Review

Updates on Inflammatory Molecular Pathways Mediated by ADAM17 in Autoimmunity

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Updates on Inflammatory Molecular Pathways Mediated by ADAM17 in Autoimmunity

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Abstract: ADAM17 is a component of the disintegrin and metalloproteinase (ADAM) family of transmembrane proteases with immunoregulatory activity in multiple signaling pathways. The functional ADAM17 is involved in "ectodomain shedding" of many substrates belonging to growth factors, cytokines, receptors, and adhesion molecules. The ADAM17-dependent pathways are known to be crucial in tumor development and progression and in the modulation of many pathological and physiological processes. In the last decade, ADAM17 was considered the driver of several autoimmune pathologies, and numerous substrate-mediated signal transduction pathways were identified. However, the discoveries made to date lead researchers to try to clarify the multiple mechanisms in which ADAM17 involved, and to identify any molecular gaps between the different transductional cascades. In this review, we summarized the most recent updates on multiple regulatory activity of ADAM17, focusing reported data on the field of autoimmunity.

Keywords: ADAM17; inflammation; autoimmunity

1. Introduction

Metalloproteinases (MMPs) are a set of enzymes that catalyze the proteolytic hydrolysis of peptide bonds, resulting in either the release of active molecules or the degradation of proteins. These proteolytic events are fundamental in all living cells to control processes such as tissue morphogenesis and remodeling, angiogenesis, inflammation, and autoimmunity, and unsurprisingly, they are also linked to pathological conditions when their functions are dysregulated [1]. In humans, there are numerous proteases identified in which essential roles in cellular physiology and the biological processes are tightly regulated both transcriptionally and post-transcriptionally [2,3]. ADAM17 is the most studied, and in recent years, multiple studies have focused on the molecular mechanisms of ADAM17 in diseased conditions. Over the last decade, ADAM17 has attracted considerable interest as an orchestrator of a wide range of autoimmune pathologies, largely demonstrated from research that employed genetic or inhibitory strategies to target ADAM17 in preclinical disease mouse models [4–7]. This has sparked growing conjecture that the treatment of many such disease states with drugs that block the actions of ADAM17 may offer novel therapeutic opportunities in the clinic.

In this review, we provide an update on the complex biology of the ADAM17 protease and explore the current state of knowledge regarding the molecular and cellular regulatory mechanisms of ADAM17 in autoimmune conditions. Although many pieces of the puzzle have been identified, we still do not have an overview of the regulation of ADAM17 activity. This has prevented, to date, the initially promising use of strategies for the selective inhibition of ADAM17 for therapeutic purposes. However, we felt it necessary to insert a paragraph summarizing the experimental procedures implemented using ADAM17 inhibitor biomolecules. Despite high expectations, they never made it to clinics, as the side effects they caused were more serious than the benefits.

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2. Overview of the ADAM 17 in Structure and the Regulatory Mechanisms

The protease ADAM17, also known as tumor necrosis factor-α (TNF)-α converting enzyme (TACE), was discovered in 1988 [8]. ADAM17 was synthesized as a type I transmembrane cell-surface metalloprotease in inactive form. It is largely expressed in several tissues and cell types [9,10]. The ADAM17 protein is composed by a pro-domain, a metalloprotease domain, a disintegrin domain, a cysteine-rich membrane proximal domain, a candis (conserved ADAM seventeen dynamic interaction sequence), and an intracellular cytoplasmic domain (Figure 1) [3]. The pro-domain blocks the catalytic activity of ADAM17 based on the cysteine-switch mechanism forming an inactive protein [11], and it is necessary the pro-domain cleavage to activate ADAM17 [2;12]. Furin, PC7, and PC5B pro-protein convertases can remove the ADAM17 pro-domain during activation and determine the release of its mature/active form [12]. Afterwards, the N-terminal signal sequence transfers the newly synthesized ADAM17 protein to the endoplasmic reticulum and Golgi apparatus. Based on the process of synthesis and activation of ADAM17, it is possible to distinguish the catalytic form (80 kDa), the precursor form (110 kDa), and the glycosylated form (130 kDa) [13,14].

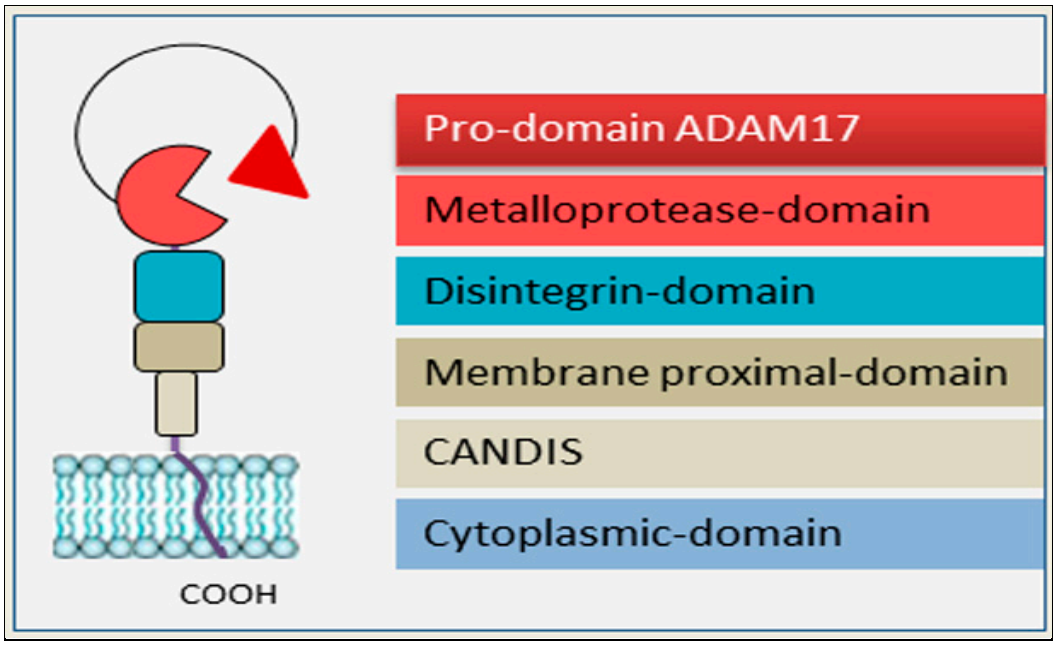

Figure 1. Schematic representation of ADAM17. ADAM17 is constituted by six different domains: a pro-domain, a metalloproteinase or catalytic domain, a disintegrin domain, a membrane-proximal domain, a Conserved ADAM-seventee N Dynamic Interaction Sequence (CANDIS), and terms with a cytosolic tail.

