A Disintegrin and Metalloproteinase—Control Elements in Infectious Diseases

Ahmad Aljohmani and Daniela Yildiz*

Institute of Experimental and Clinical Pharmacology and Toxicology, PZMS, ZHMB, Saarland University, Homburg, Germany

Despite recent advances in treatment strategies, infectious diseases are still under the leading causes of death worldwide. Although the activation of the inflammatory cascade is one prerequisite of defense, persistent and exuberant immune response, however, may lead to chronicity of inflammation predisposing to a temporal or permanent tissue damage not only of the site of infection but also among different body organs. The initial response to invading pathogens is mediated by the recognition through various pattern-recognition receptors along with cellular engulfment resulting in a coordinated release of soluble effector molecules and cytokines aiming to terminate the external stimuli. Members of the 'a disintegrin and metalloproteinase' (ADAM) family have the capability to proteolytically cleave transmembrane molecules close to the plasma membrane, a process called ectodomain shedding. In fact, in infectious diseases dysregulation of numerous ADAM substrates such as junction molecules (e.g., E-cadherin, VE-cadherin, JAM-A), adhesion molecules (e.g., ICAM-1, VCAM-1, L-selectin), and chemokines and cytokines (e.g., CXCL16, TNF-α) has been observed. The alpha-cleavage by ADAM proteases represents a rate limiting step for downstream regulated intramembrane proteolysis (RIPing) of several substrates, which influence cellular differentiation, cell signaling pathways and immune modulation. Both the substrates mentioned above and RIPing crucially contribute to a systematic damage in cardiovascular, endocrine, and/or gastrointestinal systems. This review will summarize the current knowledge of ADAM function and the subsequent RIPing in infectious diseases (e.g., pathogen recognition and clearance) and discuss the potential long-term effect on pathophysiological changes such as cardiovascular diseases.

Keywords: metalloproteinase, infection, regulated intramembrane proteolysis, SARS – CoV, cardiovascular

INTRODUCTION

Inflammation is a defensive process by which the immune system responds to an external or internal stimulus aiming to remove the injurious insult and initiate the healing process (1, 2). One major inflammatory insult is infection caused by viruses, prions, bacteria, fungi, and parasites. Besides the infectious particles themselves, their released toxins may cause severe disease (3).

The response to invading pathogens follows a well-defined cascade. The initial recognition of the pathogen occurs through germline-encoded pattern-recognition receptors (PRRs) such as the Toll-like receptors (TLRs), C-type lectin receptors, NOD-like receptors, retinoic acid-inducible gene I (RIG)-like receptors, cyclic GMP-AMP synthase and stimulator of interferon
genes (cGAS_STING), and scavenger receptors which are not only expressed by immune cells but also non-immune/tissue cells such as endothelial and epithelial cells (4–6). The pathogens themselves provide pathogen-associated molecular pattern (PAMP) such as lipopolysaccharide, lipoteichoic acid, and flagellin as bacterial component as well as nucleic acids mostly associated with viral infection. Activation of the PRRs by PAMPs and the cellular uptake of the pathogens result in the release of danger molecules and cytokines such as interleukin-1β (IL-1β), IL-6, IL-18, and tumor necrosis factor-α (TNF-α) orchestrating the immune response and defense. Chemoattraction and activation of neutrophils, T cells, monocytes and dendritic cells promote antigen presentation, pathogen phagocytosis and immune modification (7, 8) allowing for pathogen clearance, resolution of inflammation, and initiation of tissue homeostasis restoration. However, uncontrolled inflammation and insufficient clearance may lead to chronic inflammation and permanent tissues damage in the worst case leading to organ failure and sepsis (9).

ADAMs belong to the class of metalloproteinases and consist of 34 members, in which 22 are well-described in human (10, 11). ADAMs are transmembrane molecules consisting of an N-terminal metalloproteinase pro-domain, followed by a disintegrin domain, an epidermal growth factor (EGF)-like domain, a cysteine-rich domain, a transmembrane domain and a cytoplasmic domain (12). As the EGF-like domain is missing in ADAM10 and ADAM17, the membrane-proximal domain is often referred to as stalk region (12, 13). Twelve of the human ADAM members (ADAM8, 9, 10, 12, 15, 17, 19, 20, 21, 28, 30, and 33) are proteolytically active upon removal of the pro-domain that blocks the zinc atom (14). The proteolytic cleavage of transmembrane substrates close to the cell surface is referred to as ectodomain shedding and results in the release of the soluble ectodomains. These ectodomains may act as agonists (e.g., TNF-α and EGF), driving the inflammatory surrogate, or antagonists (e.g., TNFR and IL-1R), decreasing the inflammatory responsiveness and driving the resolution of inflammation (for review see (15, 16)). The transmembrane and the cytoplasmic domain remain as cell-associated fragment and can be further processed by regulated intramembrane proteolysis (RIPing) through, e.g., γ-secretases (17), as a downstream event. The resulting C-terminal intracellular domains (ICDs) fulfill divergent functions, e.g., acting as endogenous inhibitor (e.g., syndecans (18)) or transcription factor (e.g., Notch (19)).

Regulation of ADAMs occurs on the posttranslational rather than transcriptional level. Posttranslational regulation includes the cleavage of the inhibiting pro-domain by furin (e.g., ADAM9, 10, and 17) and autocatalytic activation (e.g., ADAM8), the change in cellular distribution, the release from intracellular stores, interaction with partners for cellular trafficking and signaling as well as conformational changes (15). Dysregulation of the proteolytic activity of ADAMs is a core factor in a number of pathologies such as cardiovascular disease, asthma, cancer, inflammation, and neurodegenerative disease (20–24). Although the general function of ADAMs in inflammatory diseases is well-described, their specific contribution in infectious diseases, especially in vivo (Table 2) is only partly understood. This review will summarize the current knowledge of ADAMs’ function in infectious diseases addressing pathogen recognition and entrance, toxin handling, phagocytosis and clearance, cytokine release, leukocyte recruitment, resolution of inflammation and repair/regeneration, as well as local and systemic changes (Table 1). The RIPing may influence further signaling pathways leading to immune modulation. Both ADAM function and the subsequent RIPing may lead to long-term effects on pathophysiological changes causing, e.g., cardiovascular diseases.

**ADAM10**

**Pathogen recognition: Pathogen recognition is the first step of infection sensing. Cleavage of PRRs may cause [1] signaling initiation, [2] limitation of receptor-pathogen interaction, or [3] release of soluble scavenger receptor with opsonizing or antagonistic function. In the case of CD163, a scavenger receptor for both Gram-positive and Gram-negative bacteria (83), *Staphylococcus aureus* (*S. aureus*) leads to ADAM10-dependent release of soluble CD163, which binds to fibronectin on the bacterial surface resulting in further opsonization and higher clearance by phagocytes (41). Under certain conditions such as 1,25-dihydroxyvitamin D3 treatment, ADAM10 is able to shed TLR4 thereby limiting the inflammatory response to LPS (29). The third PRR is the receptor for advanced glycation end products (RAGE). Together with its secreted isoform (esRAGE), ADAM10-cleaved RAGE (cRAGE) builds the soluble fraction (sRAGE) (84), which has been shown to exert a detrimental action in *Pseudomonas aeruginosa* (*P. aeruginosa*) infection (56). However, a subsequent decrease of mature ADAM10 indicates a strict regulation and a time-dependent action of ADAM10 during *P. aeruginosa* infection (85). Besides its action in bacterial entry, ADAM10 might also be involved in viral recognition. T cell immunoglobulin and mucin domain (TIM)-1 and 4 are shed by ADAM10 (30), of which TIM-1 was shown to act as the receptor for the Zaire Ebola virus (31).

**Pathogen entrance/phagocytosis and toxin handling:** ADAM10 may not only influence the initial pathogen interaction via cleavage of PRRs but also through its action as receptor itself. ADAM10 functions as a receptor for the *S. aureus* α-hemolysin (Hla) resulting in toxicity even at a low concentration (40). It was further shown that the intracellular domain of ADAM10 facilitates nuclear entry and replication of HIV-1 (86). CXCR6, the receptor for CXCL16 was previously identified as the HIV-1 coreceptor Bonzo (87). CXCL16, which is cleaved by ADAM10, exists as transmembrane form, mediating bacterial adhesion and phagocytosis, and soluble ectodomain with chemotactic function (27, 28, 88).

