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A Review of ADAMTS15: Structure and Roles in Premature Rupture of Membranes

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Abstract— The ADAMTS are a group of proteinases containing the thrombospondin motifs. ADAMTS15 is a member of ADAMTS family and plays a crucial role in the proteoglycan degradation. Overexpression of ADAMTS15 gene promotes the breakdown of extracellular matrix (ECM) which associated in several diseases including initiation of premature rupture of membrane (PROM) process. Moreover, ADAMTS15 and long chains noncoding RNA (lncRNA) has a positive feedback loop trough PROM. In contrast, collagen expression has negative feedback towards ADAMTS15 expression followed by occurring of PROM. This review provides an overview of current knowledge of ADAMTS15, including its structure, regulation of ADAMTS15 and their role in PROM.

Keywords— ADAMTS15, structure, aggrecanases, PROM

1. Background

The ADAMTS (A Disintegrin and Metalloproteinase with Thrombospondin motifs) is group of family protein consist of 20 types with different role in cellular mechanism. ADAMTS is proteolytic activity and expression in various human tissues including liver, endotheliocyte, skeletal muscle, ovary, connective tissue, placenta, skin, lung, brain, heart, skeletal muscle, kidney, stem cells and others [1]. ADAMTS substrates are aggrecan, versican, procollagen, brevican, cartilage oligomeric matrix protein (COMP), vonWillebrand factor (vWf), and α2-Macroglobulin (α2M). Furthermore, ADAMTS family was grouped based on substrates into five categories involving aggrecanases or proteoglycanases, the procollagen N-propeptidases, the cartilage oligomeric matrix protein-cleaving enzymes, the von-Willebrand Factor proteinase, and orphan enzymes [2]. Each group consists of different types of ADAMTS family.

The first subgroup is aggrecanases including ADAMTS 1, 4, 5, 8, 9 and 20. The second as procollagen N-propeptidases subgroup is ADAMTS 2, 3 and 4. The cartilage cleaing enzyme contains ADAMTS7, 12 and von-Willebrand Factor proteinase contains ADAMTS13. Furthermore, orphan enzyme subgroups contain ADAMTS 6, 10, 16, 17, 18 and 19 [2]. ADAMTS 15 specifically associated with aggrecan degradation belongs to first group which called aggrecanases. The ADAMTS15 expressed in specific tissue and

correlated with several diseases including premature rupture of membranes (PROM) [5]. Recent study reported that PROM associated with ADAMTS15, lncRNA and collagen expression [6]. However, the mechanism is still unclear.

This review provides a structure of ADAMTS15 followed by their regulation in molecular perspective, correlation with long chains of noncoding RNA (lncRNA), and the links with PROM disease.

2. Structure of ADAMTS15

ADAM metallopeptidase with thrombospondin type 1 motif, 15 (ADAMTS15) encodes 950 amino acids with molecular weight of 103.3 kDa and the location of ADAMTS15 gene is 11q24.3 [5,7-9]. The glycosylation position is at 141, 591, 623, and 679 of amino acid sequences encodes asparagine. The gene has an active site which interacts to calcium and two sites of natural variants. The catalytic domain of active site has a role to degrade protein [8]. The ADAMTS15 domain was illustrated and organized by multiple domains including signal peptide, propeptide, chain peptide and disulfide bond [5,8]. The domain illustration showed in Figure 1.

The N-terminal globular domain binds hyaluronan and the C-terminal globular domain relates to selectins. Cofactor of ADAMTS15 is zinc which binds to active site and share several proteins involving a propeptide domain, metalloproteinase domain a disintegrin-like domain, and a thrombospondin type 1 motif (TSP1). Domain that conserved cysteine inhibits the enzyme. However, zinc ion activates the peptide release of the enzymes when the cysteine is dissociated [2,8].

Peptidase M12B and disintegrin is located in 218-427 and 428-515 of amino acid (aa), while TSP type 1 located at 516-571, 839-895, and 896-949 of amino acid. Cysteine motif and spacer located at 172-179 aa and 701-838 aa. There are three natural variants reported which located at 623, 770 and 878 aa. At position of 623, the variant is asparagine to serine which not associated to any kind of disease while at 770 (glutamine to arginine) and 878 (cysteine to glycine) are associated to colorectal cancer [8]. ADAMTS15 localization is in extracellular and mostly pericellular while TSP 1 interacts with extracellular matrix.