ADAM17 is widely regulated through several mechanisms, including proteolysis, phosphorylation, glycosylation, methylation, and acetylation [15]. Therefore, ADAM17 has numerous interactions with various proteins that modulate a myriad of intracellular signaling pathways. Recently, the membrane proteins iRhom1 and iRhom2 have been identified as key regulators of ADAM17 function and have become important components for the transport of ADAM17 to the cell surface and its activation [16,17]. They belong to the rhomboid protein family, which comprises both the rhomboid intramembrane proteases iRhom1 and iRhom2. In several tissues, iRhoms form proteolytic complexes with ADAM17 but not with other ADAMs [17], helping ADAM17 to the surface transport via cell membrane and thus facilitating the activation of ADAM17. These data are confirmed by the experimental use of iRhoms- deficient mice in which ADAM17 maturation, trafficking, and proteolytic shedding of substrates were, as expected, abolished [16]. Furthermore, it has been demonstrated that ADAM17 shedding stimuli determine the phosphorylation of the N-terminal cytoplasmic tail of iRhom2 through the activation of mitogen-activated protein kinases (MAPKs). This phosphorylation process determines the detachment of

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ADAM17 from the complexes formed with iRhom2, thus promoting the proteolytic activity of ADAM17 [18].

ADAM17 participates actively, playing a central role in several epidermal growth factor receptor (EGFR) signaling pathways by shedding EGFR ligands as amphiregulin (AREG) or transforming growth factor (TGF-α) [19]. Indeed, it was demonstrated that ADAM17-mediated AREG shedding determines, subsequently, the activation of the ERK1/2 signaling pathway. The activation of the ADAM17/AREG/EGFR/ERK1/2 pathway leads to an increased release of the pro-inflammatory cytokines in salivary glands, augmenting the inflammatory status that characterizes autoimmune rheumatic disease Sjögren's syndrome (SS) [20]. Other investigators have also shown that phorbol-12-myristate-13-acetate (PMA) and EGF induce phosphorylation on ADAM17 in an ERK-dependent manner [4]. Given these different activation mechanisms, it is likely that ADAM17 activity is regulated in a tissue-specific and stimulus-specific manner [2,4,21]. A very recent discovery, deriving from the sad period of the severe acute respiratory syndrome coronavirus (SARS-CoV) pandemic period, concerns the role played by virus cell entry. ADAM17 can cleave the SARS-CoV-1/2 receptor ACE2 and the SARS-CoV2 spike protein, which is an important requisite for efficient infections [22].

Given the enormous number of discoveries that are accumulating in recent years on the activation of ADAM17, numerous strategies have also been implemented to study the role of ADAM17 in the physiology and pathology of human tissues. Genetic manipulation techniques were used to create the homozygous Adam17ex/ex mice that exhibit eye, skin, and heart defects with reduced levels of soluble ADAM17 substrates [4;6]. These in vivo data confirm the observations made in several patients in which homozygous and heterozygous mutations in the ADAM17 gene have been associated with inflammatory skin and bowel lesions, heart conditions, and a predisposition to infections [12].

As part of all these discoveries that improve knowledge of the mechanisms in which ADAM17 plays a fundamental role as an activator of traditional cascades, our interest has focused on autoimmune diseases, which represent a thriving field of research, given the impact on the health of patients. ADAM17 has attracted considerable interest as a key enzyme in autoimmune disease pathogenesis, since it is responsible for the release of soluble TNF-α. The increased release of TNF-α depends on the dysregulated expression and/or activation of ADAM17 observed in several autoimmune disorders [17,20,23], as rheumatoid arthritis (RA), SS, systemic lupus erythematosus (SLE), psoriasis, and Crohn's disease (CD) [17,24]. Furthermore, in recent years, a correlation has been identified between chronic inflammation that characterizes autoimmune diseases and a fibrotic evolution of the organs affected by these pathologies. More and more scientific evidence supports the involvement, in this process, of the activation of an epithelial-to-mesenchymal transition (EMT) program [11,25]. The following paragraphs will explore the most recent findings related to ADAM17-dependent pathways activated in autoimmune diseases.

3. Latest Discoveries on ADAM17-Mediated Pathways in Autoimmunity

Dysregulation of ADAM17-mediated signalling pathways is associated with several inflammatory autoimmune diseases [23], but the molecular mechanisms involved in this class of pathologies are not yet completely clear. In this paragraph, we will report the most recent discoveries on the involvement of ADAM17 in molecular pathways activated in autoimmune diseases in order to guarantee the creation of a substrate on which new therapeutic perspectives can germinate.

3.1. Updates on ADAM17-Mediated Interleukins (IL) Regulation (IL-6; IL-1; IL-15) in Autoimmune Diseases

3.1.1. IL-6

Originally identified as the protease responsible for cleavage of the membrane-bound cytokine TNFα [8], in the following years, ADAM17 was found to be also responsible for cleavage of the membrane-bound IL-6R [26] and for around 80 additional transmembrane protein substrates [8].

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IL-6 is a four-helical cytokine with pleiotropic activities, which is synthesized by many cell types upon appropriate stimulation and which can act on many cell types during several disease states such as inflammation and cancer [27]. IL-6 exerts its function through binding to the alpha-receptor Interleukin-6 receptor (IL-6R). The membrane-bound IL-6R can be cleaved from ADAM17 [6]. The soluble IL-6R (sIL-6R) can still bind its ligand IL-6, and the complex of IL-6 and sIL-6R can bind to gp130 and induce dimerization of signaling. This mode of signaling has been called IL-6 trans-signaling [28]. While gp130 is expressed on all cells in the body, IL-6R is only expressed on some cells, including hepatocytes, some leukocytes, and some epithelial cells. Since IL-6 shows only measurable binding to the IL-6R but not to gp130, it follows that IL-6 can only act on cells, which express the IL-6R [26]. Since gp130 is ubiquitously expressed, IL-6 trans-signaling can lead to the stimulation of virtually every cell in the body [26]. The dimerized gp130 leads to an activation of the tyrosine kinase Janus kinase 1 (JAK1), which is constitutively associated with the cytoplasmic portion of gp130. JAK1 phosphorylates tyrosine residues within the cytoplasmic portion of gp130. This leads to the recruitment of the adapter protein and phosphatase SHP2 that initiates MAP kinase and PI3 kinase signaling [29]. Furthermore, phosphorylated tyrosine residues recruit the cytoplasmic transcription factors STAT1 and STAT3, which thereupon become phosphorylated, dimerize, and translocate into the nucleus, where they bind to DNA and stimulate the transcription of gp130 target genes [29]. One of the earliest gp130 target genes is the gene coding for SOCS3. The SOCS3 protein is recruited to the membrane proximal tyrosine residue within the gp130 cytoplasmic tail, where it inhibits the activity of JAK1. Therefore, SOCS3 is a negative feedback inhibitor of gp130 signaling [29]. Recently, it was shown that gp130 activation leads to the phosphorylation and activation of the YAP pathway (Figure 2). This pathway was shown to be important in the development of autoinflammatory and autoimmune diseases [30]. It is clear now that stimulation with the IL-6/sIL-6R complex leads to the activation and stimulation of all gp130 proteins on the cell surface, resulting in a higher signal amplitude [28].

