

## Role of ADAMs in Cancer Formation and Progression

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**Abstract** The ADAMs (a disintegrin and metalloproteinase) comprise a family of multidomain transmembrane and secreted proteins. One of their best-established roles is the release of biologically important ligands, such as tumor necrosis factor- $\alpha$ , epidermal growth factor, transforming growth factor- $\alpha$ , and amphiregulin. Because these ligands have been implicated in the formation and progression of tumors, it might be expected that the specific ADAMs involved in their release would also be involved in malignancy. Consistent with this hypothesis, emerging data from model systems suggest that ADAMs, such as ADAM-9, ADAM-12, ADAM-15, and ADAM-17, are causally involved in tumor formation/progression. In human cancer, specific ADAMs are up-regulated, with levels generally correlating with parameters of tumor progression and poor outcome. In preclinical models, selective ADAM inhibitors against ADAM-10 and ADAM-17 have been shown to synergize with existing therapies in decreasing tumor growth. The ADAMs are thus a new family of potential targets for the treatment of cancer, especially malignancies that are dependent on human epidermal growth factor receptor ligands or tumor necrosis factor- $\alpha$ .

The ADAMs (a disintegrin and metalloproteinase) are members of the metzincin superfamily of matrix metalloproteinases (MMP; for review, see refs. 1, 2). Together with the snake venom metalloproteinases and the ADAMs containing thrombospondin sequences (ADAMTS), they constitute the adamalysin subfamily. To date, 21 functional ADAMs have been described in humans and 40 in different organisms.<sup>4</sup> The ADAMs are involved in diverse biological functions, including fertilization, adhesion, migration, and proteolysis (1, 2). Recently, specific ADAMs were implicated in a number of diseases, including rheumatoid arthritis, Alzheimer's disease, atherosclerosis, asthma, and cancer (for review, see refs. 2, 3). The aim of this article is to review the role of ADAMs in cancer. First, however, a brief description of the structure and biological functions of the ADAMs is presented.

### Structure of ADAMs

A typical ADAM protein consists of a number of conserved domains. These include: a signal peptide, a propeptide, a MMP domain, a disintegrin sequence, a cysteine-rich region, an EGF-like domain, a transmembrane sequence, and a cytoplasmic tail (1–3). The prodomain of ADAMs, possessing a protease domain, maintains catalytic inactivity until it is removed by a

furin-type proprotein convertase or by autocatalysis. As with MMPs, a cysteine switch in the prodomain is believed to keep the protease in an inactive state.

Approximately 50% of the ADAMs possess the catalytic consensus sequence HEXXH in their protease domain. Because some of these were shown to be proteolytically active, it is assumed that all ADAMs containing an HEXXH sequence have protease activity. Although ADAMs can hydrolyze a diverse range of substrates, at least *in vitro* (1–3), the primary substrates seem to be the ectodomain of transmembrane proteins (1). Cleavage of these proteins by ADAMs usually occurs at the juxtamembrane region.

Downstream of the protease domain is the highly conserved disintegrin region. The disintegrin domain contains ~90 amino acids and is found in all ADAMs. Its primary role is in cell adhesion, especially in binding ADAMs to integrins. The binding of most ligands to integrins occurs via the RGD (Arg-Gly-Asp) sequence. However, with the exception of human ADAM-15, which attaches to  $\alpha\beta3$  and  $\alpha5\beta1$  using the RGD motif (4, 5), other ADAMs lack this sequence. For example, a number of different ADAMs bind to integrins through the conserved sequence RX6DLPEF (6). In general, it seems that any integrin can bind to multiple ADAMs whereas, conversely, any ADAM can attach to several integrins (6, 7).

On the C-terminal side of the disintegrin domain is the cysteine-rich region. This region has been implicated in cell adhesion and substrate recognition. Thus, in ADAM-12, this region has been shown to bind to the cell adhesion protein syndecan (8); in ADAM-10, it bound to the EphA3/ephrin-A5 complex (9) whereas in ADAM-17, it was required for IL-IR II shedding (10).