3. Regulation of ADAMTS15

ADAMTS15 expressed in several human tissues involving lung, ovary, kidney, and heart. The cellular component of ADAMTS15 is collagen-containing extracellular matrix (ECM) [1]. The ECM is a substrate of cell that has functions in tissue architecture and function [11]. Recent study reported that ADAMTS15 is associated and had a role with several diseases such as spinal injury, cancer and follicle rupture [1,12-13]. To regulate the diseases, ADAMTS15 degrade and remodel the ECM. The ECM interacts to the cells with component such as integrin to regulate adhesion, proliferation, apoptosis or differentiation [14]. Collagens are the main structure of ECM and classify into type 1, 2, 3, 5, and 7 as fibrillar group and rest of them are non-fibrillar group. Collagen fibrils provide tensile strength to the ECM. The ECM is contained numerous fibrous protein and proteoglycans (PGs) including aggrecan attached glycosaminoglycans (GAGs) side chains [11,15].

The GAGs classified into four groups which were chondroitin sulphates, dermatan sulphates, keratan sulphates, and heparan sulphates [15]. Keratan and chondroitin sulphates bind to aggrecan while heparin sulphates bind to many growth factors, which trap the growth factors in the ECM. To regulate the ECM including organization or degradation, the main component is cleavage process of ECM by proteinase. This

process leads remodeling, releasing growth factors and re-organization as well [11,15]. There were several proteins that had a role to cleavage the ECM or substrate called as proteases.

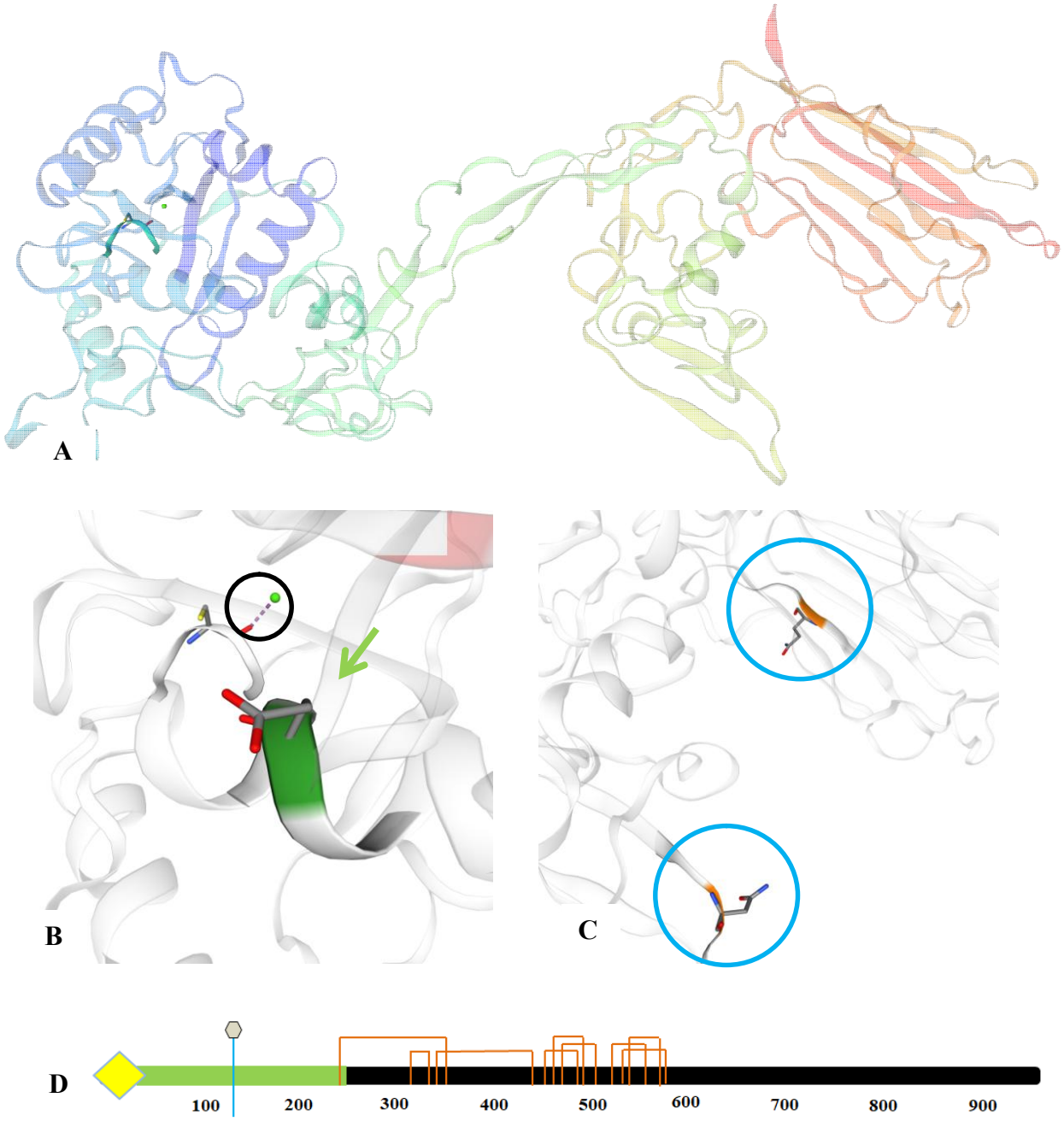

Figure 1. 3D structure of ADAMTS15 performed by swiss model [10] (A), active site (green arrow) interactions with calcium (black circle) (B), two sites of natural variants (blue circles) (C), domain structure and organization of ADAMTS15 encodes 950 aa encodes signal peptide (1-17 aa) (yellow), propeptide (18-212 aa) (green), chain (213-950) (black), and disulfide bond in several sites of sequences (orange) (D)