**Cell recruitment and polarization:** ADAM10 is not only essential for the general recruitment of inflammatory cells (49), but also for the development of specific T cell responses. One crucial substrate of ADAM10, indicated by the lethality of ADAM10 knockout mice (81), is Notch which has divergent immune modulatory functions in infection. Upon infection with *Listeria monocytogenes* (*L. monocytogenes*), Notch downstream signaling results in pro-inflammatory polarization of macrophages to the classical M1 subtype (44). However,
| Step                                      | Protease | Substrate                  | Effect of shedding or non-proteolytical event                                                                 | References |
|------------------------------------------|----------|----------------------------|-------------------------------------------------------------------------------------------------------------|------------|
| Pattern recognition and entrance         | ADAM9    | EMCV entry receptor        |                                                                                                             | (25, 26)  |
|                                          | ADAM10   | CXCL16                     | Membrane bound scavenger receptor vs. soluble chemoattractant                                              | (27, 28)  |
|                                          |          |                            | TLR4 Reduced LPS responsiveness                                                                         | (29)       |
|                                          |          |                            | HIV nuclear entry and replication by ICD interaction                                                      | (30)       |
|                                          | ADAM17   | TIM-1                      | Change in Zaire Ebolavirus recognition                                                                    | (31)       |
|                                          |          | TNF-α                      | Enhanced bacterial uptake                                                                                   | (32)       |
|                                          |          | Gp96                       | Protection against C. trachomatis reinfecion                                                               | (33)       |
|                                          |          | TNFR-1                     | Enhanced infection with C. trachomatis                                                                      | (34)       |
|                                          |          |                            | HPV entry through ERK1/2 activation                                                                      | (35)       |
|                                          |          |                            | Persistent HCV infection                                                                                    | (36)       |
|                                          |          |                            | Escape of immune recognition by CMV                                                                       | (37)       |
|                                          |          |                            | Reduced entrance of SARS-CoV2                                                                             | (38)       |
|                                          |          |                            | Change in HIV-1 attachment                                                                                 | (39)       |
| Toxin handling                           | ADAM10   | CD163                      | Receptor for S. aureus α-hemolysin (Hla)                                                                  | (40)       |
| Phagocytosis                              | ADAM10   | CD163                      | Opsonization and enhanced phagocytosis                                                                    | (41)       |
|                                          | ADAM17   | TNF-α                      | Change in phagocytic capacity                                                                            | (32)       |
|                                          |          | L-selectin                 | Enhanced clearance of K. pneumoniae in neutrophils                                                        | (42)       |
|                                          |          | CD163                      | Enhanced phagocytosis of S. aureus                                                                        | (41, 43)  |
| Mediator release and cell polarization    | ADAM10   | Notch                      | M1 macrophage and T H2 polarization                                                                       | (43)       |
|                                          | ADAM17   | IL-6R                      | Trans-signaling and CCL-2 release                                                                         | (39)       |
|                                          |          | EGFR ligands               | IL-1 secretion by epithelial cells                                                                        | (40)       |
|                                          |          | TNF-α                      | Inflammatory cytokine release                                                                             | (41)       |
|                                          |          |                            | Enhanced inflammatory cell recruitment by integrin signaling                                              | (42)       |
| Cell recruitment                         | ADAM10   | L-selectin                 | Time-dependent leukocyte recruitment and improved survival in bacterial infection; clonal expansion of cytotoxic T cells in virus infection | (49)       |
|                                          | ADAM17   |                            |                                                                                                             |            |
| Tissue damage, resolution of inflammation and systemic changes | ADAM9    | CD46                       | Non-apoptotic cell death upon HIV infection                                                                | (53)       |
|                                          | ADAM10   | TIM-1/4                    | Restriction of complement activation                                                                     | (54)       |
|                                          |          | FasL                        | Apoptotic cell clearance                                                                                  | (33)       |
|                                          |          | RAGE                       | Reduced killing capacity of T cells                                                                        | (55)       |
|                                          |          | HB-EGF                     | Enhanced pathogenesis upon P. aeruginosa infection                                                         | (56)       |
|                                          |          | BTC                        | Mucin overproduction and obstruction                                                                       | (57)       |
|                                          |          | E-cadherin                  | Cell apoptosis upon EPEC infection                                                                       | (58)       |
|                                          |          | VE-cadherin                 | Disruption of epithelial integrity, metastasis                                                           | (59)       |
|                                          |          |                            | Disruption of endothelial integrity                                                                       | (60)       |
|                                          | ADAM17   | TNF-α                      | Endotoxic shock, T cell lethality, increase of MMP expression                                             | (61–64)    |
|                                          |          | L-selectin                 | HIV release from central memory CD4 T cells                                                                | (65)       |
|                                          |          | IL-6R                      | Systemic response and increase in lethality                                                                | (66)       |
|                                          |          | HB-EGF                     | Ulcus formation upon infection with H. pylori                                                             | (67)       |
|                                          |          | TNFR/II                    | Reduced inflammatory burden                                                                               | (68)       |
|                                          |          | TNFR/II                    | CMV persistence                                                                                           | (68)       |
|                                          |          | ICAM                       | Leukocyte recruitment and endothelial damage                                                               | (69)       |
|                                          |          | VCAM                       | Leukocyte recruitment and endothelial damage                                                               | (69)       |
|                                          |          | syndecan-1                 | Leukocyte recruitment and endothelial damage                                                               | (69)       |
|                                          |          | ACE2                       | Arterial fibrillation and heart failure in SARS-Cov2 infection                                             | (71, 72)   |

ADAM proteases shed many general mediators of inflammation like TNFα, IL-1R, and IL-6R and repair/regeneration like growth factors [for review see (15)]. This table only summarizes (non)proteolytical functions, which have been mechanistically studied in infectious diseases with a direct link to ADAM proteases, e.g., genetic knockout or pharmacological inhibition.
TABLE 2 | Infectious diseases in ADAM knockout animals.

| Transgene          | Approaches            | Pathogens                                    | Observation                                                                                                                 | References |
|--------------------|-----------------------|----------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|------------|
| Tamoxifen-inducible Adam10-/- | Staphylococcus aureus skin infection | Decrease in abscess size and protection against dermonecrotic lesions (73, 74)                                                | (73, 74)  |
| Adam17fl/flx       | Listeria monocytogenes infection | Diminished IL-6 receptor (IL-6R) trans-signaling in leukocyte subsets (64)                                                   | (64)      |
| Epithelial         | SPC-rTA/TetO-Cre/Adam10 flox/flx | Staphylococcus aureus-Hla induced pneumonia | Reduction of epithelial gap formation and lethal pneumonia (60)                                                               | (60)      |
| Leukocytes         | CD4-Adam10-/-          | Listeria monocytogenes infection             | No contribution to IL-6R trans-signaling (64)                                                                                | (64)      |
|                    | LysM-Adam10-/-         | Polymicrobial sepsis                         | Improved survival rate, reduced bacterial spread and pro-inflammatory cytokine secretion (75, 76) | (75, 76)  |
|                    | Adam17 flox/flx/Nav1-Cre | E. coli induced peritonitis                  | Improved survival rate, decreased bacterial load and neutrophil recruitment (50, 77)                                        | (50, 77)  |
|                    | Adam17fl/flx/CD4-Cre   | Listeria monocytogenes infection             | No influence on T cell response (78)                                                                                         | (78)      |
|                    | Adam17-/- in CD8 T cells | Influenza A (H1A) infection                 | Reduced macrophage and neutrophil infiltration and decreased lethality (79, 80)                                               | (79, 80)  |
|                    | F5-Tg TCRVLPD8+CD8+ T cells (LΔP: shedding resistant L-selectin) | Vaccinia virus infection | Lack of rapid clonal expansion of cytotoxic T cells (52) | (52)      |
|                    | Adam10 DC-/-           | Alternaria alternate (allergic asthma)       | Reduced eosinophils recruitment, serum IgG1 and IgE (45)                                                                      | (45)      |

Mentioned are studies in which the animals were exposed to the pathogen itself and not only a specific PAMP like LPS. Notably, knockout of ADAM10 and ADAM17 results in pre-/perinatal lethality or death shortly after birth (81, 82).

in allergic asthma induced by Alternaria alternata challenge, the T helper cell type 2 response was reduced upon Notch deficiency (45). Notch cleavage may also regulate invasiveness and epithelial to mesenchymal transition in epithelial cells infected with Epstein Barr virus (89). Tissue damage, resolution of inflammation, and systemic changes: There exist several evidences that ADAM10 does not only act in the initial phase of infection but is also involved in the development of tissue damage, the resolution of inflammation or development of systemic effects. E-cadherin and vascular endothelial (VE)-cadherin are junction molecules shed by ADAM10 in epithelial and endothelial cells, respectively (90, 91). Several pathogens, including P. aeruginosa, S. aureus and Helicobacter pylori (H. pylori) have been shown to induce cadherin shedding, thereby disrupting endothelial and epithelial barrier integrity leading to sepsis formation and persisting skin infection (59, 60, 73, 74, 92). Besides the mentioned molecules, shedding of growth factors such as heparin-binding EGF-like growth factor (HB-EGF) in epithelial cells may also contribute to persistent infection, e.g., through induction of mucin overproduction and obstruction (57). EGF receptor (EGFR) transactivation was further shown to induce epithelial cell apoptosis upon exposure to enteropathogenic E. coli (EPEC) (58). One essential step in the defense process and resolution of the concurrent infection is the removal of these apoptotic cells. Soluble TIM-1 and TIM-4 bind to phosphatidylserines on the surface of apoptotic cells, which could either prevent their engulfment or mediate phagocytosis by TIM-protein interaction (30). Furthermore, ADAM10 mediated shedding of Fas ligand (FasL) may reduce the killing capacity of T cells and their subsequent apoptosis, which could result in chronic inflammation (55). Additionally, ADAM10 sheds CD46 from apoptotic epithelial cells, which may reflect a strategy for restricted complement activation (54). As obvious, ADAM10 functions during different phases of infection (Tables 1, 2) and has to be tightly regulated via disease-specific mechanisms, which have to be taken into account when thinking about ADAM10 based treatment strategies.