The cytoplasmic C-terminal tail varies in sequence and size among the different ADAM family members. This region is rich in proline residues and thus may interact with Src homology 3 domain-containing proteins. Indeed, a number of proteins

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<sup>4</sup> <http://www.people.virginia.edu/~7Ejw7g/Table.of.the.ADAMs.html>

## Translational Relevance

The ADAMs (a disintegrin and metalloproteinase) have two clearly defined biological roles, proteolysis and cell adhesion. As proteases, their main substrates are transmembrane proteins, such as the precursor forms of growth factors. Specifically, two ADAMs, ADAM-10 and ADAM-17, have been shown to release and activate several ligands for the epidermal growth factor receptor (EGFR)/human EGFR (HER) family of receptors. These ligands include epidermal growth factor (EGF), transforming growth factor (TGF)- $\alpha$ , and amphiregulin. All of these ligands have been implicated in cancer development and progression.

Consistent with their ability to release tumor-promoting factors, several ADAMs have been shown to play a role in the pathogenesis of cancer. Indeed, in several human cancers, levels of multiple ADAMs correlate with features of aggressive disease and poor outcome. Specific ADAMs are thus potential new markers for predicting the metastatic potential of newly diagnosed cancers. The main clinical utilization of ADAMs, however, is likely to be as targets for new anticancer treatments. Several selective ADAM inhibitors, especially against ADAM-10 and ADAM-17, have been shown to synergize with existing therapies (including trastuzumab and tyrosine kinase inhibitors) in inhibiting tumor cell growth. Currently, at least one of these inhibitors is undergoing clinical trials against multiple cancer types. ADAM inhibitors would be expected to be particularly beneficial in cancers that are dependent on EGFR/HER-2 signaling.

have been shown to interact with the cytoplasmic tail of ADAMs, including Src, growth factor receptor binding protein 2, phosphatidylinositol 3-kinase, Eve1, PACSIN2, and PACSIN3 (for review, see ref. 2).

The biological consequence of these interactions, however, is unclear.

## Functional Consequences of ADAM Proteolytic Activity

Although the ADAMs are implicated in a broad range of biological activities, this review will focus mostly on activities that are likely to be relevant to the formation or progression of cancer. These include the release of TNF- $\alpha$  by ADAM-17 and the shedding of HER/EGFR ligands by multiple ADAMs.

**Shedding of TNF- $\alpha$  by ADAM-17.** One of the first membrane proteins shown to be shed by an ADAM was TNF- $\alpha$  by ADAM-17 (also known as TNF- $\alpha$  converting enzyme or TACE). Indeed, the original purification of ADAM-17 was based on its ability to hydrolyze both peptide and full-length TNF- $\alpha$ -based substrates at their physiologic cleavage site (11, 12). The *in vivo* evidence implicating ADAM-17 in TNF- $\alpha$  release was the finding that T cells derived from ADAM-17-deficient mice (TACE <sup>$\Delta$ Zn/Zn $\Delta$</sup> ) lost almost all of their ability to shed TNF- $\alpha$  (11). All of these findings, when taken together, make it likely that ADAM-17 is a physiologic sheddase for TNF- $\alpha$ .

TNF- $\alpha$  is a pluripotent peptide with multiple activities potentially important in tumor formation and/or progression

(13). Although pharmacologic doses of TNF- $\alpha$  are used to treat certain cancers (14), endogenous levels seem to play a role in cancer initiation and progression (13). Thus, results from animal studies show that TNF- $\alpha$  is involved in the initiation or progression of skin, liver, intestinal, and ovarian (15–18) malignancies. The potential mechanisms by which TNF- $\alpha$  plays a role in malignancy include its ability to up-regulate MMP expression, induce angiogenic factors, enhance cell migration, promote the epithelial-to-mesenchymal transition, induce expression of the transcription factor nuclear factor  $\kappa$ B, and induce reactive oxygen species that damage DNA (13, 16, 19, 20). TNF- $\alpha$  has been referred to both as a mutagen (20) and as a tumor promoter (21).

Because ADAM-17 catalyzes the formation of active TNF- $\alpha$ , it might also be expected to play a role in malignancy via the generation of this cytokine. To our knowledge, however, no study has directly shown that ADAM-17-catalyzed release of TNF- $\alpha$  is involved in cancer formation or progression.

**Shedding of HER ligands by ADAM-10, ADAM-15, and ADAM-17.** The HER (also known as ErbB) proteins belong to the subclass I of the superfamily of receptor kinases. There are four members of the family: EGFR/ErbB1/HER1, HER2/ErbB2, HER3/ErbB3, and HER4/ErbB4. At least two members of this family (i.e., EGFR and HER2) mediate cell growth, cell survival, cell migration, angiogenesis, and invasion (for a review, see ref. 22). Because of their key role in these processes, altered expression of EGFR and HER2 has been implicated in the formation/progression of multiple cancer types. Indeed, these two proteins are currently among the best-validated targets for cancer treatment (23). This is especially true for HER2 in breast cancer (23).

