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ADAM17: A Gatekeeper in Immune-Oncology?

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Abstract

Recent therapeutics searching to reactivate and target the immune system to destroy tumors have demonstrated remarkable success in the treatment of patients with previously intractable disease such as metastatic melanoma. Current research is enlarging the spectrum of targets and strategies for enhancing the immune response against tumors, in order to further improve treatment efficacy. In that respect, ADAM17, has frequently been described for it's over expression or over activation in the tumor microenvironment. ADAM17 is responsible for the shedding of a large number of receptors and ligands involved in immune tumor targeting and the deregulation of this activity should be considered when developing therapeutic strategies. The aim of this review is to summarize the spectrum of ADAM17 substrates and its potential role in tumor immune modulation.

Keywords

ADAM17, Shedding, Sheddase, Immunotherapy

Introduction

A disintegrin and metalloprotease 17 (ADAM17) a cell surface protease of the metzincin family was discovered in 1997 as the protein responsible for the extracellular cleavage or shedding of TNF-α and was originally named TNF-α converting enzyme (TACE) [1]. A further twenty ADAMs have since been described in humans albeit that only thirteen have functional protease domains [2]. ADAM17 and the closely related ADAM10 have been the most widely studied due to the large range and often overlapping substrate specificities of the two enzymes [2] and in particular due to their association with pathologies including cancer, inflammatory disorders and Alzheimer's disease [3]. The biological activity of the two enzymes differ however, ADAM10 being constitutively active [4,5], whereas ADAM17 is an inducible sheddase [5-8]. The inducible nature of ADAM17 shedding activity corresponds to its role in inflammatory responses [9-12] and wound healing [13,14] responding to various upstream signals including lysophasphatidic acid (LPA) [15], bradykinin [16], lipopolysaccharide (LPS) [17] and through the activation of different protein kinase C sub classes [18,19].

The role of ADAM17 in the release of soluble TNF-α led to considerable interest and numerous clinical trials have been conducted of small molecule inhibitors for the treatment of rheumatoid arthritis [20], however, lack of specificity and toxicity coupled with the development of TNF targeting immunotherapies has slowed further clinical development. The dual specificity small molecule inhibitor of ADAM17/ADAM10, INCB7839, was evaluated in phase II clinical trials for the treatment of Trastuzumab resistant breast cancer [21], and demonstrated reduced shedding of a number of evaluated substrates [22].

ADAM17 is the major inducible sheddase for the ErbB ligands; Amphiregulin [23], TGF-α [24], Epiregulin [25], Epigen [26], HB-EGF [27] and certain members of the Neuregulin family [28], and thus implicates itself in a wide range of developmental and repair pathways. It is indeed the excessive shedding of certain ligands, in particular Amphiregulin [29], HB-EGF [30] and TGF-α [31] that are associated with a wide range of cancer pathologies through the downstream effect upon the ErbB receptors and in particular EGFR. The therapeutic potential for targeting ADAM17 in this context has been considered previously in excellent review articles and thus will not be repeated here [3,32,33]. Beyond the shedding of growth factors and the direct impact on neoplastic growth, ADAM17 is involved in the shedding of a broad range of factors implicated in the activation, recruitment and resolution of innate and adaptive immune responses. The shedding of these different factors is an intrinsic mechanism in the control of the immune and inflammatory response, however, in certain cancers this may be deregulated through the over expression [34-37] or over activation [38] of ADAM17.

The implication of the immune system in tumor surveillance and destruction has been a subject of debate for decades since the original hypothesis of immunosurveillance was proposed by Burnet [39,40] and Thomas [41]. More recently the concepts of T-cell exhaustion [42] and tumor immune evasion [43] have been added to this complex game of cat and mouse. The study of immune modulation has recently yielded new therapeutic options for health care practitioners and patients, through the approval of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) targeted by Ipilimumab [44] and more recently programmed cell death 1 (PD-1) targeted by Nivolumab [45] and Pembrolizumab [46]. These treatments have been approved for the use in the treatment of metastatic melanoma, Nivolumab also being approved for use in squamous non-small cell lung cancer (NSCLC) [47,48]. These targeted therapies represent only the first in a raft of products currently under evaluation that offer great potential to reactivate a suppressed or exhausted immune system. The number of receptors and ligands that mediate the migration, activation and maintenance of inflammatory and immune responses essential to the immune surveillance machinery that have been identified as substrates for ADAM17 is already long and probably incomplete.