At first, matrix metalloproteinases (MMPs) are the main protein that has been reported as protease that involved in ECM degradation. Once repairing or remodeling processes were occurred, the activities of MMPs were increased [11]. This protease can degrade all type of ECM protein which has an important role also in organogenesis [16]. In addition, ADAMTS family which classified into 20 types of protein including

ADAMTS15 also can cleavage the ECM substrate especially aggrecan which known as aggrecanases or proteoglycanolytic [2].

4. The Feedback of ADAMTS15 and Noncoding RNA in PROM

Noncoding RNAs (ncRNA) is dominating the RNA total (about 98%) while the mRNA only reaches about 1-2%. The ncRNA is transcribed from introns, promoters, antisense of gene or pseudogenes which may regulate several mechanisms. Although, the ncRNA is not translated mRNA, they can regulate the gene expression of mRNA. Furthermore, ncRNA is divided into two groups which are long (> 200 nucleotides) and short strands (< 200 nucleotides). Short strands are micro RNA (miRNA) while long strands are lncRNA [13,17].

Padang *et al.,* [6] showed that lncRNA is associated with premature rupture of membranes (PROM) and supported ADAMTS15 to increase the expression through inhibiting the miRNA activity. The expression of ADAMTS15 broke down the collagen as substrate which initiated the remodeling processes. In contrast, the expression of ADAMTS15 was low while the collagen was high in patient without PROM condition [6].

The suggested mechanism illustrated in Figure 2. The transcribed ADAMTS15 which located in cytoplasm with miRNA has negative feedback while the ADAMTS15 has positive feedback trough lncRNA. In the non-PROM case, the expression of ADAMTS15 was regulated by miRNA, so the mRNA expression was suppressed, thus low concentration of ADAMTS15 was detected. However, when the ADAMTS15 expressed in PROM patient, lncRNA was increased also which protected the mRNA from miRNA. Furthermore, the expression of ADAMTS15 was detected in high level [6,13]. It leads the biosynthesize of ADAMTS15 protein and degrades the substrate. Degrading substrate was weakening the ECM induced PROM process.

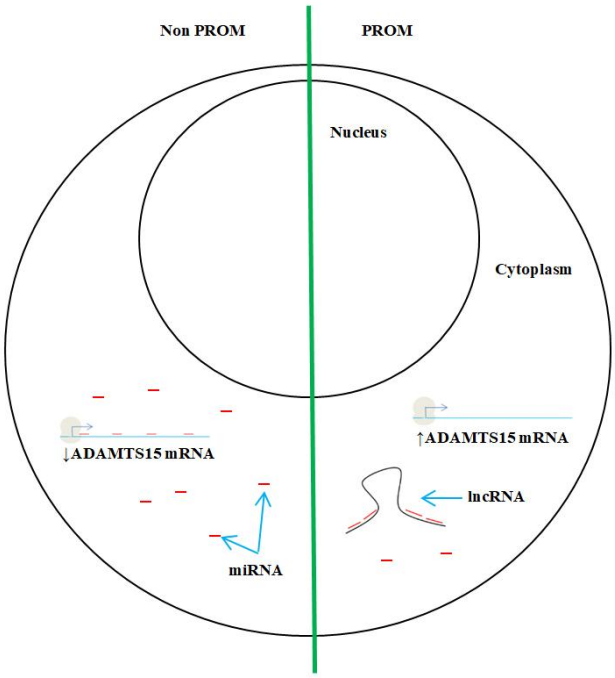

Figure 2. ADAMTS15 expression in patient with or without PROM, left side showed the miRNA regulate the expression of ADAMTS15 while right side showed lncRNA suppressed miRNA activity followed by increasing the ADAMTS15 expression

5. The Role of ADAMTS15 in PROM Disease

Premature rupture of membranes (PROM) leads baby born with immature of organ function caused by the amniotic membrane rupture [18,19]. The PROM often associated with infection of pathogen [20]. Recent study reported that patients with PROM expressed significantly higher of ADAMTS15 compared to patients without PROM [6]. To explain the processes, we served the suggested mechanisms in molecular level when PROM occurred.