The HER tyrosine kinases are activated by a number of ligands that are initially synthesized as transmembrane precursors. These ligands can be divided into three main groups: (a) EGF, TGF- $\alpha$ , amphiregulin, and epigen, which specifically bind to EGFR; (b) heparin-binding (HP)-EGF, epiregulin, and betacellulin, which bind to EGFR or HER4; and (c) neuregulin (also known as heregulin), which binds to HER3 and HER4 (22, 23). Although no naturally occurring ligand has yet been identified that binds directly to HER2, this receptor is the preferred dimerization partner for the other three ligand-activated HER members.

Most of the HER ligands can be released from their precursor forms by specific ADAMs. Knockout studies with the use of mouse embryonic cells showed that ADAM-17 was the major sheddase for TGF- $\alpha$ , amphiregulin, HB-EGF, and epiregulin whereas ADAM-10 was primarily responsible for the release of EGF and betacellulin (24). In certain situations, however, other ADAMs may release HER ligands. Thus "gain of function" experiments showed that ADAM-8 as well as ADAM-17 can shed amphiregulin (25). Similarly, overexpression of ADAM-8, ADAM-9, ADAM-12, ADAM-17, and ADAM-19 as well as ADAM-10 was able to release EGF (25). Release of the active form of the ligand is necessary for biological activity (26, 27).

ADAM-mediated release of HER ligands can be activated by a number of physiologic and pharmacologic stimuli. Among the best-studied stimuli are agonists for G protein-coupled receptors (i.e., the binding of these agonists to their receptor results in ADAM-mediated release of HER ligands and trans-activation of EGFR; ref. 28).

The specific ADAM involved in EGFR transactivation seems to vary with the cell type and G protein-coupled receptor agonist. Thus, Gschwind et al. (29) showed that lysophosphatidic acid-induced proliferation and motility of squamous carcinoma cells *in vitro* involved ADAM-17 cleavage of proamphiregulin followed by activation of EGFR. In the kidney cancer cell lines Caki2 and A498, lysophosphatidic acid was found to regulate migration, proliferation, and survival as a result of ADAM-17 releasing HB-EGF, followed by transactivation of EGFR (30, 31). In ACHN kidney cells, however, ADAM-10 was responsible for the release of HB-EGF (31). Finally, in bladder cancer cells, lysophosphatidic acid induced proliferation, migration, and survival after ADAM-15-mediated release of amphiregulin (31).

Unlike with ADAM-17-mediated release of TNF- $\alpha$ , there are a number of reports from model systems showing that ADAM-17-catalyzed shedding of HER ligands is involved in malignancy (see below).

### Evidence of a Role for ADAMs in Cancer

Based on their potential to release ligands capable of stimulating cell proliferation as well as migration, it might be expected that certain ADAMs would be involved in malignancy. Emerging data from different model systems support this hypothesis, especially for ADAM-9, ADAM-12, ADAM-15, and ADAM-17. This evidence is briefly reviewed below.

**ADAM-9.** Peduto et al. (32) reported that well-differentiated prostate cancers developed in ADAM-9-deficient mice compared with poorly differentiated tumors in control mice expressing ADAM-9. These investigators also showed that overexpression of ADAM-9 in mouse prostate epithelial cells gave rise to epithelial hyperplasia and prostate intraepithelial neoplasia, a putative precursor lesion for prostate cancer (32). In studies on prostate cancer cell lines in culture, overexpression of ADAM-9 was found to be associated with the conversion of LNCaP cells to an androgen-independent and metastatic state (33). In a different model system, Mazzocca et al. (34) showed that a soluble form of ADAM-9 secreted by hepatic stellate cells promoted colon cancer cell invasion *in vitro*. This activity required both protease activity and binding to  $\alpha 6\beta 4$  and  $\alpha 2\beta 1$  integrins.