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The following sections will expand on the implications of the deregulated shedding by ADAM17 of immune regulatory substrates in the tumor environment.

NK Cell Tumor Targeting

Epithelial tumors have been found to express MHC class I chain–related molecules (MICs) [49] that act as ligands for NKG2D on γδ and CD8+αβ T cells and NK cells and elicit cytolytic targeting of the tumors [50]. The presentation of MICA and MICB results from the stress induced state of the tumor and targets these cells for destruction. Elevated levels of MICA/B have been described in a wide range of solid tumors including breast, lung, ovarian, prostate, renal and colon carcinomas [51]. Further investigation demonstrated that tumors positive for MICA/B expression demonstrated a 60-70% decrease of the NKG2D expression in tumor infiltrating lymphocytes (TILs) and peripheral blood mononuclear cells (PBMCs) and this is believed to contribute to the loss of NKG2D mediated tumor targeting [52]. Tumors positive for MIC expression demonstrated measurable levels of soluble MIC in the serum of patients that is absent in the serum of MIC$^-$tumors. The protein disulfide isomerase ERp5 [53,54] has been shown to modulate the configuration of cell surface MICA/B and renders them susceptible to shedding by ADAM17 and to a lesser extent ADAM10 [50,55]. The extracellular shedding of MICA and MICB is not exclusive to ADAM17 and ADAM10 and indeed their secretion in exosomes has been observed in certain tumor cell lines [55] thus the specific targeting of MICA and or B may provide a more precise therapeutic outcome [56] than inhibiting their shedding. The NKG2D ligands expressed on tumors are not restricted to the MIC as indeed UL16 binding proteins (ULBP) are also presented and shed from tumors. The presentation and shedding of NKG2D ligands be they MIC or ULBPs represents a primary mechanism of lymphocyte tumor targeting, however, shedding is not the only regulatory device controlling this interaction, down regulation of the receptor or the ligand by a myriad of strategies can have the same net effect, these alternative strategies were detailed in a recent review [57].

Recently an additional tumor expressed ligand for NK cell engagement has been described, a member of the B7 family of immune regulatory proteins, B7-H6 [58]. Tumor expressed B7-H6 has been shown to engage with the activating receptor NKp30 on NK cells to enhance anti tumoral cellular. Preclinical evidence suggests that T-cell recruitment through B7-H6 addressed BiTes [59] and NK recruitment via bispecific tumor antigen/B7-H6 fusion proteins [60] demonstrate that the potential of B7-H6 to recruit an anti-tumor immune response is significant. The presentation of B7-H6 at the tumor cell surface is controlled as with MICA/B through extracellular shedding by ADAM17 and ADAM10, siRNA inhibition implicating a greater role for ADAM17 [61]. The detection of elevated levels of soluble B7-H6 in the serum of a subset of melanoma patients [61] suggests that NK cell targeting via B7-H6 can be silenced through the down regulation of NKp30 similar to the effect observed with MICA/B and NKG2D and may further contribute to the attenuation of innate anti tumoral cellular cytotoxicity. The full scope of proteases capable of shedding B7-H6 has yet to be fully explored, however, at present the targeted inhibition of ADAM17 represents a potentially important mechanism to reactivate B7-H6 mediated NK cell tumor targeting.