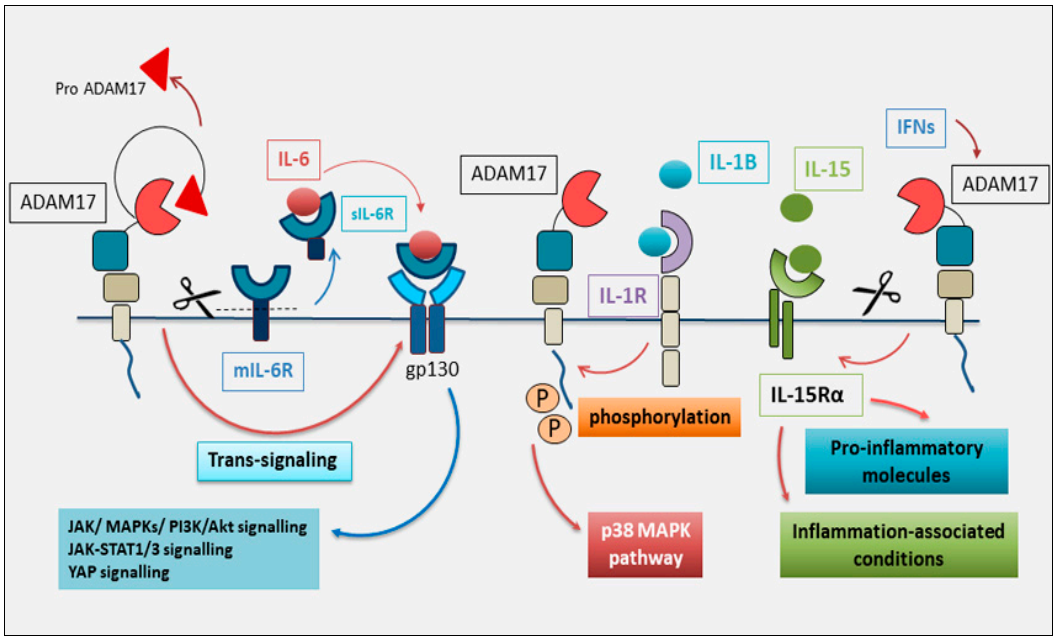

Figure 2. Interactions of ADAM17 with IL-6, IL-1β, and IL-15. ADAM17, through trans signalling, cleaves the membrane interleukin-6 receptor (mIL-6R) to release soluble (s) IL-6R, which then binds to free IL-6 to form a signal-transducing receptor complex with gp130 and induce its dimerization. The dimerized gp130 leads to the activation of the JAK1/MAP kinase and PI3 kinase signaling and recruits the cytoplasmic transcription factors STAT1 and STAT3. Activation of gp130 also leads to the phosphorylation and activation of the YAP pathway. The process of activation of ADAM17 is mediated by IL-1β that phosphorylates the cytoplasmic residue T735 and activates the p38 MAP kinase pathway. Interferons (IFNs) also upregulate cleavage of cell surface IL-15Rα /IL-15 complex in an ADAM17-dependent manner, inducing the expression of inflammatory cytokines and

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subsequently an inflammatory status. ADAM17 (disintegrin and metalloprotease 17); gp130 (glycoprotein 130); IFNs (interferons); JAK1 (janus kinase); MAPK (Mitogen Activated Protein Kinase); IL-6 (interleukin 6); IL-1β (interleukin 1 beta); IL-15 (interleukin 15); STAT (signal transducer and activator of transcription); PI3K (phosphatidylinositol 3 kinase).

3.1.2. IL-1β

Recent studies have demonstrated that the cytoplasmic domain of ADAM17 underwent phosphorylation when cells are treated with stimuli such as Phorbol 12-myristate 13-acetate (PMA), EGF, various growth factors such as nerve growth factor (NGF) [21], fibroblast growth factor (FGF), transforming growth factor β (TGF-β) and interleukin-1β (IL-1β) [31].

In understanding the process of IL-1β-mediated activation of ADAM17, studies examining a threonine-to-alanine mutation at cytoplasmic residue 735 (T735>A) in ADAM17 have played a key role. These studies have highlighted how this mutation is sufficient to abrogate the ability of ADAM17 to respond and activate following stimulation with IL-1β, a process that involves the p38 MAPK pathway [31].

Phosphorylation of the cytoplasmic residue T735 of ADAM17 is, therefore, considered by some authors as a crucial step in the process of activation of ADAM17 mediated by IL-1β and the p38 MAP kinase pathway. The characteristic inhibitory function performed by T735 is given as an explanation, which must necessarily undergo phosphorylation to determine the activation of ADAM17. This activation would therefore be independent of the role played by its cytoplasmic domain [32]. On the other hand, some authors suggest that this mechanism can be considered feasible only in certain experimental conditions, while the stimulation of ADAM17 by IL-1β would depend exclusively on the activation of p38 MAPK, and not on the phosphorylation of T735 or the cytoplasmic domain of ADAM17 [32,33] (Figure 2).

3.1.3. IL-15

IL-15 belongs to the four α-helix family of cytokines (including IL-2, IL-4, IL-7, IL-9 and IL-21) [34]. Differently from the receptors for IL-4, IL-7, IL-9 and IL-21 that are heterodimeric (a ligand-specific α chain binding the common γ (γc) chain), the receptors for IL-2 and IL-15 share an additional β chain (IL-2/15Rβ) leading to the formation of the heterotrimeric receptor for IL-15 [35]. Both IL-15Rα and IL-15 are expressed by a variety of tissues and cell types, including monocytes/macrophages, keratinocytes, fibroblasts, nerve, muscle, and epithelial cells [36], and different isoforms of human and murine IL-15Rα, derived from alternative splicing of the IL-15Rα gene, were known [37]. The knowledge related to the activity of IL-15Rα derived mainly from the use of recombinant soluble IL-15Rα which prevents murine collagen-mediated arthritis [38], inhibits local inflammation induced by subcutaneous carrageenan administration in mice [39], and decreased cardiac allograft rejection in mouse experimental model [40]. However, few data concerning the existence of natural sIL-15Rα were reported in the literature. Recently, the presence of the natural soluble IL-15Rα (sIL-15Rα) in a mouse serum was demonstrated. Furthermore, murine fibroblasts constitutively release sIL-15Rα into the culture medium, and this process is further stimulated by PMA. Interestingly, both the constitutive and PMA-inducible IL-15Rα cleavage is ADAM17-dependent, as demonstrated in inhibitory studies [41]. A step forward has been made by demonstrating that type I interferons (IFNs) also upregulate cleavage of cell surface IL-15Rα /IL-15 in an ADAM17-dependent manner [42]. This observation is the first demonstration that Type I IFNs are a regulator of ADAM17 activity. Given the cleavage activities performed by ADAM17 on many pro-inflammatory molecules [23], it can be asserted that the proteolytic regulation of ADAM17 mediated by Type I IFNs has the capability to alter immune responses during autoimmunity and inflammation-associated conditions (Figure 2).

3.2. ADAM17/Notch Signaling

It has been widely demonstrated, in recent years, that Notch activates an intracellular cascade, conserved throughout evolution, implicated in the regulation of various cellular processes [43]. For

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this reason, aberrant regulation of NOTCH or mutations in its coding gene may have pathological consequences [43].