**ADAM-12.** ADAM-12 has been implicated in both experimental breast and prostate cancers. In the PyMT mouse model, overexpression of ADAM-12 was found to promote breast cancer progression (35). The effect of ADAM-12 on progression seemed to result from decreased apoptosis in tumor cells and increased apoptosis in stromal cells. In a different mouse model system (i.e., the WT<sup>10</sup> model), a deficiency of ADAM-12 reduced prostate tumor growth and progression (36). In this model, expression of ADAM-12 was located in a subpopulation of stromal cells adjacent to tumor cells.

**ADAM-15.** In 2003, Horiuchi et al. (37) reported that a deficiency of ADAM-15 in a mouse model for retinopathy resulted in reduced neovascularization compared with control animals. Consistent with the finding of decreased neovascularization, smaller tumors were formed in the ADAM-15-deficient mice compared with control mice after injection with melanoma cells (37). More recently, Najj et al. (38) found that down-regulation of ADAM-15 in the prostate cancer cell line PC3 decreased migration and adhesion to specific extracellular

protein matrix proteins, such as fibronectin, vitronectin, and laminin. *In vivo*, loss of ADAM-15 decreased metastasis to bone. Using breast cancer cell lines, the same authors reported that ADAM-15 cleaved cadherin E after growth factor deprivation (39). The shed form of cadherin E bound to and transactivated HER2/HER3, resulting in increased migration and proliferation. Thus, enhanced HER2/HER3 signaling is a potential mechanism by which ADAM-15 could contribute to cancer progression.

**ADAM-17.** It was mentioned above that ADAM-17 mediated the shedding of a number of HER ligands, including TGF- $\alpha$  and amphiregulin. Using a mouse model, Borrell-Page et al. (26) showed that ADAM-17-catalyzed shedding of TGF- $\alpha$  was necessary for tumor formation by Chinese hamster ovary cells. Although the precursor form of TGF- $\alpha$  bound to EGFR, receptor phosphorylation and activation only occurred after ADAM-17-catalyzed shedding of the soluble form.

Using a three-dimensional culture model of human breast cancer progression, Kenny and Bissell (27) reported that either knockdown of ADAM-17 expression with the use of small interfering RNA or inhibition of protease activity with the use of a low-molecular weight inhibitor (TNF- $\alpha$  protease inhibitor-2) reversed the malignant phenotype. Both the small interfering RNA and low-molecular weight inhibitor mediated their effect by preventing release of amphiregulin and TGF- $\alpha$ . In a further study using breast cancer cells, McGowan et al. (40) showed that overexpression of ADAM-17 increased *in vitro* invasion and proliferation whereas down-regulation decreased both these actions.

In renal cancer cells, silencing of ADAM-17 was found to restore a dependence on exogenous growth factors, reduce invasion, and block *in vivo* tumor formation (41). These effects seemed to result from a failure to release TGF- $\alpha$  (41). Finally, ADAM-17 has been shown to increase motility of prostate cancer cells *in vitro* (42). This increased motility resulted from the release of the membrane protein transmembrane protein with EGF and two follistatin motifs (TMEFF2).

### ADAMs in Human Cancers

Studies on human cancers suggest that several ADAMs are overexpressed in cancer vis-à-vis surrounding normal tissue or benign tumors of the same organ (for review, see refs. 3, 43). Furthermore, in cancer, ADAM expression levels frequently correlate with parameters of tumor progression and aggressive disease. Thus, in lung cancer tissue, overexpression of ADAM-28 correlated with the presence of lymph node metastases (44). In breast cancer, ADAM-9 expression was significantly higher in node-positive than node-negative primary cancers whereas the active form of ADAM-17 was increased in high-grade versus low-grade tumors (40, 45). Also in breast cancer, ADAM-17 levels were an independent predictor of patient outcome (i.e., predicted outcome independent of conventional prognostic criteria; ref. 46). In prostate carcinoma, ADAM-9 levels were significantly associated with prostate-specific antigen relapse-free survival (47) whereas ADAM-15 was significantly correlated with Gleason grade (48). The finding of increased ADAM expression in more advanced and aggressive human cancers is consistent with a role for these molecules in cancer progression. The mechanism(s) responsible for the increased expression of ADAMs in human malignancies, however, remains to be investigated.



## ADAMs as Targets for Anticancer Therapies

Because specific ADAMs have been shown to promote cancer initiation and progression (see above), it is reasonable to hypothesize that blocking their actions would slow or prevent progression. In recent years, a number of selective synthetic inhibitors against a small number of ADAMs have been described (49–57). The majority of these use hydroxamate as the zinc-binding group and are designed to interact with the prime site subsites (S1'-S3') of the MMP-like catalytic site (50). Whereas most inhibit MMPs as well as ADAM-17, some are relatively selective for specific ADAMs, especially ADAM-10 and ADAM-17 (49–57).