Fas/FasL and ADAM17

The Fas receptor (Fas, CD95) /Fas ligand (FasL, CD95L) interaction is a key mediator of cellular apoptosis and is essential to the regulation of the adaptive immune response, failures in this system resulting in autoimmune lymphoproliferative syndrome [62]. In the tumor environment compromised Fas signaling renders cells resistant to immune surveillance and induced apoptosis [63], the expression of Fas and FasL by tumor cells being shown to promote tumor growth [64]. The tumor counter attack hypothesis promotes the possibility that the expression of FasL by tumors results in the apoptosis of infiltrating lymphocytes either through cell contact or the release of FasL presenting microvesicles [65]. At present the distribution of FasL on certain tumor types appears ambiguous [66] and its activity when present has been described as either the induction of T-cell apoptosis or the down regulation of the T-cell receptor(TCR) component CD3ε [67]. ADAM10 has been shown to mediate the constitutive shedding of FasL from T lymphocytes [5] potentially maintaining lymphocyte homeostasis, whereas ADAM17 has been shown to be rapidly up regulated upon cellular activation along with recruitment of FasL to the cell surface [68]. The deregulated shedding activity of ADAM17 described in the tumor environment coupled with tumor expressed FasL create the potential for a potent inhibition of T-cell induced apoptosis of tumor cells through competition for Fas binding.

Antibody Dependent Cellular Cytotoxicity Regulation

Perhaps of immediate clinical relevance is the capacity of immunotherapies targeting tumors to illicit antibody dependent cellular cytotoxicity (ADCC) such as is observed with Her2 targeting Trastuzumab and Pertuzumab [69] and the CD20 targeting Rituximab [70]. Antibody bound to its target tumor antigen ligates the FcγRIII and invokes cytokine release and degranulation of NK cells. Two isoforms of FcγRIII exist CD16a and CD16b, the first a trans membrane protein the second attached to the membrane via a glycophosphatidylinositol anchor. CD16a is found predominantly on NK cells [71], whereas CD16b is found exclusively on neutrophils [72]. Extensive research has been performed to enhance antibody CD16a activation of cellular cytotoxicity through modulation of the primary protein sequence of the antibody or modification of the post translational glycosylation [73]. Obinutuzumab a monoclonal antibody targeting CD20 developed by GlycArt/Roche that relies on reduced fucosylation to enhance its ADCC activity was the first approved antibody using enhanced ADCC for the treatment of chronic lymphocytic leukemia [74]. The ligation of CD16a to tumor bound antibody Fc domains results in the release of INFγ and TNFα from NK cells, however it has recently been observed that this is accompanied by a proportional loss of CD16a and the adhesion molecule L-selectin (CD62L) [71]. Inhibiting ADAM17 was shown to reduce CD16a and CD62L shedding from NK cells upon cytokine activation or through Rituximab ligation to Raji cells [75]. The inhibition of ADAM17 also provoked an increase in intracellular INFα and TNFα in the activated NK cells although there was no increase in Raji cell lysis [76].

The potential therapeutic impact of inhibiting ADAM17 in this context remains unclear as no enhanced cell lysis by ADCC was observed, however, the increased levels of TNFα and INFγ may indeed impact the immune surveillance response in a heterogeneous and intact lymphatic system. The murine CD16 orthologue is not shed [75] and thus limits the study of this potential activation at present. The significance of CD62L shedding will be considered in a later section of this review.

Neutrophil Mediated Antibody Targeted Tumor Destruction

The efficacy of therapeutic monoclonal antibodies in the elimination of tumors is largely attributed to their direct effect on the target antigen and the induced elimination by ADCC and Complement Dependent Cytotoxicity (CDC), somewhat less well defined is the implication of Neutrophils in the elimination of tumors. Indeed the observation that elevated neutrophil to lymphocyte ratios in cancer patients is prognostic for shorter overall survival [77] an effect suspected to be mediated via the maintenance of a chronic inflammatory state and the production of angiogenic factors. None the less it has recently been demonstrated that neutrophils alone, at least in the experimental conditions tested, were sufficient to mediate an antibody targeted anti tumoral immune response [78]. The Fcγ receptor CD16b is shed from the cell surface of neutrophils by ADAM17 following cell activation via IgG immune complex or during apoptosis. The cleavage site of CD16a and b have been shown to be conserved and are located in the membrane proximal domain of each protein [75] despite the different membrane attachment mechanisms of

