding both in culture medium of HCT116 cells and serum of mice bearing human HCT116 xenografts (1). The functional relevance of HER-ligand shedding following 5-FU was further solidified after the addition of exogenous EGF ligands to the culture medium resulted in decreased 5-FU-induced cell death (1).

HER ligands are synthesized as transmembrane precursors that are cleaved by catalytically active members of the ADAM (a disintegrin and metalloproteinase) family. ADAM enzymes are Zn²⁺-dependent, modular cell surface proteases that are cleaved by catalytically active members of the ADAM (a disintegrin and metalloproteinase) family. ADAM enzymes are Zn²⁺-dependent, modular cell surface proteins of the adamalysin protein family, which participate in cellular adhesion and proteolytic cleavage of various cell surface molecules. ADAMs are also important mediators of cell signaling events, which determine cellular fate, proliferation, and growth, and are thus important in numerous physiological and pathophysiological processes. Out of the 21 ADAMs identified within the human genome, 13 are proteolytically active (5).

Several studies have indicated that different ADAMs such as ADAM-9, -10, -12, -15, and -17 can induce EGFR activation through ectodomain cleavage, resulting in ligand shedding and receptor activation in an autocrine and paracrine manner (5). The current study used specific small interfering RNAs (siRNA) directed against ADAM-9, -10, -12, -15, and -17 to determine which ADAM family members play a significant role in regulating chemotherapy-induced EGFR activation and TGF-α shedding. Experiments showed that only silencing of ADAM-17 significantly decreased TGF-α shedding and EGFR activity following 5-FU (Fig. 1B).

ADAM-17 (also known as CD156b, cSVP, MGC71942, and tumor necrosis factor converting enzyme or TACE) is one of the most well studied of the ADAM enzymes. It was discovered and characterized in 1997 by two research groups as the enzyme that releases membrane-bound tumor necrosis factor (TNF)-α precursor to a soluble form (6, 7). Located on chromosome 2p25, ADAM-17 is a multidomain protein comprised of 824 amino acids and is widely expressed in various tissues including the brain, heart, kidney, and skeletal muscle (6). It has few sequence similarities with other ADAM enzymes and...
shows only a 30% sequence homology with its closest relative ADAM-10 (8).

The most well-known function of catalytically active ADAMs is the cleavage or shedding of various transmembrane proteins' ectodomains, resulting in enhanced juxtacrine and paracrine signaling (5). Depending upon the ligand and/or receptor undergoing cleavage, ADAM-17 activity can regulate multiple cell signaling pathways and responses and is essential in normal mammalian development as indicated by numerous knockout studies and gene expression studies that showed that ADAM-17 expression changes during embryonic development and adult life (6, 8).

Numerous studies have shown that members of the ADAM family including ADAM-17 may be involved in regulating EGFR activation via proteolytic processing of EGFR-ligand precursors such as TGF-α, EGF, AREG, and epiregulin (EREG) and can be induced by cellular stress (5, 9). The current study showed that ADAM-17 activity significantly increased after 5-FU treatment in HCT-116 cells as well as HCT116 xenografts, which correlated with the effect of chemotherapy on HER ligand shedding in vitro and in vivo. Strikingly, ADAM-17 was also shown to regulate SN-38- and oxaliplatin-induced HER ligand shedding and EGFR activation in multiple CRC cell lines irrespective of p53, KRAS, or BRAF mutational status. Furthermore, when ADAM-17 siRNA or the small molecule ADAM10/17 inhibitor GW280264 × was combined with chemotherapy in different CRC cell lines, Kyuula and colleagues observed a synergistic activation of apoptosis. By overexpressing ADAM-17 in cell lines and xenograft mouse models, ADAM-17 activity was increased, resulting in increased TGF-α, AREG and heregulin ligand shedding, EGFR activation, and enhanced tumor growth. Moreover, clones with increased ADAM-17 activity levels had a decreased response to chemotherapy compared with the empty vector clones and abrogated chemotherapy-induced apoptosis. This study combined with previous reports, which indicated ADAM-17 overexpression in primary and metastatic CRC compared with normal colonic epithelium (10), substantiate ADAM-17 as an important regulator in CRC response to chemotherapy and suggest that targeting ADAM-17 in conjunction with chemotherapy may have therapeutic potential in CRC.

To date, therapeutic agents such as cetuximab and panitumumab, which target the inhibition of EGFR, have been approved for the treatment of metastatic CRC (mCRC). Although the EGFR protein is expressed in approximately 85% of mCRC tumors, only patients with the wild-type KRAS gene show a clinical benefit from treatment with EGFR inhibitors such as cetuximab (11). KRAS encodes a small G protein that links ligand-dependent receptor activation to intracellular pathways of the EGFR signaling cascade. Mutations within KRAS, commonly at codons 12

---

**Fig. 1.** The role of ADAM-17 in the growth factor receptor-mediated prosurvival response. A, in response to 5-FU, CRC cells show an increase in ADAM-17 activity, which results in increased growth factor shedding and an EGFR-mediated prosurvival response. B, inhibition of ADAM-17 activity either through a siRNA gene silencing mechanism or the ADAM10/17 inhibitor GW280264 × results in decreased ADAM-17 activity, decreased ligand shedding, abrogated EGFR activity, and synergistic activation of apoptosis when combined with chemotherapy.

---

**Cell proliferation**

**Cell survival**

**Invasion and metastasis**

**Tumor-induced neoangiogenesis**
and 13, cause constitutive activation of KRAS-associated signaling and are associated with decreased efficacy of cetuximab (11). Kyula and colleagues provide strong evidence for ADAM-17 as a potential therapeutic target in the treatment of mCRC. By inhibiting ADAM-17, a greater effect could be achieved due to its role in the activation of multiple receptor tyrosine kinases such as EGFR, IGF-IR, and VEGFR, as well as the fact that ADAM-17 regulated 5-FU-induced EGFR activation and ligand shedding regardless of p53, KRAS, or BRAF mutation status (1). However, the role of ADAM-17 in controlling many physiological and pathophysiological processes raises concern about whether it is possible to specifically target ADAM-17 in cancer without altering the enzyme’s function in other tissues. Even though specific inhibitors of ADAM-17 exist, there remains a potential for numerous side effects that must be fully evaluated prior to acceptance of ADAM-17 inhibitors as an effective therapeutic approach. Because of both the pro-proliferative and inhibitory nature of the enzyme, altering ADAM-17 without specificity to the disease could be problematic. Because of its ubiquitous nature, clarification of the mechanisms regulating ADAM-17 activity is crucial in developing effective therapy. Lastly, an alternative approach for increasing chemotherapeutic efficacy might be the use of small molecules or antibodies that block shedding of a specific substrate by obscuring the cleavage site without inhibiting the actual enzyme. Future studies will be required to clarify these concerns.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Received 05/10/2010; accepted 05/12/2010; published OnlineFirst 06/22/2010.

References

Clinical Cancer Research

ADAM-17: A Target to Increase Chemotherapeutic Efficacy in Colorectal Cancer?

Adam M. Lee and Robert B. Diasio


Updated version
Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-10-1059

Supplementary Material
Access the most recent supplemental material at:
http://clincancerres.aacrjournals.org/content/suppl/2010/06/29/1078-0432.CCR-10-1059.DC1

Cited articles
This article cites 10 articles, 3 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/16/13/3319.full.html#ref-list-1

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.