ADAM17

In addition to ADAM10, ADAM17 which is also known as tumor necrosis factor-α converting enzyme (TACE) (48) may play a divergent role during the different phases of bacterial, viral, and fungal infection. Pathogen recognition, entrance and phagocytosis: ADAM17 may influence the initial recognition and uptake of invading of pathogens by the cleavage of PRRs such as scavenger receptors and TLR2 and TLR4 (93, 94). However, it was recently shown that the limitation of bacterial uptake by ADAM17 in monocytes occurs in a cell-autonomous manner in parts dependent on TNF-α without significant changes in the surface expression of these receptors (32). Nevertheless, release of soluble CD163 from monocytes contributed to the recognition and phagocytosis of S. aureus (41, 43). In neutrophils, however, efficient bacterial clearance was dependent on ADAM17 activation and subsequent L-selectin shedding (42). Further, ADAM17 mediated shedding of the Chlamydia trachomatis receptor glucose regulated protein 96 (Gp96) protected against re-infection (33), whereas reduction of TNFRII expression on the cell surface facilitated the infection (34). With respect to viral infection ADAM17 facilitated the entry of the human papillomaviruses (HPV) (35), and led to downregulation of CD16
on natural killer (NK) cells during chronic hepatitis C virus (HCV) infection resulting in a lack of infection eradication (36). Furthermore, L-selectin was shown to support the preferential infection of central memory CD4+ T cells, with L-selectin shedding by ADAM17 being required for viral release (65).

**Cell recruitment and mediator release:** ADAM17 sheds several junction and adhesion molecules like VCAM-1, ICAM-1 and JAM-A, which was shown to influence leukocyte recruitment and endothelial damage in both viral and sterile infection (69, 95, 96). Deficiency of ADAM17 in leukocytes resulted in enhanced recruitment of neutrophils to the site of infection, decreased bacterial load, and improved survival in both polymicrobial sepsis and peritonitis (50, 75, 77). Further investigations in models of sterile infection revealed a time-dependent effect of ADAM17 in neutrophil recruitment, which is dependent on L-selectin shedding at early time points (49–51). One essential step in the orchestration of the inflammatory response is the release of soluble mediators such as cytokines and growth factors. Stimulation of human airway epithelial cells with heat inactivated *S. aureus* and *P. aeruginosa* led to upregulation of ADAM17 surface expression and colocalization with IL-6R, initiating receptor trans-signaling and subsequent CCL-2 release (46). Similarly, ADAM17-mediated transactivation of EGFR was required for the upregulation of IL-1 in primary keratinocytes infected with *S. aureus* (47). The analysis of BAL samples from patients with community-acquired pneumonia showed that ADAM17 is involved in both the release of pro-inflammatory cytokines like TNF-α and IL-1β as well as their neutralizing soluble receptors (97). Furthermore, release of TNF-α by CD8+ T cells was essential for CXCL2 release and leukocyte recruitment upon influenza A infection (79). Additionally, L-selectin shedding promoted early clonal expansion of CD8+ T cell derived cytotoxic T cells in vaccinia virus infection (52).

**Tissue damage, resolution of inflammation, and systemic changes:** Released mediators and their receptors do not only orchestrate the local immune response but are responsible for the systemic immune response resulting in either resolution of inflammation or in chronicity and damage of other organs. TNF-α shedding has been shown to be crucial for tissue damage and lethality in endotoxin shock, *S. pneumoniae* (serotype 3) caused meningitis, and *L. monocytogenes* infection, the latter one being further accompanied by IL-6R trans-signaling (61–64, 98). TNF-α is central during HIV infection and AIDS pathogenesis, in which a complex regulatory mechanism was observed. Nef induces both endocytosis of ADAM17, resulting in intracellular TNF-α cleavage, and ADAM17 release on extracellular vesicles, leading to release of TNF-α upon ingestion by PBMC, thereby decreasing the number of circulating CD4 lymphocytes (99, 100). Thus, the amount of circulating TNF-α has to be tightly regulated, e.g., through its soluble receptors TNFRI and TNFRII, which are shed by ADAM17 (67). On the one hand, enhanced shedding of TNFRs may reduce the inflammatory burden (80); on the other hand it may lead to reduced defense and persistent infection (68). A similar divergent function may apply for growth factor shedding. On the one hand, HB-EGF–mediated EGFR activation was shown to contribute to gastrointestinal ulcers and cancer formation upon *H. pylori* (66, 101, 102). On the other hand, TGF-α was required for β-defensins-3 (hBD-3) up-regulation upon *Candida albicans* infection (103).

**Escape mechanisms:** ADAM17 does not only orchestrate the immune response but is also used by pathogens to escape the defense mechanisms. CMV promotes the shedding of MICA, an NK group 2D (NGK2D) receptor ligand, mimicking the tumor strategy in modulating immune recognition by NK cells and cytotoxic T cells (37). Furthermore, ADAM17 proteolytically cleaves the Ebola virus (EBOV) surface glycoprotein GP, which is known to block the antibodies responsible for virus neutralization (104). Thinking about treatment options, e.g., for polymicrobial sepsis (105), ADAM17 might be a suitable target in infectious diseases. However, due to its divergent functions (Tables 1, 2), as further addressed in the COVID-19 section, a substrate-specific, time-specific and site-specific therapeutic intervention has to be considered to achieve the best beneficial effect and reduction of severe side-effects.

**ADAM8**

ADAM10 and ADAM17 as ubiquitously expressed proteases seem to play a central function in infectious diseases. Only a few studies have addressed the role of ADAM8. ADAM8 is less abundantly expressed with highest expression in leukocytes and carcinoma cells and seems to be dispensable for normal development and homeostasis (106, 107). In sterile inflammation caused by *E. coli* LPS, mainly leukocytic ADAM8 contributed to leukocyte recruitment in the acute phase of lung inflammation (108). ADAM8 protein expression was found to be upregulated during the formation of multinuclear giant cells by human salivary gland cells upon infection with human parainfluenza virus type 2 (HPIV2) (109). Further, macrophages of HIV-1 positive patients showed an upregulation of ADAM8 gene expression. In patients with periodontal diseases, which are mainly induced by bacteria and characterized by uncontrolled inflammation, a high protein expression ADAM8 was found in the gingival crevicular fluid, highly correlating with disease severity and destruction of the periodontal tissues (110). After non-surgical periodontal therapy, ADAM8 levels decreased and correlated with improvements in clinical parameters (111). Not only viral and bacterial infection may be influenced by ADAM8, but also infection by fungi. Transcriptional profiling of heart tissues mice infected with *Candida albicans* revealed an upregulation of ADAM8 gene expression, which was linked to cardiomyopathy and extracellular matrix remodeling (112). Thus, it seems feasible that ADAM8 plays a more important role in disease progression and chronicity vs. resolution of inflammation rather than in pathogen recognition and toxin handling.

**ADAM9**

ADAM9 expression was clearly shown in the brain, the lung, the developing heart, and the retina as well as several cell types such as fibroblasts, neutrophils, and platelets (15). Although ADAM9 is less abundantly expressed than ADAM10 and
ADAM17, it is involved in several steps of inflammation, including cytokine release, neutrophil activation, endothelial transmigration, and growth factor signaling (15, 113–115). Enhanced mRNA expression in the blood, which was mostly restricted to monocytes and neutrophils, has been found in patients with influenza caused pneumonia, respiratory syncytial virus (RSV) infection, active tuberculosis, and several other bacterial infections, whereas stimulation with PAMPS only marginally increased ADAM9 transcript abundance compared to healthy volunteers [for review see Rinchai et al. (116)]. Further, ADAM9 mRNA expression increased in cystic fibrosis patients during acute exacerbation, with its decline being an independent predictor of the antibiotic treatment response (117).

Mechanistic studies in infection highlight the relevance of ADAM9 during viral infection from pathogen entrance to systemic changes. ADAM9 was shown to be an important and specific factor for encephalomyocarditis virus (EMCV) entry, which was inhibited upon ADAM9 knockout in myeloid leukemia derived cells and HEK293T cells (25, 26). Interestingly, pharmacological inhibition of ADAM9 did not show any effect, suggesting a non-proteolytical function of ADAM9 as EMCV receptor (25). Furthermore, ADAM9 mRNA was highly expressed in central memory CD4 T cells during chronic HIV infection, which associated with movement to cell cycle phases G1 and S leading to non-apoptotic cell death (53). ADAM9 knockout protected against remodeling processes like elastin degradation and subsequent reduction in lung compliance in LPS-induced ALI (118). Thus, it seems feasible that ADAM9 is not only involved in the acute phase of infection but also in the decision between resolution of inflammation, chronicity, and systemic changes. Further evidences for systemic changes upon upregulation of ADAM9 are given by enhanced development of metastases during hepatitis B virus-related hepatocellular carcinoma (119).

CATALYTIC INFLUENCE OF OTHER ADAM PROTEASES ON INFECTIOUS DISEASES

Although 22 ADAM proteases have been reported in humans, only 12 display catalytic activity based on the presence of the zinc-dependent metalloproteinase domain (14). ADAM10 and ADAM17 together with ADAM8 and ADAM9 seem to be the most relevant ADAM proteases in infection; however, some studies point toward an additional influence of ADAM12, ADAM15, and ADAM33. Two ADAM12 genetic mutations (rs11244787 and rs1871054) led to an increased risk to transfer Trypanosoma cruzi, a parasitic euglenoids, from the mother to the newborn (120). Single nucleotide polymorphism (SNP) analysis revealed that an ADAM33 SNP was associated with a higher risk to develop severe RSV bronchiolitis with airway remodeling in premature infants (121, 122). In addition, children with acute infectious pneumonia of viral etiology showed an increased protein expression of ADAM28 and ADAM33 in the lung, which was correlated with the severity of infection and is likely to be involved in the chronicity and fibrosis development (123). So far, the contribution of ADAM15 has been only investigated in models of sterile infection. In both, LPS-induced ALI and sepsis ADAM15 deficiency protected against vascular endothelial barrier dysfunction, resulting in reduced neutrophil transmigration (124, 125). Further, in vitro studies revealed a more complex action of ADAM15 in inflammation and infection. Whereas, negative regulation of ADAM15 mediated by microRNA-147b significantly improved endothelial barrier dysfunction (126), ADAM15 dampened the TLR3 and TLR4 stimulated pro-inflammatory cytokine production (127). Thus, further studies are required to specify the stimulus- and cell-type specific contribution of single ADAM proteases in infectious diseases.