In mammals, the Notch protein family includes four different Notch receptors (identified by Notch 1-4) [44]. Structurally, the four Notch receptor variants are type I membrane proteins, characterized by an extracellular ligand-binding domain (NECD) (N-terminal), a transmembrane domain (TMD), and an intracellular domain (NICD) (C -terminal) [44]. What characterizes each variant of the receptor is the NICD domain, necessary for receptor/ligand interactions and fundamental to then trigger the activation of the transcriptional cascade, which will lead to the modulation of the expression of specific target genes [45]. Notch is activated following binding to a specific ligand, which triggers a series of cascades of proteolytic cleavages. Ligands include five single-pass integral membranes belonging to the Serrate family (Jagged1 and Jagged2) and to the Delta-like family (delta-like 1 (DLL1) ligand, delta-like 3 (DLL3) ligand, and delta-like 4 (DLL4) ligand), which collectively belong to the Delta/Serrate/Lag-2 (DSLs) family [46]. Similar to the structure of Notch, DSL ligands are also transmembrane receptors, and for activation of NOTCH-mediated pathways to occur, a direct cell-cell interaction (trans-activation) must necessarily occur [46]. Following binding to Notch, NICD undergoes a process of ubiquitination via the E3 ligase Mind Bomb-1 [47]. This initiates a process of endocytosis of the Notch ligand/NECD complex within the cell, expressing the receptor acting as the ligand. It has been demonstrated that this endocytosis process is mediated by commonly involved factors such as Clathrin, Dynamin, Epsin, and Picalm. Once this endocytosis process has started, the subsequent phases of NOTCH activation are characterized by successive proteolytic cleavages. Specifically, ADAM17 plays a primary role in the proteolytic cleavage of NOTCH, followed by the proteolytic activity of the gamma-secretase complex, which includes presenilin, PSENEN/PEN-2, APH1, and nicastrin [48]. Whether gamma-secretase cleavage occurs at the membrane or endosomal compartment is still under investigation. The result is the release of the intracellular active fragment, namely the NICD [49] into the cytosol and NICD translocation into the nucleus.

The translocation of NICD within the nucleus determines its binding to the DNA transcription factor known as RBP-Jκ (recombination signal binding protein for the immunoglobulin kappa J region), which is fundamental in both activation and repression of genes whose activation depends on the NOTCH transduction cascade [49]. When NICD is not present in the nucleus, RBP-Jκ acts as a repressor of gene transcription, assisted by the co-repressor complex (Co-R) characterized by the presence of a histone deacetylase. The binding of NICD to RBP-Jκ in the nucleus determines the conversion of RBP-Jκ, which acts as a transcriptional activator, thanks to the recruitment of histone acetyltransferases (HAc) and through the recruitment of additional coactivators of the NOTCH signalling named Mastermind-like transcription factors (MAML) [50]. The association between NICD, RBP-Jκ and MAML generates a ternary Notch transcription complex (NTC), and this leads to the cascade activation of further transcription factors acting on specific downstream genes, such as the hairy/enhancer of split (Hes) and the hairy/split enhancer with the YRPW motif (Hey) [51]. Hes and Hey proteins are proteins that act as repressors and have a key role in the regulation of various NOTCH-mediated phenomena, including the regulation of chronic inflammation that characterizes autoimmune diseases [52,53].

The activation scheme reported here represents the canonical NOTCH-mediated pathway (Figure 3); however, some authors have reported the existence of an alternative pathway of Notch activation that has the T cell receptor (TCR)/CD28 complex as its main actor, a process that appears to occur in the absence of ligand [54]. The study of this alternative route presents numerous doubts to be clarified.

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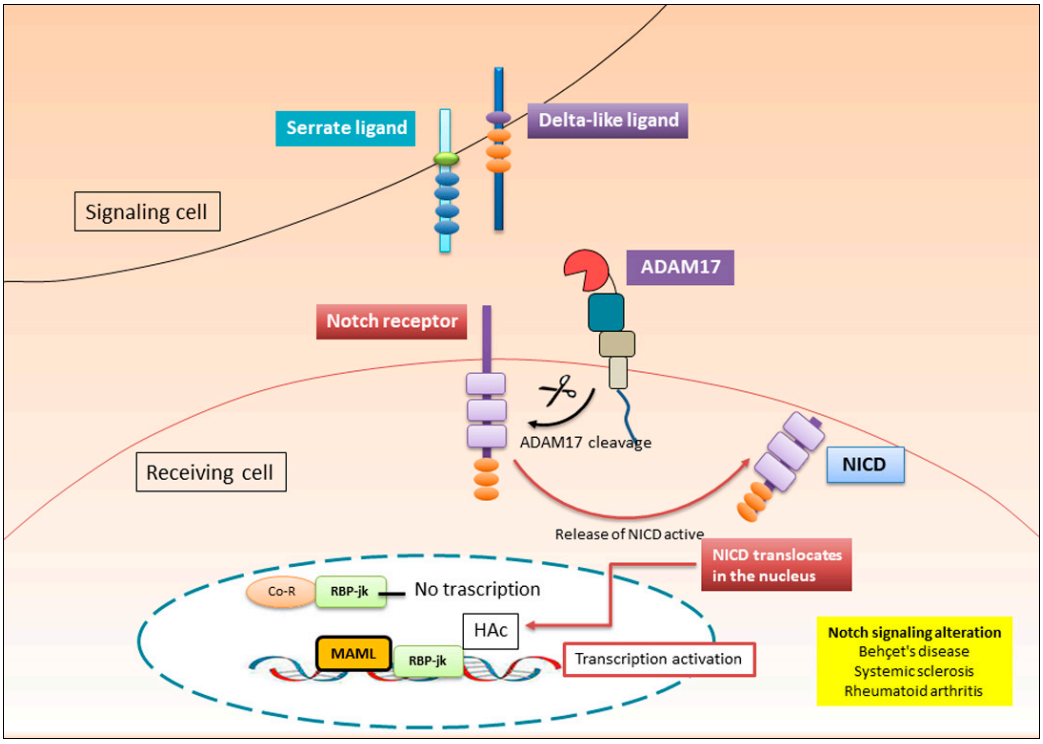

Figure 3. Notch signaling pathway. Notch receptor binds to a Delta-like or Serrate family of ligands located on the cell membrane. Notch receptor is processed by ADAM17, and the cleavage results in the release of the active component, NICD, in the cytoplasm. NICD translocates to the nucleus and binds to the conserved DNA binding transcription factor RBP-Jκ. In the absence of interactions with the NICD, RBP-Jκ represses transcription by interacting with the co-repressor (Co-R) complex. Otherwise, transcriptional activation occurs when the NICD binds to RBP-Jκ in the nucleus, therefore converting RBP-Jκ from a repressor to an activator of transcription recruiting of HAc and activation of the MAML family, thus, promoting the transcription of target genes. co-repressor (Co-R); HAc (histone acetyltransferases); MAML (activation of the Mastermind-like); NICD (Notch intracellular domain); Notch (Neurogenic locus notch homolog protein); RBP-Jκ (recombination signal binding protein for immunoglobulin kappa J region).

3.2.1. Role of ADAM17/NOTCH Signaling in Autoimmune Diseases

The involvement of NOTCH in molecular mechanisms and complex cascade activations has been studied in various pathological conditions, but the correlation with the proteolytic activity of ADAM17 has not always been evaluated. In this paragraph, we will analyze the most recent discoveries, analyzing the correlation between ADAM17 and NOTCH signaling in autoimmune diseases. An alteration of the complex mechanism of NOTCH activation has been demonstrated in various autoimmune diseases, and this represents a considerable step forward in the possibility of identifying therapeutic solutions that can reduce the state of chronic inflammation that characterizes these pathologies.