these receptors. Circulating levels of soluble CD16b are high due presumably to the high daily turnover of neutrophils by apoptosis, in the order of 10 [11] cells per day in a healthy adult [72]. The targeted inhibition of ADAM17 and ADAM10 in patients treated with INCB7839 demonstrated an almost two fold decrease in circulating CD16 [72] although the study did not discriminate between CD16a and b. Selective inhibition of ADAM17 and ADAM10 was able to determine that ADAM17 is principally responsible for the shedding of CD16b from neutrophils. As with NK cells, neutrophils shed CD62L via ADAM17 [79], and conditional knock out models demonstrated that the loss of ADAM17 resulted in up to ten times more CD62L on neutrophils, resulting in slow rolling [79] and more rapid infiltration to sites of inflammation [9,79], albeit that overall infiltrating neutrophil levels were lower [9]. Soluble CD62L has been described at relatively high levels in normal serum, the mean value determined as 1.6 µg/ml [80], in vitro experiments demonstrated that this physiological level was already sufficient to reduce leukocyte binding.

Adaptive and Innate Immune Targeting of Tumors

Whereas NK cells have a range of targeting receptors that recognize damaged or infected cells that are subsequently targeted for destruction, the adaptive cellular immune response functions through a separate system of cellular markers and receptors that normally differentiate self from non-self and in the case of tumor immune targeting recognize aberrant cell surface markers including phosphatidylserine or major his to compatibility (MHC) presented tumor specific peptides. The functioning of the T cell response to tumors has been recently reviewed [81] as has the exhaustion of T cells that leads to tumor progression [82] and how current immune checkpoint inhibitors are redressing this [83], and as such will not be discussed here. There are however, a number of additional immune checkpoints that are involved in T cell tumor targeting that are once again targets for shedding.

Activated T cells and NK cells express Lymphocyte-activation gene 3 (LAG-3, CD223), a receptor that binds MHC class II proteins on antigen presenting cells (APCs) [84] and is a negative regulator of activated T cell proliferation and cytokine production. LAG3 has been shown to be constitutively shed from the surface of cells by ADAM10 [84] the absence of constitutive LAG-3 shedding through ADAM10 knock down or the expression of non-cleavable LAG-3 resulting in reduced T cell proliferation or cytokine release [84]. ADAM17 shedding of LAG-3 has been shown to be induced as a result of T cell receptor (TCR) activation via protein kinase θ signalling. T cell activation has been shown to increase 12 fold the level of shedding of LAG-3 [84]. Myeloid derived suppressor cells (MDSC) have recently been shown to up regulate cellular LAG-3 levels in exhausted CD4+ and CD8+ T cells [85], although it was not described in this study if the shedding of LAG-3 was modulated.

The inhibitory immune check point receptor, T-cell immunoglobulin and mucin-domain containing-3 (TIM-3) is expressed on effector and regulatory T cells, tumor associated dendritic cells (TADCs) and macrophages [86,87]. The ligand for TIM-3, the C type lectin galectin-9, itself expressed on tumor cells and MDSCs, induces cell death and exhaustion of CD8+ T cells. TADC expressed TIM-3 has also been shown to bind free high mobility group protein 1 (HMGB1) preventing the transport and presentation of DNA released from dying tumor cells and preventing activation of the innate immune response [87]. TIM-3 has recently been identified as a substrate for ADAM17 and ADAM10 [86] with ADAM10 being demonstrated as the physiologically induced sheddase of TIM-3 in LPS activated CD14+ monocytes. The precise role of TIM-3