RIPing IN INFECTIOUS DISEASES

Not only the released ectodomains but also the remaining transmembrane and intracellular fragments may regulate the infectious response. Intramembrane cleaving proteases, such as the γ-secretase presenilin 1 (PSEN1), liberate the ICD which might act as antagonist [e.g., syndecan-1 and 4 (18)] or translocate to the nucleus acting as transcription factor [e.g., Notch (128, 129)]. Prerequisite to γ-secretase action is the previous cleavage by α-secretases (e.g., ADAM9, ADAM10, and ADAM17 (130)) or β-secretases [e.g., BACE (131)]. The function of the Notch ICD (NICD) as transcriptional regulator is widely accepted (132). The NICD translocates to the nucleus, where it binds to the DNA-binding protein RBP-J with subsequent recruitment of superenhancers initiating transcription of Notch downstream targets like Hes5 (133). This does not only regulate transcriptional activity but may also regulate on the level of translation. It was shown that Notch1-RBP-J signaling is required for the activity of the MNK1/eIF4E axis, which controls the rapid induction of IRF8 upon TLR4 stimulation on the protein level. Thereby, Notch1 controls the IRF8 dependent expression of M1 macrophage-associated genes like Il12a and Nos2 (44). Syndecan-1 and 4 are subjected to constitutive and inflammation-induced shedding by ADAM17 (134). However, it seems that syndecan-1 plays a more prominent role in infectious diseases, which is already obvious from the huge variety of interaction partners including matrix proteins, proteases, cytokines, and growth factors [for review see (135)]. P. aeruginosa, S. aureus and S. pneumoniae were shown to induce syndecan-1 shedding correlating with susceptibility and systemic spread (70, 136, 137), and syndecan-1 serves as attachment receptor for HIV-1 (39). It has been reported that the SICD might acts inhibitory during tumor cell migration and that it might be essential for exosomal release (18, 135); however, a specific function in infectious disease has not been reported so far. Similarly, it is obvious from the mentioned studies that E-cadherin plays in important role in acute and chronic infectious diseases and has been recently reviewed (138). The EICD is associated with beta-catenin and α-catenin and thereby linked to the cytoskeleton. The disassembly of this complex upon ectodomain shedding and RIPing releases β-catenin, thereby orchestrating the canonical Wnt signaling pathways as integral component of the host.
response to infection (139, 140). However, it is important to note that E-cadherin is cleaved not only by ADAM10 and other metalloproteinase but also by bacterial proteases themselves. If these remaining transmembrane fragments are subjected to RIPing is still under investigation (138). Furthermore, the E-cadherin c-terminal fragment 2, produced by PSEN1, was shown to increase the degradation of transmembrane amyloid precursor protein (APP) derivatives, preventing the formation of the AICD and promoting the non-amyloidogenic degradation (141). Many in vitro and in vivo evidences including the analysis of patients’ samples point toward a contribution of infection to the late-onset of Alzheimer disease. A strong association was shown for infection with Chlamydia pneumoniae (C. pneumoniae) [for review see (142)]. Infection of astrocytes with this intracellular pathogen showed an increase of BACE and PSEN1 expression, whereas the activity of ADAM10 was reduced, resulting in enhanced production of beta-amyloid (143). However, the overall mechanisms how infection contributes to late-onset of Alzheimer disease is still not clear. Apart from its sheddase activity, RIPing of ADAM10 itself has been reported. In macrophages infected with HIV-1, ADAM10, cleavage by ADAM15 resulted in the release of the intracellular domain by RIPing, mediating the above described support of viral translocation (86, 144). Besides γ-secretase, which belongs to the aspartyl intramembrane proteases, rhomboids, site-2 protease, and Ras-converting enzyme 1 are intramembrane proteases. However, due to their subcellular localization these proteases are not involved in RIPing of ADAM substrates (145). Thus, there are clear evidences that RIPing by γ-secretase plays an important function in infectious diseases; however, little is known about the exact consequences of these processes.

SARS-COV-2 AND COVID-19

There are only a few examples, in which a direct pathogen-ADAM protease-target molecule axis has been established. Besides ADAM10/S. aureus (40) and ADAM9/EMCV (25, 26), the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing COVID-19 is the most prominent example, showing the diverse protective and progressive action of ADAM proteases in infectious diseases. The extracellular domain of angiotensin converting enzyme II (ACE2), a crucial shedding substrate for ADAM17 (146), functions as cellular receptor for the virus’ spike (S) protein (147). ACE2 is highly expressed in the lung and myocardium, and it has been speculated that ADAM17 overexpression could play a milestone protective role through mediating shedding of ACE2 leading to downregulation of its surface expression, inhibiting the key entrance of SARS-CoV-2 and further blocking circulation virus particles (71). After ligation of ACE2 with the spike protein, a proteolytic cut of the S glycoprotein mediated by furin is a crucial step for virus entry (148). One mediator regulating furin expression on the transcriptional level is Notch1 (149). Both, ADAM10 and ADAM17 are able to shed Notch1 and thereby activate down-stream signaling processes. However, cleavage occurs context dependent, with ADAM10 being responsible for ligand-induced signaling, whereas ligand-independent signaling requires ADAM17 (150). Ectodomain shedding of Notch1 is followed by γ-secretase cleavage leading to regulation of Notch targeting genes such as furin and enhancement of ADAM10 activity (149). On the other hand, Notch1 has been shown to function as negative regulator of ADAM17 through the transcription of miRNA-145 (151). Thus, inhibition of ADAM10/ADAM17 in intending to block Notch signaling resulting in downregulation of furin expression and its activation circle may serve as an important approach to prevent viral entry and SARS-CoV-2 infection (38). On the other hand, ADAM17 is the main sheddase of TNF-α and further involved in IL-6R shedding (48). Both, IL-6 and TNF-α are important components of the cytokine storm observed in COVID-19 patients (152). With respect to TNF-α, inhibition of ADAM17 as preventive mechanism could be desired. However, the effect on IL-6 signaling would be limited to ADAM17-dependent IL-6R trans-signaling but would not affect the binding of IL-6 to membrane-bound IL-6R or soluble IL-6R derived from alternative mRNA splicing (153, 154). Furthermore, ACE2 depletion on the cell surface is a key pathological feature of SARS-CoV-2 infection, disabling its protective role and consequently resulting in cardiovascular diseases such as atrial fibrillation and heart failure (72). Furthermore, down-regulation of ACE2 severely worsened the outcome in SARS-CoV infection (155), and pharmacological inhibition and gene silencing of ADAM17 showed a markedly decrease of infection in in vitro and in vivo models (156). Thus, the role of ADAM proteases during SARS-CoV-2 infection is controversy and has to be carefully evaluated for potential treatment options.

SILENT EFFECTS OF INFECTION—CARDIOVASCULAR DISEASE DEVELOPMENT

As mentioned above, local infection may cause severe side-effects in other organs or the whole body, such as sepsis formation upon infection with P. aeruginosa (157) and the development of hepatocellular carcinoma metastases upon hepatitis B virus infection (158). The most prominent example is in these days the development acute coronary syndromes, arrhythmias, exacerbation of heart failure, thromboembolism, and myocarditis upon SARS-CoV-2 infection, which may be related to the hyper-inflammatory response [for review see (159)]. TNF-α is one of the most essential cytokines that coordinates the host response against intracellular pathogens, including apoptosis for pathogen deposition, upregulation of adhesion molecules on endothelial cell and leukocytes for inflammatory cell recruitment and initiation of the systemic response and the action as negative regulator through the interaction with TNFRs (160, 161). Although this activity is tightly regulated, constantly elevated levels of TNF-α (e.g., chronic infection or cytokine storm) may cause detrimental vascular damage through the induction of endothelial apoptosis, vascular remodeling, pro-coagulatory effects such as enhanced expression of tissue factor, oxidative stress, and recruitment of inflammatory cells while reducing...
NO production and the number of regenerating stem cells [for review see (162, 163)]. Several studies have shown the direct link between infection and atherosclerosis development, e.g., with *C. pneumonia* and *Pyrophromonas gingivalis* (164, 165). Based on autoimmune diseases, it is widely discussed if anti-TNF-α therapy could be used as treatment option in cardiovascular disease, but further studies are required for proof of concept (162). It is important to note that such a treatment would again enhance the susceptibility for infection (166). Besides TNF-α, ACE2 plays an essential role in SARS-CoV infection. As a consequence of infection, ACE2 is downregulated on the surface accompanied by enhanced levels of angiotensin II (Ang II) and activation of the renin-angiotensin system (167). It was shown that the conversion of Ang II to Ang 1-7 by ACE2 has cardioprotective function and that the described dysregulation of ACE2 is not unique for SARS-CoV-2, thus prompting toward administration of soluble ACE2 to prevent organ failure (168). Similar divergent functions of Notch
activation in cardiovascular damage have been described. On the one hand, Notch exerts a pro-inflammatory action through the polarization of inflammatory cells and the production of IL-6 through the delta-like ligand 4/Notch1 axis (44, 45). On the other hand, it was shown that ADAM10-dependent signaling through Notch1 and Notch4 cleavage controls organ-specific vascular bed formation (169) and could be a therapeutic option to enhance the regenerative capacity of endothelial progenitor cells (170). Both Notch1 signaling and the shedding of E-cadherin were shown to contribute to endothelial malfunction upon S. aureus infection (40, 74, 171). Furthermore, infection with Neisseria meningitidis resulted in cleavage of the anticoagulant endothelial protein C receptor (EPCR) and impairment of protein C activation, thereby increasing the risk of thrombosis formation (172). Of course, a huge variety of ADAM substrates have been shown to be involved in vascular biology (15). The membrane-bound IL-6R was upregulated on SMCs of patients suffering from pulmonary arterial hypertension (173), and IL-6R trans-signaling critically contributed to pancreatitis-associated lung injury and in infection with L. monocytogenes (64, 174). Furthermore, ADAM8 is involved in the development of acute and chronic inflammatory lung diseases, and soluble ADAM8 was shown to be associated with atherosclerosis and myocardial infarction (175). Thus, it is obvious that both ectodomain shedding and RIPing in infection may contribute to the development of cardiovascular diseases. However, which substrates contribute in a time- and context-dependent manner has still to be investigated for the development of effective treatment options.