Behçet's disease (BD) is an auto-inflammatory disease characterized by altered transcription or mutations in several genes of currently unknown etiology, with ulcerative lesions affecting multiple organs [55,56]. Similar to other autoimmune diseases, the characterization of the pathogenesis of BD is not yet complete; certainly, a genetic predisposition associated with environmental factors, lifestyle habits, and epigenetic modifications could predispose to the onset of repeated inflammatory phenomena that tend to become chronic, as detected in BD pathology [56].

In reality, BD presents characteristics bordering on autoimmune diseases and auto-inflammatory conditions; like autoimmune diseases, it is closely related to alterations and mutations of the major histocompatibility complex (HLA), showing a close association with the HLA-B* allele 51 [57]; furthermore, it presents an activation of Th1 and Th17 cells and an overproduction of inflammatory cytokines such as IL-18, INF-ϒ, IL-2 and IL-12, IL-21, IL-2, IL-23, IL-17F and IL-17A, IL-

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6, TNF, and transforming growth factor-β (TGF-β) [58]. Nonetheless, specific characteristics of auto-inflammatory diseases such as the presence of hyperactive neutrophils with production of ROS (reactive oxygen species), phagocytosis, chemotaxis, and absence of serum autoantibodies have recently been highlighted in BD patients [59], with typical periods of remission and worsening of symptoms. In this intricate prospectus of potential mechanisms involved in the onset of BD, in recent years an involvement of NOTCH signaling in BD has also been evaluated and demonstrated. By analyzing the activation of the NOTCH-mediated transductional cascade in BD patients with uveitis, one of the hallmarks of BD [60], the authors demonstrated the ADAM-17/NOTCH-dependent activation of inflammatory mechanisms characterized by the consequent activation of Th17 [60]. This was confirmed by in vitro experiments based on the use of γ-secretase inhibitors, capable of preventing Notch activation by blocking its cleavage at the cell surface [60].

Systemic sclerosis (SSc) is considered an autoimmune disease with a high fibrotic component, which in recent years has been included among the diseases characterized by an epithelial to mesenchymal transition (EMT)-dependent fibrosis [61,62]. The more advanced stages of the disease are characterized by an excessive accumulation of extracellular matrix (ECM) proteins. This appears to be determined by the activation of an EMT program, which leads to the differentiation of a very high number of fibroblasts [61,62]. This affects the functionality of various organs, modifying their architecture, and this represents the main cause of death in SSc patients [63]. The most studied pathogenetic mechanisms over the years have concerned the production of cytokines and pro-fibrotic factors such as TGFβ, PDGF, MCP-1, IL-4, and IL-13. Very recent research has highlighted a predominant role of transductional cascades mediated by the activation of Wnt, Hedgehog, and the Notch in the pathogenesis of SSc [64]. Studies have been conducted on skin biopsy specimens collected from SSc patients and in vivo mouse models treated with ROS or bleomycin to induce an SSc-like syndrome. A clear activation of NOTCH was demonstrated with a consequent increase in NICD expression. This is due to an activation of ADAM17, which involves the proteolytic cleavage of NOTCH and the release of NICD into the cytoplasm; furthermore, an overexpression of the Jagged-1 ligand and an increase in transcription of the target gene HES-1 have been demonstrated in both skin and lungs [64]. Confirmation of the involvement of the ADAM17/NOTCH pathway in SSc comes from studies that have used inhibitors, such as siRNAs directed against Notch genes, which prevented the development of fibrotic tissue in the mouse model [65]. The data obtained from similar studies have allowed us to hypothesize that the NOTCH transductional cascade acts in the phase of collagen synthesis in fibroblasts [66]. Therefore, any therapeutic treatments could act in the early stages of fibrotic evolution.

Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic inflammation of the joints that causes swelling, pain, and impaired function. Although multiple mechanisms have been studied as responsible for the pathogenesis of RA [67] and many have also been correlated with each other, the role of the ADAM17/NOTCH pathway has only recently been evaluated as a possible cause of the activation of genes expressed in an altered manner in RA [68]. Notch signaling appears to be activated in synovial cells, inducing these cells to produce an enormous amount of pro-inflammatory cytokines [68]. Furthermore, during experiments conducted on a murine macrophage model, an overexpression of NICD was evaluated and demonstrated to be correlated with an activation of ADAM17, according to the canonical NOTCH signaling activation pathway. The increase in NICD expression was positively correlated with an increase in the production of TNF-α and interleukin (IL)-6 [69], once again supporting the involvement of ADAM17 as an activating factor of both cytokines evaluated.

Even in synovial cells similar to fibroblasts, an activation of NOTCH has been demonstrated, leading to an exacerbation of the inflammatory condition, mediated by the production of TNF-α and IL-6 [70]. In support of this involvement of NOTCH in RA inflammatory conditions, it has also been demonstrated that in macrophages, IFN-γ, a powerful activator of these cells, determines an increase in the expression of jagged-1 with a simultaneous reduction of expression of the Delta-like family proteins DLL1 and DLL4 [71], resulting in a worsening of the clinical signs of RA. A confirmation of the canonical pathway of NOTCH activation in RA is derived from experimental mouse models in

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which rheumatoid arthritis is simulated with inclusion by collagen II. The use of a plasmid encoding Jag1 reduced the severity of the disease [72]. Similarly, the use of a neutralizing antibody against notch3 attenuated the inflammatory characteristics [73] (Figure 3).

3.3. Updates on the Involvement of the Axis ADAM17/Amphiregulin/EGFR in Autoimmune Diseases

AREG is a heparin-binding molecule capable of binding to the EGF receptor, EGFR [74]. The name amphiregulin (AREG) derives from its bifunctional activity. If on the one hand it is able to stimulate the growth of healthy or tumor cells, on the other it can perform an inhibitory function on the proliferation of various tumor cell lines [75]. Synthesized from its gene, located in humans on chromosome 4q13-21, it initially takes the form of a transmembrane polarized glycoprotein (pro-AREG). This precursor, Pro-AREG, consists of an extracellular heparin-binding N-terminal domain, a hydrophobic transmembrane domain, and a carboxy-terminal domain with high homology to the corresponding EGF domain [76,77].

The AREG precursor is subsequently subjected to proteolytic cleavage, which leads to the release of the functionally active soluble form of AREG [75]. The proteolytic cleavage of the AREG precursor is carried out by ADAM17, and this is the reason why it is often referred to as the ADAM17/AREG axis [76,77].

When active AREG binds to EGFR, the activation of intracellular cascade pathways that are involved in the regulation of cellular metabolism and the cell cycle results; furthermore, ADAM17/AREG-dependent pathways are involved in phenomena of chronic inflammation [78–80]. The activation of the ADAM17/AREG axis has been demonstrated in various inflammatory conditions and in various autoimmune diseases, characterized by a chronic inflammatory state [18,82].

Interesting was the demonstration that, during the activation or maintenance of an inflammatory state, AREG is expressed not only by cells of the immune system [77], but also by unexpected ones like the epithelial ones, now recognized as active players in the secretion or regulation of the levels of pro-inflammatory cytokines [81,83].