Once the pathogen is infected the cell, MMPs family are activated to degrade the ECM such as collagen [12]. The ECM surrounded cells provides structural support, substrate, cell shape, proliferation, differentiation and cell death. The degradation of collagen induces remodelling of substrate structure leading to weakening membrane [21,22]. Furthermore, ADAMTS15 and lncRNA are up-regulated. ADAMTS15 is non-MMPs proteolytic which supported MMPs to break down the ECM substrates [23]. In the normal state of condition, the expression of ADAMTS15 can be regulated by miRNA with suppressing the ADAMTS15 synthesis process. However, the lncRNA suppressed the miRNA activity through binding interaction to form a double helix resulted accumulation of the ADAMTS15 expression [13].

In addition, the increasing STAM gene expression also associated with PROM. The STAM gene is probably involved with PROM through regulation of pro-inflammatory and apoptosis. The increasing expression of pro-inflammatory factors regulated by STAM includes IL-β, IL-6 and TNF-α. Furthermore, the recent study showed that p53 has an important role to induce apoptosis or cell death program in the infected cells [23,24,25]. All of the mechanism induces to oocyte release from follicle and degrades the basement membrane leads to rupture. The suggested mechanism was showed in Figure 3.

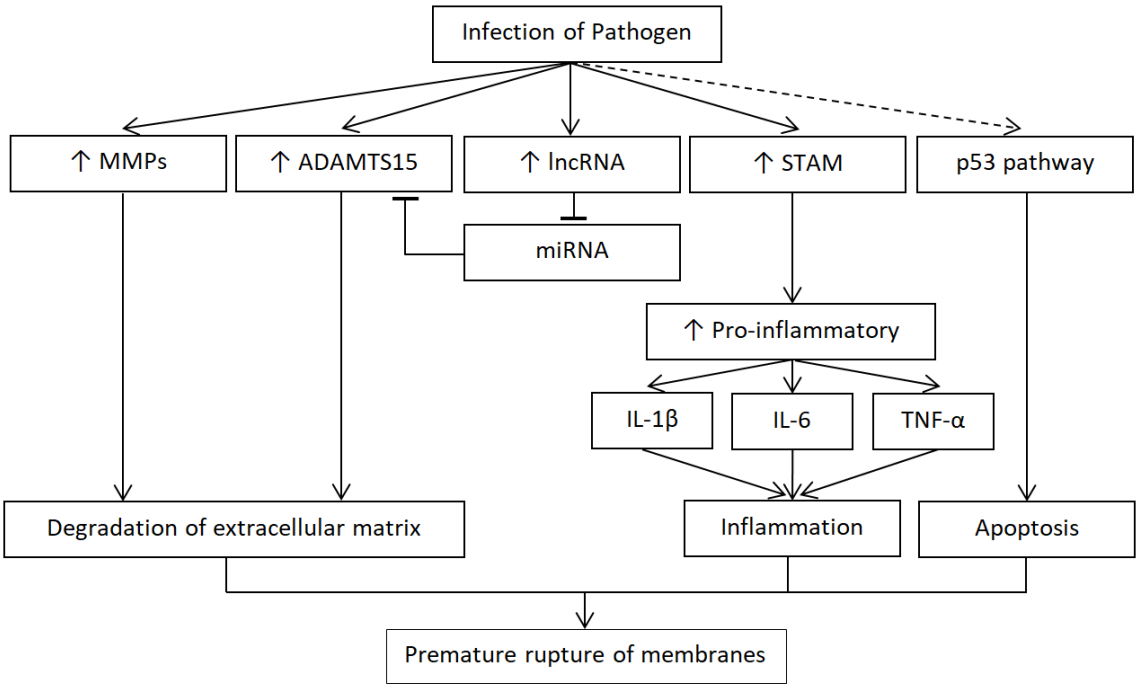

Figure 3. The mechanism premature rupture of membranes caused by infection of pathogen

6. Conclusion

ADAMTS15 is a member of ADAMTS family which are a group of 20 member proteins to regulate the ECM remodelling. The ADAMTS15 play a key role in variety of disease including PROM. Overexpression of ADAMTS15 initiated to increase the PROM process.

7. Abbreviations

ADAMTS : A Disintegrin and Metalloproteinase with Thrombospondin motifs
COMP : cartilage oligomeric matrix protein
vWf : vonWillebrand factor
α2M : α2-Macroglobulin
PROM : premature rupture of membranes
lncRNA : long chains of noncoding RNA
TSP1 : thrombospondin type 1 motif
AA : amino acid
ECM : extracellular matrix
PGs : proteoglycans
GAGs : glycosaminoglycans
MMPs : matrix metalloproteinases
ncRNA : noncoding RNAs
miRNA : micro RNA

8. Conflict of Interests

The authors report no conflict of interests in this work.

9. Acknowledgments

None

10. References

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