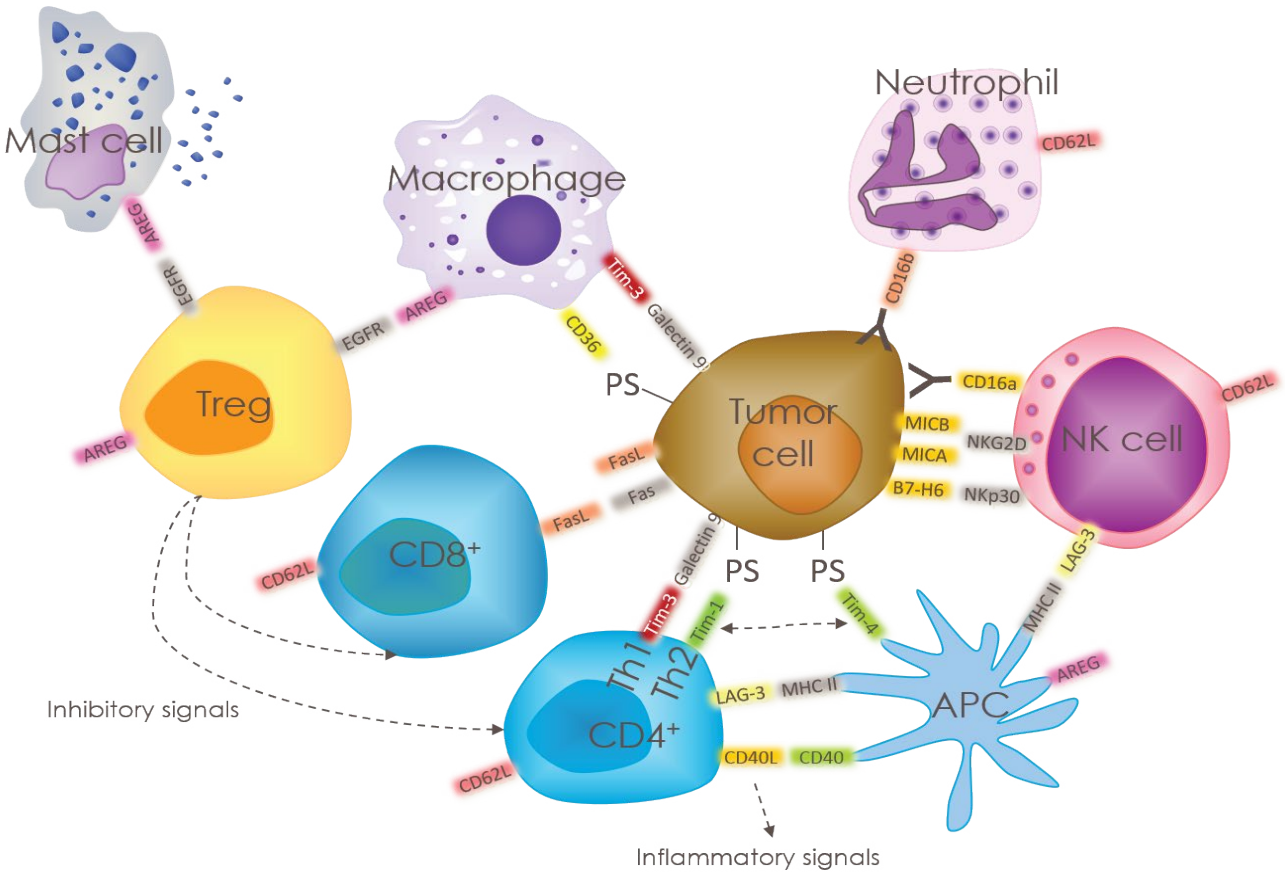

Figure 1: Substrates of ADAM17 in the tumor microenvironment. Substrates of ADAM17 are indicated in colored, molecules not shed by ADAM17 are in grey. CD62L; L-seclectin, CD16b; Fc gamma receptor III B, CD16a; Fc gamma receptor IIIA, MICA/B; MHC class I chain–related molecule A/B, NKG2D; Killer cell lectin-like receptor subfamily K member 1, B7-H6; Natural cytotoxicity triggering receptor 3 ligand 1, NKp30; Natural cytotoxicity triggering receptor 3, LAG-3; Lymphocyte activation gene 3 protein, MHCII; HLA class II histocompatibility antigen, AREG; Amphiregulin, Tim-1/3/4; T-cell immunoglobulin and mucin domain-containing protein 1/3/4, CD40; Tumor necrosis factor receptor superfamily member 5, CD40L; CD40 ligand, Fas; Tumor necrosis factor receptor superfamily member 6, FasL; Tumor necrosis factor ligand superfamily member 6, CD36; Platelet glycoprotein 4.

shedding in the attenuation or activation of an anti tumoral immune response remains to be further qualified as indeed would the impact of inhibiting over active ADAM17 in the tumor microenvironment.