The mechanism underlying the interaction between AREG and EGFR has been clarified and is based on the need for EGFR to undergo dimerization and autophosphorylation in order to become active [84]. The dimerization of EGFR can also occur in the absence of a ligand, but it is now known that its activation depends on a conformational change following the interaction with the ligand, which brings two contiguous receptors closer together and induces their phosphorylation [85]. Unlike the EGFR ligands EGF or TGF-α, AREG has a lower affinity for EGFR due to a different amino acid positioned at the level of its receptor-binding domain [86]. This means that the receptor is not internalized and degraded at the lysosome level, resulting in constant activation of downstream pathways [86].

There are various pathways activated by the ADAM17/AREG/EGFR axis, among which the most studied are the Ras-Raf/MAPK pathway, the PI3K/Akt pathway, or the pathway involving the activation of STAT, and lately attempts have been made to identify molecular bridges between all these mechanisms [87,88]. Current findings have demonstrated that both the pro- and anti-inflammatory roles of AREG are implicated in the pathogenesis of autoimmune conditions. In psoriasis, an overexpression of AREG in keratinocytes has been found, responsible for the inflammatory characterization of the disease [89]. Furthermore, an abnormal expression of the ADAM17/AREG axis has been demonstrated in salivary gland epithelial cells (SGEC) in patients with Sjögren's syndrome [81]. Along the same lines of research, EGFR blockade using tyrosine kinase inhibitors has proven to be a valid attempt to keep kidney damage under control in an experimental model of acute autoimmune glomerulonephritis (GN) [90]. In the same experimental setting, AREG gene silencing appears to have a significantly positive effect on renal protection from damage caused by altered inflammatory parameters [91].

The role of EGF and EGFR has been extensively studied in SS and correlated with the ADAM17/AREG activation axis [92,93]. All of these factors appear to be overexpressed in epithelial duct cells in the salivary glands, particularly in areas of lymphocyte infiltration and tissue alteration.

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The activation of the EGF/EGFR system in SS involves the metalloproteinase ADAM17 [20]. The identified mechanism demonstrated that, in SS, EGFR is a potent activator of the ERK1/ERK2 pathway (also known as the MAPK3/MAPK1 pathway). Elucidating signal transduction pathways, EGFR-mediated activation of ERK1/2 downstream effectors in SS SGEC depends on AREG activation in an ADAM17-dependent manner. This was corroborated by the use of AGREG-specific neutralizing antibodies which significantly reduced EGFR transactivation and ERK1/2 phosphorylation. Furthermore, specific inhibitors of ADAM17 and EGFR led to a deactivation of the ADAM17/AREG/EGFR/ERK pathway, and to a decrease in the synthesis of pro-inflammatory cytokines [20]. Other data in the literature indicate that an altered EGF/EGFR/ERK pathway is involved in the exacerbation of chronic inflammation in other autoimmune diseases, such as SLE [94] and psoriasis [95].

In contrast to these pro-inflammatory functions, AREG was also shown to have potent immunosuppressive effects. As a mechanism, AREG seems to act on Tregs to enhance their anti-inflammatory properties [96]. Independent research groups provided observations supporting an immunosuppressive role of AREG in experimental models of autoimmune uveoretinitis [97] and SLE [98].

Currently researchers are aiming to define that the ADAM17/AREG axis has an impacting role on the immune response, but sometimes contradictory, depending on whether the inflammation is acute, in which AREG would act in a pro-inflammatory manner, or chronic, in which AREG would predominantly have an anti-inflammatory effect.

A schematic representation of the molecular pathways involving ADAM17/AREG axis is reported in Figure 4.

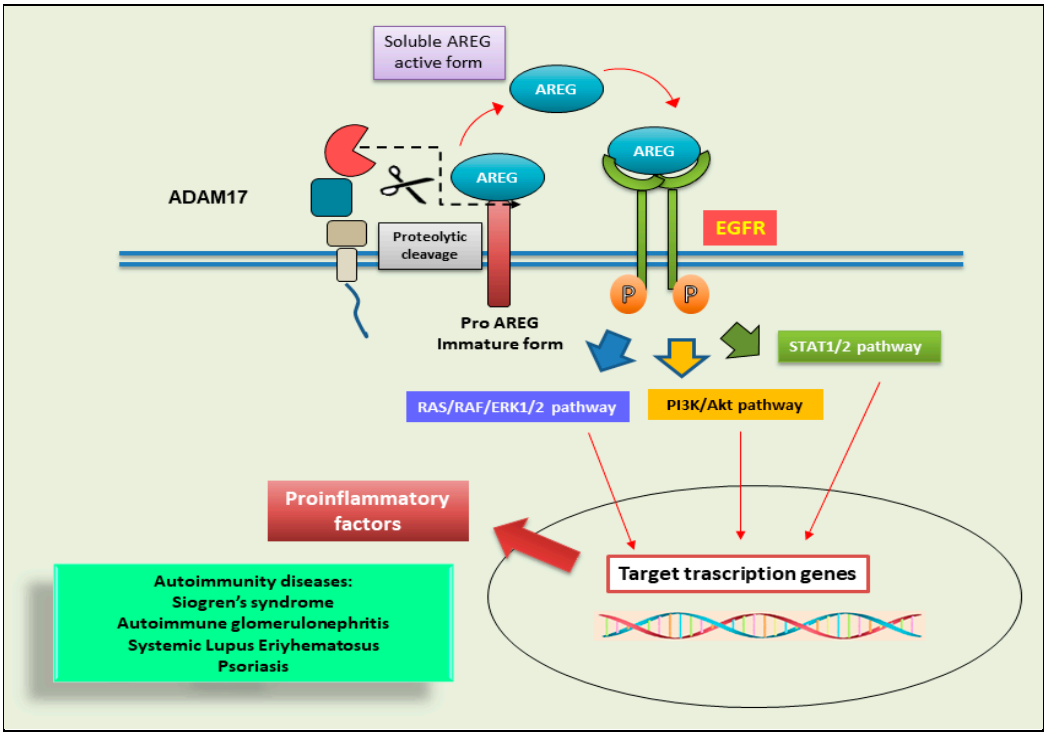

Figure 4. ADAM17 activation triggers AREG-dependent pathways. Mature ADAM17 cleaves EGFR that releases EGFR in mature form; mature EGFR binds soluble AREG and initiates EGFR-mediated intracellular signaling, including ERK 1/2, PI3K/AKT and STAT1/2 pathways. These pathways are involved in chronic inflammation and autoimmune conditions. ADAM17 (disintegrin and metalloprotease 17); AKT (a serine/threonine protein kinase); amphiregulin (AREG); EGFR (epidermal growth factor receptor); pro-AREG, proamphiregulin; sAREG, soluble amphiregulin; ERK (Extracellular signal-regulated kinase); PI3K (phosphatidylinositol 3-kinase); STAT1 (signal transducer and activator of transcription).

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3.4. ADAM17 Involvement in the EMT Program Activation in Autoimmune Diseases

In light of the latest discoveries on the roles played by ADAM17 in the pathogenetic mechanisms of autoimmune diseases, which we have discussed extensively in this review, an update on the role of ADAM17 in the phenomenon of epithelial to mesenchymal transition (EMT) could not be missed [99].