One of the most widely investigated selective ADAM inhibitors described is INCB3619, an orally active compound that selectively inhibits ADAM-10 and ADAM-17 with half maximal inhibitory concentration (IC<sub>50</sub>) values of 14 and 22 nM/L, respectively (Incyte Corporation; refs. 52, 53). In contrast, the IC<sub>50</sub> for ADAM-8, ADAM-9, and ADAM-33 were 1,000, >5,000, and 1,036 nM/L, respectively. Similarly, little selectivity was found for most of the classical MMPs investigated. Consistent with its ability to inhibit ADAM-10 and ADAM-17 at low levels, INCB3619 blocked the release of TGF- $\alpha$ , HB-EGF, amphiregulin, and heregulin at nanomolar concentrations (53).

Using non-small cell lung cancer cell lines in culture, Zhou et al. (52) reported that INCB3619 increased apoptosis and reduced the apoptotic threshold for paclitaxel. Importantly, in a xenograft model of these cells, INCB3619 decreased tumor growth and enhanced the therapeutic benefit of paclitaxel. In a further study on lung cancer, mice bearing non-small cell lung cancer xenografts were administered gefitinib, INCB3619, or a combination of the two agents. When used singularly, neither gefitinib nor INCB3619 were effective. However, in combination, INCB3619 and gefitinib significantly reduced tumor growth (52). In preclinical models, INCB3619 has also been shown to synergize with cisplatin in reducing the growth of head and neck cancers, and with paclitaxel in inhibiting the growth of breast cancer (53). In contrast to the broad-spectrum MMP inhibitors previously used in clinical trials (58, 59), preliminary findings suggest that administration of INCB3619 is not associated with musculoskeletal side effects (53).

An inhibitor related to INCB3619 [i.e., INCB7839 (Incyte Corporation); ref. 54], when combined with lapatinib, completely prevented growth of human breast cancer xenografts in mice (55). INCB7839 has been evaluated in a phase 1b trial in 30 patients with different types of chemorefractory cancers (56). Overall, the drug was well tolerated with no significant toxicities that might be expected from inhibition of classical

MMP activity (musculoskeletal side effects) or tyrosine kinase inhibition (skin rash). Five patients, however, developed deep-vein thrombosis. Of 20 patients with evaluable disease, 6 experienced stabilization.

Another selective ADAM inhibitor is known as WAY-022 (Wyeth-Aherst; ref. 57). WAY-022, which is a selective inhibitor of ADAM-17, was found to decrease DNA replication and cell growth in colorectal cancer cells (57). Furthermore, the combination of suboptimal concentrations of WAY-022 with an EGFR monoclonal antibody or a selective EGFR kinase inhibitor resulted in cooperative growth inhibition (57).

These preclinical findings suggest that selective ADAM inhibitors might be of value in the treatment of certain cancers. Before proceeding to clinical studies with ADAM inhibitors, however, the following points should be taken into consideration:

- There should be evidence that the ADAM(s) being targeted contribute to either cancer formation or progression.
- It might be an advantage if the inhibitors also target MMPs validated for their role in malignancy (e.g., MMP-1, MMP-2, and MMP-7). On the other hand, they should not inhibit "protective" MMPs, such as MMP-3 or MMP-8 (60).
- Trials should use ADAM inhibitors in combination with chemotherapy and/or anti-HER drugs.
- The target ADAM level in tumor tissue should be measured before treatment to identify patients who are more likely to respond.
- Biomarkers that reflect inhibition of the target ADAM *in vivo* should be identified.

## Conclusion

Based on available data, it seems that the main role of ADAMs possessing proteinase activity is ectodomain shedding of membrane proteins. Several of the ligands released by ADAMs mediate effects that are potentially important in cancer. Consistent with this possibility, specific ADAMs have been implicated in both the formation and progression of malignancy in model systems. Indeed, emerging preclinical data suggest that selective ADAM inhibitors may be novel anticancer agents. Clearly, these preliminary findings require confirmation. If confirmed, ADAM inhibitors may be particularly useful in treating tumors that depend on HER or TNF- $\alpha$ -mediated signaling.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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