**CONCLUSION AND OUTLOOK**

ADAM proteases fulfill different functions from pathogen recognition to resolution of the concurrent inflammation and the development of systemic effects (Tables 1, 2, Figure 1). Thereby, they are essential control elements of infectious diseases. However, there a still some limitations with respect to the development of effective ADAM based therapeutic intervention. First, a lot of evidences are based on clinical studies not integrating the divergent functions of substrates in different cell types such as reported for Notch. Second, we did not discuss the complex regulation of ADAM proteases by interaction partners such as tetraspanins for ADAM10 [for review see (176)] and iRhombs for ADAM17 [for review see (177)] or the inhibition by endogenous inhibitors such as tissue inhibitor of metalloproteinase (TIMP) 1 or 3 (37, 178, 179). Of course, dysregulation of these factors may critically contribute to function of ADAM proteases in infectious diseases. Third, we focused on catalytic functions of ADAM proteases with direct evidences from infection studies. However, their general contribution by catalytic and non-catalytic functions to cell migration [for review see (180)] may further influence the defense against pathogens. Fourth, species specific differences in the use of cleavage events as has been reported for IL-6R (181) draw an even more complex view of the ADAM protease web in infection. Nevertheless, this web highlights a huge variety of molecular targets for the treatment of infectious diseases. Targeting ADAM proteases themselves could include inhibition of expression, maturation, or activation, inhibition of the active site by small molecules, application of the inhibitory pro-domain, or inhibition of substrate recognition [for review see (182)]. So far, clinical trials failed due to detrimental side-effects through global changes of ADAM activity and disturbance of tissue homeostasis and developmental processes or lack of efficacy [for review see (12, 13, 23, 183)]. However, several clinical trials are ongoing to address the activation of ADAM10 for the treatment of Alzheimer disease [for review see (184)]. Thus, future studies will have to address ADAM protease functions in a pathogen-, time-, and substrate-specific manner to evaluate specific and efficient treatment options with no or minimal side-effects.

**AUTHOR CONTRIBUTIONS**

AA and DY viewed the literature and wrote the review.

**FUNDING**

This work was supported by the DFG grant DR1013/1-1 (DY).

**ACKNOWLEDGMENTS**

We would like to thank the HIPS-UdS TANDEM initiative for the support.

**REFERENCES**

1. Ferrero-Miliani L, Nielsen OH, Andersen PS, Girardin SE. Chronic inflammation: importance of NOD2 and NALP3 in interleukin-1beta generation. *Clin Exp Immunol.* (2007) 147:227–35. doi: 10.1111/j.1365-2249.2006.03261.x
2. Medzhitov R. Inflammation 2010: new adventures of an old flame. *Cell.* (2010) 140:771–6. doi: 10.1016/j.cell.2010.03.006
3. Chen L, Deng H, Cui H, Fang J, Zuo Z, Deng J, et al. Inflammatory responses and inflammation-associated diseases in organs. *Oncotarget.* (2018) 9:7204–18. doi: 10.18632/oncotarget.23208
4. Ozinsky A, Underhill DM, Fontenot JD, Hajjar AM, Smith KD, Wilson CB, et al. The repertoire for pattern recognition of pathogens by the innate immune system is defined by cooperation between toll-like receptors. *Proc Natl Acad Sci USA.* (2000) 97:13766–71. doi: 10.1073/pnas.250476497
5. Hopfner KP, Hornung V. Molecular mechanisms and cellular functions of cGAS-STING signalling. *Nat Rev Mol Cell Biol.* (2020) 21:501–21. doi: 10.1038/s41580-020-0244-x
6. Rehwinkel J, Gack MU. RIG-I-like receptors: their regulation and roles in RNA sensing. *Nat Rev Immunol.* (2020) 20:537–51. doi: 10.1038/s41577-020-0288-3
7. Fujiwara N, Kobayashi K. Macrophages in inflammation. *Curr Drug Targets Inflamm Allergy.* (2005) 4:281–6. doi: 10.2174/15680105422024
8. Nathan C. Neutrophils and immunity: challenges and opportunities. *Nat Rev Immunol.* (2006) 6:173–82. doi: 10.1038/nri1785
9. Zhou Y, Hong Y, Huang H. Triptolide attenuates inflammatory response in membrane glomerulo-nephritis rat via downregulation of NF-kappaB signaling pathway. *Kidney Blood Press Res.* (2016) 41:901–10. doi: 10.1159/000452591

10. Seals DE, Courtneidge SA. The ADAM family of metalloproteases: multidomain proteins with multiple functions. *Genes Dev.* (2003) 17:57–30. doi: 10.1101/gad.1039703

11. Andreini C, Banci L, Bertini I, Elmi S, Rosato A. Comparative analysis of the ADAM and ADAMTS families. *J Proteome Res.* (2005) 4:881–8. doi: 10.1021/pr0500906

12. Giebeler N, Zigrino P. A disintegrin and metalloprotease (ADAM): historical overview of their functions. *Toxins.* (2016) 8:122. doi: 10.3390/toxins8040122

13. Lambrecht BN, Vanderkerken M, Hammad H. The emerging role of ADAM metalloproteases in immunity. *Nat Rev Immunol.* (2018) 18:745–758. doi: 10.1038/s41577-018-0068-5

14. Takeda S, ADAM and ADAMTS family proteins and snake venom metalloproteinas: a structural overview. *Toxins.* (2016) 8:155. doi: 10.3390/toxins8050155

15. Dreymundler D, Priesemsmyer J, Groth E, Ludwig A. The role of ADAM-mediated shedding in vascular biology. *Eur J Cell Biol.* (2012) 91:472–485. doi: 10.1016/j.ejcb.2011.09.003

16. Dreymundler D, Uhlig S, Ludwig A. ADAM-family metalloproteases in lung inflammation: potential therapeutic targets. *Am J Physiol Lung Cell Mol Physiol.* (2015) 308:L325–43. doi: 10.1152/ajplung.00294.2014

17. Jurisch-Yaksi N, Sannerud R, Annaert W. A fast growing multidomain proteins with multiple functions. *Genes Dev.* (2005) 19:881–99. doi: 10.1159/000452591

18. Pasqualon T, Pruesmeyer J, Jankowski V, Babendreyer A, Groth E, et al. The transmembrane CXC-chemokine ligand 16 is induced during infect. *Eur J Cell Biol.* (2012) 91:472–99. doi: 10.1016/j.ejcb.2011.09.003

19. van Eerdewegh P, Little RD, Dupuis J, Del Mastro RG, Falls K, Simon J, et al. The role of adams in notch signaling. *J Immunol.* (2004) 172:6362–7. doi: 10.4049/jimmunol.172.10.6362

20. Pandal N, Bohme L, Gurumurthy RK, Maurer A, Szczepak AJ, Rudel D. Reduced display of tumor necrosis factor receptor 1 at the host cell surface supports infection with Chlamydia trachomatis. *J Biol Chem.* (2008) 283:6438–48. doi: 10.1074/jbc.M708422200

21. Esteso G, Luzon E, Sarmiento E, Gomez-Caro R, Steinle A, Murphy G, et al. Altered microRNA expression after infection with human cytomegalovirus leads to TIMP3 downregulation and increased shedding of metalloprotease substrates, including MICA. *Immunol. (2014) 193:1344–52. doi: 10.1016/j.jimmunol.1303441

22. Rizzo P, Viecelli Della Sega F, Fortini F, Marracino L, Razeppi C, Ferrari R. COVID-19 in the heart and the lungs: could we “Notch” the inflammatory storm? *Basic Res Cardiol.* (2020) 115:31. doi: 10.1007/s00395-020-0791-5

23. Saphire AC, Bobardt MD, Zhang Z, David G, Gally PA. Syndecans serve as attachment receptors for human immunodeficiency virus type 1 on macrophages. *J Virol.* (2001) 75:9187–200. doi: 10.1128/JVI.75.19.9187-200.2001

24. Wilke GA, Bubeck Wardenburg J. Role of a disintegrin and metalloprotease 10 in Staphylococcus aureus alpha-hemolysin-mediated cellular injury. *Proc Natl Acad Sci USA.* (2010) 107:13473–13478. doi: 10.1073/pnas.1001815107