EMT represents a highly regulated cascade activation program characterized by the loss of the typical characteristics of epithelial cells that take on a mesenchymal appearance. The cells that undergo EMT, in fact, show an alteration and a decrease in epithelial adherens junctions, no longer present the apical-basal polarity, and show alterations at the cytoskeletal level [100,101]. By acquiring mesenchymal characteristics, these modified cells are largely responsible for the formation of metastases due to their high migration and replication capacity and are implicated in the fibrotic transformation of tissues, causing loss of functionality of the implicated organs [99,102].

Since ADAM17 is responsible for the shedding and activation of various pro-inflammatory molecules [1], and persistent inflammation is certainly implicated in the fibrotic evolution of various autoimmune diseases, very recent research has evaluated the involvement of ADAM 17 in EMT [11] in these diseases. A correlation has been identified between the overexpression of ADAM17 and the degree of fibrotic evolution in patients with degenerative fibrotic evolution of autoimmune diseases. Furthermore, from a molecular point of view, ADAM17 represents a crucial factor in a series of transductional cascade mechanisms activated in EMT [103–105] (Figure 5).

Although the involvement of ADAM17 in the activation of the EMT program has been widely studied, the studies carried out concern the field of oncology or fibrotic diseases. Attention is currently shifting to the field of autoimmune diseases, in which an EMT-dependent fibrotic evolution has been identified, and the results are very promising.

Idiopathic pulmonary fibrosis (IPF) is an autoimmune disease characterized by damage and activation of alveolar epithelial cells, infiltration of inflammatory cells, activation of an EMT program, and accumulation of extracellular matrix (ECM) proteins [104]. During the progression of IPF, lung epithelial cells undergo an EMT-mediated de-differentiation process, transforming into fibroblasts and causing an increasingly severe process of fibrotic degeneration with collagen deposition and architectural distortion [106]. A recent report demonstrated that ADAM17 determines, furthermore, the angiotensin-converting enzyme 2 (ACE-2) ectodomain shedding that was observed in lung fibrotic evolution in IPF [107].

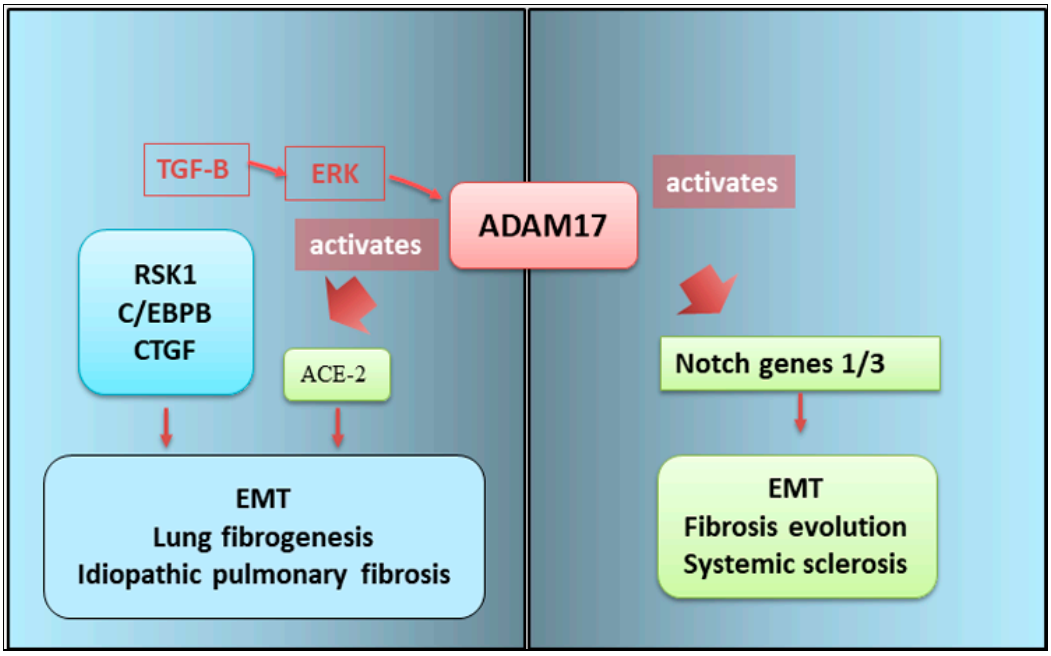

Figure 5. ADAM17 promotes fibrogenesis via EMT activation. Representative scheme shows the results of TGF-β-induced CTGF expression mediated via the ERK/ADAM17/RSK1/C/EBPβ pathway in lung epithelial cells, promoting fibrosis process in idiopathic pulmonary fibrosis. ADAM17

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activates Notch gene transcription that led to fibrotic conditions in systemic sclerosis. ADAM17, a disintegrin and metalloprotease 17; C/EBPβ (CCAAT Enhancer Binding Protein Beta); CTGF (CCN2 cellular communication network factor); EMT (epithelial mesenchymal transition); ERK (extracellular signal-regulated kinases); Notch (neurogenic locus notch homolog protein); RSK1 (ribosomal S6 kinase 1); TGF-β (transforming growth factor-beta).

In IPF, the ADAM17-mediated EMT activation is mediated by connective tissue growth factor (CTGF), a protein activated by TGF-β. CTGF was expressed at high levels in patients with IPF. The mechanism of activation seems to be triggered by TGF-β, which determines in sequence the activation of ERK, ADAM17, and ribosomal S6 kinase-1 (RSK1). The resulting transduction cascade is characterized by the phosphorylation of enhancer-binding protein β (C/EBPβ), which activates CTGF gene transcription [108].

The same ERK/ADAM17/RSK1 pathway determines the phosphorylation and activation of C/EBPβ. Therefore, ADAM17 plays a key role in the induction of EMT in response to TGF-β, which occurs via the ERK/RSK1/C/EBPβ pathway [108].

Another autoimmune disease in which the role of ADAm17 in EMT-dependent fibrosis is recognized, albeit indirectly, is SSc, characterized by an evolution of fibrotic tissue in various organs affecting the instrumental, cardiovascular, urinary, and respiratory [61]. It has been shown that the EMT program is correlated with increased expression of Notch genes (1 and/or 3). Such increased expression has been described in various epithelial cells of SSc patients and appears to be correlated with the mesenchymal transformation of such cells [64]. This would be mediated by the activation of NOTCH genes by ADAM17, as described in the canonical activation pathway. An involvement of NOTCH genes in ADAM17-mediated EMT-dependent fibrosis was confirmed by experimental procedures of inhibition of the NOTCH-mediated signal transduction pathway, which led to a decrease or slowing down of the fibrotic process [64]. However, the actual molecular bridges that connect ADAM17 to EMT remain to be clarified, and, above all, it is of primary interest to evaluate these mechanisms in other autoimmune diseases. For an overview see Figure 5.