In addition to TIM-3 the remaining human TIMs 1 and 4 have also been described as substrates for ADAM17 [88]. Expression of TIM-1 has been described on a number of immune cell types including activated T cells (preferentially Th2 cells), mast cells, natural killer cells, dendritic cells and B cells, the expression of TIM-4 is restricted to antigen presenting cells [88]. TIM-1 and 4 serve as phosphatidylserine receptors to engulf apoptotic cells, they are also known to interact with each other and regulate T cell proliferation [89]. The shed forms of TIM-1 and 4 are still capable of binding phosphatidylserine and it has been suggested that the presence of soluble receptors may inhibit engulfment and potentially attenuate an anti tumoral response through the non-proliferation of T helper cells and presentation of tumor antigens by dendritic cells.

In addition to TIM-3 macrophages express CD36 a receptor for phosphatidylserine that is necessary for efficient efferocytosis and the resolution of inflammation [90]. ADAM17 has been demonstrated to shed CD36 from macrophages, inhibition of this shedding leading to enhanced efferocytosis. The inflammatory state of the tumor microenvironment is considered a hallmark of tumor development [91] and the inflammatory state is dependent at least in part on ADAM17 mediated shedding of TNFα from macrophages [92]. The elevated shedding of TNFα in parallel to CD36 due to aberrant ADAM17 activation would promote the inflammatory state and prevent the removal of phosphatidylserine presenting cells, the inhibition of this shedding would potential resolve both of these situations.

A final activating receptor ligand pair in the form of CD40/CD40L is also involved in the activation of T cells that would ordinarily participate in the targeting of tumor cells for destruction by the immune system. Upon ligation of CD40L to its receptor CD40 pro inflammatory signals are induced with the concomitant shedding of CD40L by ADAM17 or ADAM10, the precise nature of the sheddase involved being cell type dependant [93]. The shedding of CD40 by ADAM17 has also been described in hemodialysis patients [94] and thus creates perhaps the only ligand receptor pairing for which ADAM17 regulates the shedding of both receptor and ligand. Soluble CD40L is capable of binding CD40, however, with greatly attenuated capacity to activate and thus this shedding event potentially attenuates normal T cell activation to prevent over activation. The heightened activity of ADAM17 in the tumor microenvironment may, through elevated CD40L shedding, prevent the successful activation of CD40. The development of CD40 agonists may serve to compensate this deficit although consideration should be given to the shedding of CD40 itself and its potential impact upon this therapeutic approach (Figure 1).

T Regulatory Cells

Although no receptor or ligand pairs have currently been identified that influence the proliferation or activation of regulatory T (Treg) cells to inhibit the antitumoral immune response, a more classical proliferative mechanism that is itself dependent upon ADAM17 has been described. Tregs infiltrate and proliferate in to the tumor microenvironment and participate in the attenuation of the anti tumoral immune response. Tregs express the epidermal growth factor receptor (EGFR) and it has been shown that Amphiregulin (AREG)can induce proliferation and activation of the T-cell suppressive functions [95] of Tregs. AREGis produced by multiple tumor types [29,96], but also immune cells including mast cells [95], macrophages [97], dendritic cells [98] and Tregs themselves [99], ADAM17 being responsible for the shedding of the functional serum form. Targeting the EGFR receptor has demonstrated therapeutic efficacy, the possibilityof targeting the ligands of EGFR including AREG have also been explored as therapeutic targets [100-103]. The inhibition of AREG shedding may in particular offer the additional advantage of reducing Treg activity.

Conclusion

A wide range of immunotherapies are currently being developed to enhance the capacity of the immune system to through the activation of receptors such as CD40 or the inhibition of others such as TIM-3. A second family seeks to enhance the formation of immunological synapses between immune and tumor cells through the engagement of tumor antigens and immune receptors such as NKG2D. It is worthy of note that the natural regulation of a wide range of these systems for immune tumor targeting and activation are under the control of a small number of regulatory sheddases. The sheddase is itself, in particular ADAM17, a potential source of deregulation in the tumor environment and adds an additional level of complexity to the manipulation of these natural systems. When one considers the natural role of ADAM17 is restricted to the wound healing response and the resolution of inflammation it's therapeutic targeting when over activated in the tumor environment either alone or in combination with other immune modulating therapies merit investigation.

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