25. Kneidl J, Lofller B, Ertz MC, Kalinka J, Peters G, Roth J, et al. Soluble CD163 promotes recognition, phagocytosis and killing of Staphylococcus aureus via binding of specific fibronectin peptides. *Cell Microbiol.* (2012) 14:914–36. doi: 10.1111/j.1462-5882.2012.01766.x

26. Cappenberg A, Margraf A, Thomas K, Bardel B, Mccreedy DA, Van Marck V, et al. L-selectin shedding affects bacterial clearance in the lung: a new regulatory pathway for integrin outside-in signaling. *Blood.* (2019) 134:1445–57. doi: 10.1182/blood.201900683

27. Etzerodt A, Maniecki MB, Thomas K, Mccreedy DA, Van Marck V, et al. The iRhom2/ADAM17 axis attenuates bacterial uptake by phagocytes in a cell autonomous manner. *Int J Mol Sci.* (2020) 21:5978. doi: 10.3390/ijms21159787

28. Gomez MI, Sokol SH, Muir AB, Soong G, Bastien J, Prince AS. Bacterial induction of TNF-alpha converting enzyme expression and IL-6 receptor
alpha shedding regulates airway inflammatory signaling. *J Immunol.* (2005) 175:1930–36. doi: 10.4049/jimmunol.175.3.1930

Simanski M, Rademacher F, Schroeder L, Glaser R, Harder J. The inflammasome and the epidermal growth factor receptor (EGFR) are involved in the *Staphylococcus aureus*-mediated induction of IL-1alpha and IL-1beta in human keratinocytes. *PLoS ONE.* (2016) 11:e0147118. doi: 10.1371/journal.pone.0147118

Black RA, Rauch CT, Kozlosky CJ, Peschon JJ, Slack JL, Wofson MF, et al. A metalloproteinase disintegrin that releases tissue-necrosis factor-alpha from cells. *Nature.* (1997) 385:729–33. doi: 10.1038/385729a0

Pruessmeyer J, Hess FM, Alert H, Groth E, Pasqualon T, Schwarz N, et al. Leukocytes require ADAM10 but not ADAM17 for their migration and inflammatory recruitment into the alveolar space. *Blood.* (2014) 123:4077–88. doi: 10.1182/blood-2013-09-511543

Long C, Hosseininkhani MR, Wang Y, Szirmaeppo Marcal, W. ADAM17 activation in circulating neutrophils following bacterial challenge impairs their recruitment. *J Leukoc Biol.* (2012) 92:667–72. doi: 10.1007/s00292-011-1829-0

Ardnt PG, Strahan B, Wang Y, Long C, Horiiuchi K, Walcheck B. Leukocyte ADAM17 regulates acute pulmonary inflammation. *PLoS ONE.* (2011) 6:e19938. doi: 10.1371/journal.pone.0019938

Mohammed RN, Wehenkel SC, Galkina EV, Yates EK, Preece G, Newman A, et al. ADAM17-dependent proteolysis of L-selectin promotes early clonal expansion of cytotoxic T cells. *Sci Rep.* (2019) 9:5487. doi: 10.1038/s41598-019-41811-2

Olvera-Garcia G, Aguilar-Garcia T, Gutierrez-Jasso F, Imaz-Rosshandler M, Reiss K, Lettau M, Maretzky T, Ludwig A, Hartmann D, et al. Mitochondrial targeting of the enteropathogenic *Escherichia coli* map Met is induced by *Helicobacter pylori* infection. *J Mol Biol.* (2002) 248:247–65. doi: 10.1006/jmbi.2001.4402101

Antonelli A, Di Maggio S, Rejman J, Sanvito F, Rossi A, Catucci A, et al. iRhom2 regulation of TACE controls TNF-mediated cytotoxicity and activation-induced cell death. *Cell Death Differ.* (2007) 14:1040–9. doi: 10.1038/sj.cdd.4402101

Antonelli A, Di Maggio S, Rejman J, Sanvito F, Rossi A, Catucci A, et al. The shedding-derived soluble receptor for advanced glycation endproducts sustains inflammation during acute inflammatory shock is augmented in ceramide synthase 2 null mice due to elevated TNF-alpha availability during influenza infection. *J Leukoc Biol.* (2015) 97:713–8. doi: 10.1189/jlb.3VMAB1115-496RR

B. Gheblawi M, Wang K, Viveiros A, Nguyen Q, Zhong JC, Turner AJ, et al. Angiostatin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system: celebrating the 20th anniversary of the discovery of ACE2. *Circ Res.* (2020) 126:1456–74. doi: 10.1161/CIRCRESAHA.120.317015

Inoshima N, Wang Y, Bubek Wardenburg J. Genetic requirement for ADAM10 in severe *Staphylococcus aureus* skin infection. *J Invest Dermatol.* (2012) 132:1513–6. doi: 10.1038/jid.2011.462

Powers ME, Kim HK, Wang Y, Bubek Wardenburg J. ADAM10 mediates vascular injury induced by *Staphylococcus aureus* alpha-hemolysin. *J Infect Dis.* (2012) 206:532–6. doi: 10.1093/infdis/jis192

Mishra HK, Johnson TJ, Seelig DM, Walcheck B. Targeting ADAM17 in leukocytes increases neutrophil recruitment and reduces bacterial spread during polymicrobial sepsis. *J Leukoc Biol.* (2016) 100:999–1004. doi: 10.1189/jlb.3VMAB1115-496RR

Mishra HK, Ma J, Walcheck B. Ectodomain shedding by ADAM17: its role in neutrophil recruitment and the impairment of this process during sepsis. *Front Cell Infect Microbiol.* (2017) 7:138. doi: 10.3389/fcimb.2017.00138

Long C, Wang Y, Herrera AH, Horiiuchi K, Walcheck B. In vivo role of leukocyte ADAM17 in the inflammatory and host responses during E. coli-mediated peritonitis. *J Leukoc Biol.* (2010) 87:1097–101. doi: 10.1189/jlb.1109763

Link MA, Lucke K, Schmid J, Schumacher V, Eden T, Rose-John S, et al. The role of ADAM17 in the T-cell response against bacterial pathogens. *PLoS ONE.* (2017) 12:e0184320. doi: 10.1371/journal.pone.0184320

Deberge MP, Ely KH, Cheng GS, Enelow RL. ADAM17-mediated processing of TNF-alpha expressed by antiviral effector CD8+ T cells is required for severe T-cell-mediated lung injury. *PLoS ONE.* (2013) 8:e79340. doi: 10.1371/journal.pone.0079340

Deberge MP, Ely KH, Wright PF, Thorp EB, Enelow RL. Shedding of TNF receptor 2 by effector CD8+ T cells by ADAM17 is important for regulating TNF-alpha availability during influenza infection. *J Leukoc Biol.* (2015) 98:229–34. doi: 10.1189/jlb.380914-122RR

Hartmann D, de Strooper B, Sernaerts L, Craesemert K, Herreman A, Annaert W, et al. The disintegrin/metallopeptase ADAM 10 is essential for Notch signalling but not for alpha-secretase activity in fibroblasts. *Hum Mol Genet.* (2002) 11:2615–24. doi: 10.1093/hmg/11.21.2615
Aljohmani and Yildiz Regulated Proteolysis Controls Infectious Diseases