4. ADAM17 as an Emerging Therapeutic Target for Autoimmune Diseases

Since ADAM17 has emerged as a protease that contributes to the pathogenesis of a multitude of disease states, a wide majority of small molecules synthesized so far as selective ADAM17 inhibitors were tested in tumors, chronic inflammatory diseases, and immune disorders [17,109]. More recently, investigations were warranted to assess the role of ADAM17 inhibitors in autoimmune disease since elevated expression and/or activation levels of ADAM17 were observed in biopsies of patients affected by autoimmune diseases such as IPF, Crohn's disease, RA, and psoriasis. [2,17,110,111]

Unfortunately, a contributing factor to the lack of progress of ADAM17 inhibitors in the clinic has been the adverse side-effects, such as hepatotoxicity, that accompanied the use of early generation inhibitors of ADAM17 [109]. Indeed, many ADAM17 selective inhibitors used in experimental protocols have shown a lack of efficacy in Phase II clinical trials as in RA patients' treatment; actually, the majority of these molecules entered into clinical trials were subsequently withdrawn, and none of these compounds is available on the market as a drug. In particular, the most studied ADAM17 inhibitors, Apratastat (Wyeth Pharmaceuticals), DPC 333 (Bristol-Myers Squibb Company), and INCB7839 (Incyte Corporation) have failed in phase II of clinical trials owing to their toxicity [17,112]. Apratastat, in addition to a lack of efficacy, was stopped for adverse events that occurred in RA patients. Similarly, DPC 333 was also finished treating RA, because it resulted in being ineffective and toxic for liver and muscles [113].

By contrast, anti-TNF-α biological agents, such as etanercept and infliximab, had success as therapy in alleviating the clinical symptoms of RA and ameliorating patients' lives. These antibodies were able to reduce the circulating level of TNF-α and act indirectly on ADAM17 inhibition. The most advanced among the biological drugs is INCB7839, a dual inhibitor of ADAM17 and ADAM10. Currently, it is used as therapy in association with rituximab for the treatment of non-Hodgkin lymphoma [111,114].

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In addition, recently, an inhibitor of ADAM17 based on its pro-domain entered the clinic for inflammatory conditions such as inflammatory bowel disease (IBD) [111]. Interestingly, the recombinant pro-domain protein (A17pro) has been developed as an inhibitor of ADAM17 cell surface activity *in vitro*, while *in vivo* was used in chronic autoimmune disease animal models [111].

In the last decade, researchers have identified more selective ADAM17-neutralizing monoclonal antibodies acting via different procedures, such as allosteric alteration of the binding capacity of the catalytic active site or inhibition of protein substrate linking [26]. These alternative modalities operate indirectly targeting ADAM17 substrates (such as sIL-6R) or signaling effectors associated with ADAM17 activation. In this scenario, ADAM17 is considered an attractive therapeutic target since it could govern the IL6R trans-signaling pathway and, simultaneously, could block co-existent disease-associated ADAM17-regulated pathways [26]. For example, Tocilizumab, the commercial name of anti-IL-6R antibodies, was approved for treatment of RA, and evidence has been collected for its beneficial effects on other systemic autoimmune diseases, including SLE, SSc, polymyositis, and large-vessel vasculitis [17]. On the basis of these considerations, molecules able to neutralize IL-6 trans-signaling in IPF were identified [115]. A recent study has demonstrated a temporal increase in ADAM17 in fibrotic lungs that mirrored increases in sIL-6Rα, so supporting a role for ADAM17 in generating sIL-6Rα, largely from lung macrophages. In vivo neutralization of trans signaling using the selective inhibitor recombinant gp130Fc, resulted in a reduction in pulmonary inflammation and fibrosis associated with improvement in respiratory function. Thus, neutralization of trans signaling attenuates disease and represents a promising new approach to treating IPF [115].

Remaining in the possibility of indirectly inhibiting the activation pathways mediated by ADAM17, very recently data have been collected relating to the possibility of inhibiting Notch. The ubiquitous expression of Notch receptors and ligands on many cell types leads to the concrete possibility of identifying new therapeutic approaches in the field of autoimmunity [116,117].

Considering the high levels of ADAM17 found in the psoriatic patients, this protease has become an important therapeutic target, having a crucial role in the pathogenesis of psoriasis. In a study conducted by Conway et al., GW3333, a dual inhibitor of matrix metalloproteinase (MMP) and ADAM17, was compared with other anti-TNF-α agents, demonstrating its effectiveness [116]. In addition, ADAM17 inhibitors were considered for the topical treatment of psoriasis because their effect on T-cell-mediated immune response in psoriasis plaques [118].

Given the involvement of iRhoms proteins in ADAM17-mediated mechanisms, emerging investigations have identified new inhibitors directed against the cytosolic tail of iRhom 1/2. However, it is necessary to carry out further studies to exclude that these inhibitors could, for example, block the interaction of iRhom2 with the stimulator of interferon genes (Sting), used in anti-inflammatory therapies [119]. Furthermore, silencing iRhom 1/2 genes, an attenuation of excess TNF-α release in CD was observed, and the immunosuppressive capabilities of TGF-β signaling were restored, which ultimately reverses inflammatory tissue damage, suggesting a therapeutic option to treat inflammatory autoimmune diseases such as CD and RA [120].

Nowadays, interesting advancements in the field of synthetic short RNA molecules in preclinical studies have suggested the repositioning of ADAM17 inhibitors, leading microRNA (miRNAs) in the limelight as promising future biopharmaceuticals. Thus, these studies may lead, in the near future, to the design and testing of therapeutic miRNAs as next generation drugs to target pathogenic cytokines in autoimmunity. All in all, these studies indicate that TNF. α, IL-1β, and IL-6 are relevant targets of miRNAs that are deregulated in autoimmune diseases [121]. Because these cytokines represent inducing stimuli for the pathways involving ADAM17, miRNA acting via indirect mechanisms are often found to regulate all of them. Thus, miRNA could represent interesting therapeutic targets for controlling cytokines aberrant production in autoimmune diseases [122–124].

Although the identification of therapeutically effective ADAM17 inhibitors is still complicated, and much has yet to be discovered and understood, it becomes more and more evident that there are many cogs in the ADAM17 regulatory machinery that may grant promising therapeutic strategies based on selective ADAM17 modulation.

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5. Conclusion

In recent years, numerous advances have been made to clarify the role of ADAM17, a multifunctional and pleiotropic protease involved in the shedding of multiple substrates, in various pathological conditions, including autoimmune diseases, our research focus. Despite the advances made in the knowledge of the basic mechanisms in which ADAM17 is involved in the processes of tissue homeostasis or development, the pathogenetic mechanisms in which it is implicated appear increasingly numerous and intricate. For this reason, the challenge is represented by the identification of molecular bridges that can connect these mechanisms together and thus have an overall vision. Obviously, it must be taken into account that the dysregulated expression and/or activation of ADAM17 depends on the substrate selectivity, the cellular context, and the specific stimulus that leads to the activation of this protease. Although a considerable amount of preclinical data gives hope that regulation of ADAM17 represents a valid therapeutic possibility, however, due to ineffective or toxic implications, this has yet to translate into its broad clinical implementation. Furthermore, numerous scholars have used an indirect approach in the attempt to identify potential drugs represented by the blocking or regulation of ADAM17 substrates; attempts have been made to antagonize the activity of IL-6 for example, or NOTCH. But even in this case, harmful physiological effects have been highlighted, despite contrary observations coming from preclinical mouse models, which tolerate well the administration of IL-6, or NOTCH inhibitors or antibodies directed against ADAM17 and the prodomain. In conclusion, in this review, we provide an overview of the most recent advances in the knowledge on the diverse molecular mechanisms involving ADAM17 activation in autoimmunity. The discussion of the mechanisms underlying ADAM17-mediated protein shedding could help scientists involved in translational studies to evaluate therapeutic prospects to counteract the chronic inflammation that characterizes these pathologies.

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