96. Dreymueller D, Martin C, Kogel T, Pruessmeyer J, Hess FM, Langjahr P, Diaz-Jimenez D, de La Fuente M, Rubio E, Golenbock
88. Shimaoka T, Nakayama T, Kume N, Takahashi S, Yamaguchi J, Minami M, Friedrich BM, Murray JL, Li G, Sheng J, Hodge TW, Rubin DH, et al.
84. Raucci A, Cugusi S, Antonelli A, Barabino SM, Monti L, Bierhaus A, et al.
87. Loetscher M, Amara A, Oberlin E, Brass N, Legler D, Loetscher P, et al.
82. Peschon JJ, Slack JL, Reddy P, Stocking KL, Sunnarborg SW, Lee DC, et al.
86. Loetscher P, Slack JL, Reddy P, Stocking KL, Sunnarborg SW, Lee DC, et al.
84. Raucci A, Cugusi S, Antonelli A, Barabino SM, Monti L, Bierhaus A, et al.
82. Peschon JJ, Slack JL, Reddy P, Stocking KL, Sunnarborg SW, Lee DC, et al.
86. Loetscher P, Slack JL, Reddy P, Stocking KL, Sunnarborg SW, Lee DC, et al.
96. Dreymueller D, Martin C, Kogel T, Pruessmeyer J, Hess FM, Langjahr P, Diaz-Jimenez D, de La Fuente M, Rubio E, Golenbock
88. Shimaoka T, Nakayama T, Kume N, Takahashi S, Yamaguchi J, Minami M, Friedrich BM, Murray JL, Li G, Sheng J, Hodge TW, Rubin DH, et al.
84. Raucci A, Cugusi S, Antonelli A, Barabino SM, Monti L, Bierhaus A, et al.
87. Loetscher M, Amara A, Oberlin E, Brass N, Legler D, Loetscher P, et al.
82. Peschon JJ, Slack JL, Reddy P, Stocking KL, Sunnarborg SW, Lee DC, et al.
86. Loetscher P, Slack JL, Reddy P, Stocking KL, Sunnarborg SW, Lee DC, et al.
96. Dreymueller D, Martin C, Kogel T, Pruessmeyer J, Hess FM, Langjahr P, Diaz-Jimenez D, de La Fuente M, Rubio E, Golenbock
88. Shimaoka T, Nakayama T, Kume N, Takahashi S, Yamaguchi J, Minami M, Friedrich BM, Murray JL, Li G, Sheng J, Hodge TW, Rubin DH, et al.
84. Raucci A, Cugusi S, Antonelli A, Barabino SM, Monti L, Bierhaus A, et al.
87. Loetscher M, Amara A, Oberlin E, Brass N, Legler D, Loetscher P, et al.
82. Peschon JJ, Slack JL, Reddy P, Stocking KL, Sunnarborg SW, Lee DC, et al.
86. Loetscher P, Slack JL, Reddy P, Stocking KL, Sunnarborg SW, Lee DC, et al.
96. Dreymueller D, Martin C, Kogel T, Pruessmeyer J, Hess FM, Langjahr P, Diaz-Jimenez D, de La Fuente M, Rubio E, Golenbock
88. Shimaoka T, Nakayama T, Kume N, Takahashi S, Yamaguchi J, Minami M, Friedrich BM, Murray JL, Li G, Sheng J, Hodge TW, Rubin DH, et al.
84. Raucci A, Cugusi S, Antonelli A, Barabino SM, Monti L, Bierhaus A, et al.
87. Loetscher M, Amara A, Oberlin E, Brass N, Legler D, Loetscher P, et al.
82. Peschon JJ, Slack JL, Reddy P, Stocking KL, Sunnarborg SW, Lee DC, et al.
86. Loetscher P, Slack JL, Reddy P, Stocking KL, Sunnarborg SW, Lee DC, et al.
96. Dreymueller D, Martin C, Kogel T, Pruessmeyer J, Hess FM, Langjahr P, Diaz-Jimenez D, de La Fuente M, Rubio E, Golenbock
88. Shimaoka T, Nakayama T, Kume N, Takahashi S, Yamaguchi J, Minami M, Friedrich BM, Murray JL, Li G, Sheng J, Hodge TW, Rubin DH, et al.
84. Raucci A, Cugusi S, Antonelli A, Barabino SM, Monti L, Bierhaus A, et al.
87. Loetscher M, Amara A, Oberlin E, Brass N, Legler D, Loetscher P, et al.
82. Peschon JJ, Slack JL, Reddy P, Stocking KL, Sunnarborg SW, Lee DC, et al.
86. Loetscher P, Slack JL, Reddy P, Stocking KL, Sunnarborg SW, Lee DC, et al.
96. Dreymueller D, Martin C, Kogel T, Pruessmeyer J, Hess FM, Langjahr P, Diaz-Jimenez D, de La Fuente M, Rubio E, Golenbock
88. Shimaoka T, Nakayama T, Kume N, Takahashi S, Yamaguchi J, Minami M, Friedrich BM, Murray JL, Li G, Sheng J, Hodge TW, Rubin DH, et al.
84. Raucci A, Cugusi S, Antonelli A, Barabino SM, Monti L, Bierhaus A, et al.
87. Loetscher M, Amara A, Oberlin E, Brass N, Legler D, Loetscher P, et al.
82. Peschon JJ, Slack JL, Reddy P, Stocking KL, Sunnarborg SW, Lee DC, et al.
86. Loetscher P, Slack JL, Reddy P, Stocking KL, Sunnarborg SW, Lee DC, et al.
96. Dreymueller D, Martin C, Kogel T, Pruessmeyer J, Hess FM, Langjahr P, Diaz-Jimenez D, de La Fuente M, Rubio E, Golenbock
88. Shimaoka T, Nakayama T, Kume N, Takahashi S, Yamaguchi J, Minami M, Friedrich BM, Murray JL, Li G, Sheng J, Hodge TW, Rubin DH, et al.
84. Raucci A, Cugusi S, Antonelli A, Barabino SM, Monti L, Bierhaus A, et al.
87. Loetscher M, Amara A, Oberlin E, Brass N, Legler D, Loetscher P, et al.
82. Peschon JJ, Slack JL, Reddy P, Stocking KL, Sunnarborg SW, Lee DC, et al.
117. Saavedra MT, Hughes CJ, Sanders LA, Carr M, Rodman DM, Coldren CD, et al. Circulating RNA transcripts identify therapeutic response in cystic fibrosis lung disease. Am J Respir Crit Care Med. (2008) 178:929–38. doi: 10.1164/rccm.200803-387OC

118. Roychaudhuri R, Hergruter AH, Polverino F, Lauche-Contreras ME, Gupta K, Borregaard N, et al. ADAM9 is a novel product of polymorphonuclear neutrophil: regulation of expression and contributions to extracellular matrix protein degradation during acute lung injury. J Immunol. (2014) 193:2469–82. doi: 10.4049/jimmunol.1303370

119. Xiang LY, Ou HH, Liu XC, Chen ZL, Li XH, Huang Y, et al. Loss of tumor suppressor miR-126 contributes to the development of hepatitis B virus-related hepatocellular carcinoma metastasis through the upregulation of ADAM9. Tumour Biol. (2017) 39:1010482317709128. doi: 10.1177/1027063017709128

120. Juza N, Cayo NM, Burgos M, Salvo ME, Nasser JR, Bua J, et al. Human polymorphs in placently expressed genes and their association with susceptibility to congenital Trypanosoma cruzi infection. J Infect Dis. (2016) 213:1299–306. doi: 10.1093/infdis/jiv561

121. Siezen CL, Bont L, Hodemaekers HM, Ermers MJ, Doornbos G, Yang X, Meegan JE, Jannaway M, Coleman DC, Yuan SY. A disintegrin

122. Baurakiades E, Costa VH, Raboni SM, De Almeida VR, Larsen KS, Guruharsha KG, Kankel MW, Artavanis-Tsakonas S. The Notch signalling

123. Baurakiades E, Costa VH, Raboni SM, De Almeida VR, Larsen KS, Guruharsha KG, Kankel MW, Artavanis-Tsakonas S. The Notch signalling

124. Stepp MA, Pal-Ghosh S, Tadvalkar G, Pajohesh-Ganjii A. Syndecan-1 and its expanding list of contacts. Adv Wound Care. (2015) 4:423–49. doi: 10.1089/wound.2014.0555

125. Park PW, Foster TJ, Nishi E, Duncan SJ, Klagsbrun M, Chen Y. Activation of syndecan-1 ectodomain shedding by Staphylococcus aureus alpha-toxin and beta-toxin. J Biol Chem. (2004) 279:251–8. doi: 10.1074/jbc.M308137200

126. Haynes A, Ruda F, Oliver J, Hamood AN, Griswold JA, Park PW, et al. Syndecan 1 shedding contributes to Pseudomonas aeruginosa sepsis. Infect Immun. (2005) 73:7914–21. doi: 10.1128/IAI.73.12.7914-7921.2005

127. Devaux CA, Mezouar S, Mege JL. The E-cadherin cleavage associated to pathogenic bacteria infections can favor bacterial invasion and transmigration, dysregulation of the immune response and cancer induction in humans. Front Microbiol. (2019) 10:2598. doi: 10.3389/fmicb.2019.02598

128. Marambaud P, Shioi J, Serban G, Georgakopoulos A, Sarner S, Nagy V, et al. A presenilin-1-gamma-secretase cleavage releases the E-cadherin intracellular domain and regulates disassembly of adherens junctions. EMBO J. (2002) 21:1948–56. doi: 10.1093/emboj/21.8.1948

129. Ljungberg JK, Kling JC, Tran TT, Blumenthal A. Functions of the WNT signalling network in shaping host responses to infection. Front Immunol. (2019) 10:2521. doi: 10.3389/fimmu.2019.02521

130. Agiostratidou G, Muros RM, Shioi J, Marambaud P, Robakis NK. The cytoplasmic sequence of E-cadherin promotes non-amyloidogenic degradation of A beta precursors. J Neurochem. (2006) 96:1182–8. doi: 10.1111/j.1471-4159.2005.03616.x

131. Venugopal C, Demos CM, Rao KS, Pappolla MA, Sambamurti K. Beta-

132. Balin BJ, Hammond CJ, Little GS, Hingley ST, Al-Atrache Z, Appelt DM, et al. Chlamydia pneumoniae: an etiologic agent for late-onset dementia. Front Aging Neurosci. (2018) 10:302. doi: 10.3389/fgagn.2018.00302

133. Al-Atrache Z, Lopez DB, Hingley ST, Appelt DM. Astrocytes infected with Chlamydia pneumoniae demonstrate altered expression and activity of secretases involved in the generation of beta-amyloid found in Alzheimer disease. BMC Neurosci. (2019) 20:6. doi: 10.1186/s12868-019-0484-9

134. Toussey TN, Thathiah A, Jorissen E, Raemaekers T, Konietzko U, Reiss K, et al. ADAM10, the rate-limiting protease of regulated intramembrane proteolysis of Notch and other proteins, is processed by ADAMS-9, ADAMS-15, the gamma-secretase. J Biol Chem. (2009) 284:1738–47. doi: 10.1074/jbc.M805894200

135. Kuhlne N, Dederer V, Lemberg MK. Intramembrane proteolysis at a glance: from signalling to protein degradation. J Cell Sci. (2019) 132:217745. doi: 10.1242/jcs.217745

136. Lamberti DW, Yarski M, Warner FJ, Thornhill P, Parkin ET, Smith AI, et al. Tumor necrosis factor-alpha convertase (ADAM17) mediates regulated ectodomain shedding of the severe-acute respiratory syndrome-coronavirus (SARS-CoV) receptor, angiotensin-converting enzyme-2 (ACE2). J Biol Chem. (2005) 280:30113–9. doi: 10.1074/jbc.M50311200

137. Yuan R, Zhang Y, Li Y, Liu S, Gao Y, Zhou Q. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. Science. (2020) 367:1444–8. doi: 10.1126/science.abb2762

138. Walls AC, Park YJ, Tortorici MA, Wall A, Mcgure AT, Veesler D. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell. (2020) 181:281–92.e8. doi: 10.1016/j.cell.2020.02.058

139. Qiu H, Tang X, Ma J, Shaverdashvili K, Zhang K, Bedogni B. Notch1 autoactivation via transcriptional regulation of furin, which sustains notch1 signaling by processing notch1-activating proteases ADAM10 and membrane Type 1 matrix metalloproteinase. Mol Cell Biol. (2015) 35:3622–32. doi: 10.1128/MCB.00116-15

140. Bozkulak EC, Weimaster G. Selective use of ADAM17 in activation of Notch1 signaling. Mol Cell Biol. (2009) 29:5679–95. doi: 10.1128/MCB.00406-09

141. Dobertstein K, Steinmeyer N, Hartmetz A, Eberhardt W, Mittelbronn M, Hau E, et al. MicroRNA-145 targets the metalloprotease ADAM17 and is suppressed in renal cell carcinoma patients. Neoplasia. (2013) 15:218–30. doi: 10.1593/neo.121222

142. Del Valle DM, Kim-Schulze S, Huang HH, Beckmann ND, Nirenberg S, Wang B, et al. An inflammatory cytokine signature predicts COVID-19 severity and survival. Nat Med. (2020) 26:1636–4. doi: 10.1038/s41591-020-1051-9

143. Horiiuchi S, Koyanagi Y, Zhou M, Miyoamata Y, Tanaka W, Yaki M, et al. Soluble inter leukin-6 receptors released from T cell or

144. Ajonhman and Yildiz

Regulated Proteolysis Controls Infectious Diseases
granulocyte/macrophage cell lines and human peripheral blood mononuclear cells are generated through an alternative splicing mechanism. *Eur J Immunol*. (1994) 24:1945–8. doi: 10.1002/evi.8302404857

154. Schumacher N, Rose-John S. ADAM17 Activity and IL-6 trans-signaling in inflammation and cancer. *Cancers*. (2019) 11:1736. doi: 10.3390/cancers11111736

155. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med*. (2005) 11:875–9. doi: 10.1038/nm1267

156. Haga S, Nakamura T, Yamamoto N, Sato T, Yamamoto N, et al. TACE antagonists blocking ACE2 shedding caused by the spike protein of SARS-CoV are candidate antiviral compounds. *Antiviral Res*. (2010) 85:351–5. doi: 10.1016/j.antiviral.2009.12.001

157. Kurahashi K, Kajiwara O, Sawa T, Ohara M, Gropper MA, Frank DW, et al. Pathogenesis of septic shock in Pseudomonas aeruginosa pneumonia. *J Clin Invest*. (1999) 104:743–50. doi: 10.1172/JCI17124

158. Xie Y. Hepatitis B virus-associated hepatocellular carcinoma. *Adv Exp Med Biol*. (2017) 1018:11–21. doi: 10.1007/978-981-10-5765-6_2

159. Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential effects of coronaviruses on the cardiovascular system: a review. *JAMA Cardiol*. (2020) 5:831–40. doi: 10.1001/jamacardio.2020.1286

160. Mcdermott MF. TNF and TNFR biology in health and disease. *Cell Mol Biol*. (2015) 129:278–85. doi: 10.2478/cmrb-2015-0006

161. Zhang H, Neuhofer P, Song L, Rabe B, Lesina M, Kurkowski MU, et al. IL-6 trans-signaling promotes pancreatitis-associated lung injury and lethality. *J Clin Invest*. (2013) 123:1019–31. doi: 10.1172/JCI64931

162. Mckellar GE, Mccarey DW, Sattar N, Mcinnes IB. Role for TNF in the life and death of the endothelium. *Eur Heart J*. (2010) 31:doi: 10.1161/CIRCRESAHA.115.307738

163. Zhang H, Park Y, Wu J, Chen X, Lee S, Yang J, et al. Ectopic upregulation of membrane-bound IL6R drives vascular remodeling in pulmonary arterial hypertension. *J Clin Invest*. (2018) 128:1956–970. doi: 10.1172/JCI96462

164. Chen H, Nampoothiri A, Zannad F, McKenna WJ, Cheung P, et al. Elevated expression of the metalloproteinase ADAM8 associates with vascular diseases in mice and humans. *Atherosclerosis*. (2019) 286:636–71. doi: 10.1016/j.atherosclerosis.2019.03.008

165. Machesky AL, Koo CZ, Szyrko J, Harrison N, Kanhere A, Tomlinson MG. Regulation of leukocytes by TspanC8 tetraspanins and the “Molecular scissor” ADAM10. *Front Immunol*. (2018) 9:1451. doi: 10.3389/fimmu.2018.01451

166. Crawford M, Curtis JR. Tumor necrosis factor inhibitors and infection complications. *Curr Rheumatol Rep*. (2008) 10:383–9. doi: 10.1007/s11926-008-0062-1

167. Majd M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential effects of coronaviruses on the cardiovascular system: a review. *JAMA Cardiol*. (2020) 5:831–40. doi: 10.1001/jamacardio.2020.1286

168. Zhang H, Neuhofer P, Song L, Rabe B, Lesina M, Kurkowski MU, et al. IL-6 trans-signaling promotes pancreatitis-associated lung injury and lethality. *J Clin Invest*. (2013) 123:1019–31. doi: 10.1172/JCI64931

169. Schick D, Babendreyer A, Wozniak J, Awan T, Noels H, Liehn E, et al. Elevated expression of the metalloproteinase ADAM8 associates with vascular diseases in mice and humans. *Atherosclerosis*. (2019) 286:636–71. doi: 10.1016/j.atherosclerosis.2019.03.008

170. Crawford M, Curtis JR. Tumor necrosis factor inhibitors and infection complications. *Curr Rheumatol Rep*. (2008) 10:383–9. doi: 10.1007/s11926-008-0062-1

171. Zhang H, Park Y, Wu J, Chen X, Lee S, Yang J, et al. Role of TNF-α in vascular dysfunction. *Clin Sci*. (2009) 116:219–30. doi: 10.1042/CS20080196

172. Campbell LA, Rosenfeld ME. Infection and atherosclerosis development. *Arch Med Res*. (2015) 46:339–50. doi: 10.1016/j.arcmed.2015.05.006

173. Kim HJ, Cha GS, Kim HI, Kwon EY, Lee JY, Choi J, et al. Porphyromonas gingivalis accelerates atherosclerosis through oxidation of high-density lipoprotein. *J Periodontal Implant Sci*. (2018) 48:60–8. doi: 10.5051/jps.2018.48.18.60

174. Crawford M, Curtis JR. Tumor necrosis factor inhibitors and infection complications. *Curr Rheumatol Rep*. (2008) 10:383–9. doi: 10.1007/s11926-008-0062-1

175. Ni W, Yang X, Yang D, Bao J, Li R, Xiao Y, et al. Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. *Crit Care*. (2020) 24:422. doi: 10.1186/s13054-020-03120-0

176. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-angiotensin-aldosterone system inhibitors in patients with COVID-19. *N Engl J Med*. (2020) 382:1653–9. doi: 10.1056/NEJMoa2003570

177. Albo RO, Glomski K, Haxaire C, Weskamp G, Monette S, Blobel CP. ADAM10-dependent signaling through Notch1 and Notch4 controls development of organ-specific vascular beds. *Circ Res*. (2016) 119:519–31. doi: 10.1161/CIRCRESAHA.115.307738

178. Hernandez SL, Nelson M, Sampedro GR, Bagrodia N, Defnet AM, Lec B, et al. Staphylococcus aureus alpha toxin activates Notch in vascular cells. *Angiogenesis*. (2019) 22:197–209. doi: 10.1007/s10456-018-9650-5

179. Tomlinson MG. Regulation of leukocytes by TspanC8 tetraspanins and the “Molecular scissor” ADAM10. *Front Immunol*. (2018) 9:1451. doi: 10.3389/fimmu.2018.01451

180. Dreydmueller D, Theodorou K, Donners M, Ludwig A. Fine tuning cell migration by a disintegrin and metalloproteinases. *Mediators Inflamm*. (2017) 2017:9621724. doi: 10.1155/2017/9621724

181. Garbers C, Janner N, Chalaris A, Moss ML, Floss DM, Meyer D, et al. Species specificity of ADAM10 and ADAM17 proteins in interleukin-6 (IL-6) trans-signaling and novel role of ADAM10 in inducible IL-6 receptor shedding. *J Biol Chem*. (2011) 286:14804–11. doi: 10.1074/jbc.M111.229393

182. Dreydmueller D, Ludwig A. Considerations on inhibition approaches for proinflammatory functions of ADAM proteases. *Platelets*. (2017) 28:354–61. doi: 10.1080/09537104.2016.1203396

183. Zunke F, Rose-John S. The shedding protease ADAM17: physiology and pathobiology. *Biochim Biophys Acta Mol Cell Res*. (2017) 1864:2059–70. doi: 10.1016/j.bbamcr.2017.07.001

184. Wetzel S, Seipold L, Saftig P. The metalloproteinase ADAM10: a useful therapeutic target? *Biochim Biophys Acta Mol Cell Res*. (2017) 1864:2071–81. doi: 10.1016/j.bbamcr.2017.06.005

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2020 Aljohmani and Yildiz. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided that the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.