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Review Article

Thrombomodulin in skin diseases

Dermatology and Venerology

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ABSTRACT

Background: Thrombomodulin (TM) is a glycoprotein presented as a transmembrane molecule on the surface of the cell. It was originally recognized in vascular endothelium. TM is one of the natural anticoagulant mechanisms. TM has also anti-inflammatory functions in addition to its function in hemostasis. TM is an important cofactor that influences various biological conditions. Inflammatory and thrombotic disorders can display changes in TM expression and its partner proteins. On the other hand, in multiple autoimmune inflammatory disorders, several previous studies have recognized TM as a cofactor. TM was also recognized in other types of the cells rather than the vascular endothelium, including the epidermal keratinocytes. However, the function of TM in the skin and its role in the pathogenesis of skin diseases has been investigated in only a few studies.

Objective: to highlights the recent findings relevant to the role of TM in the skin and some dermatological diseases including psoriasis.

Conclusion: TM has diverse and complex functions other than its role as an anticoagulant protein making it a target in the future for various approaches to the treatment of several inflammatory, proliferative and immune- mediated disorders.

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INTRODUCTION

Thrombomodulin (TM) is a glycoprotein presented as a transmembrane molecule on the surface of the cell. It is expressed predominantly on vascular endothelium [1]. TM has a role in many major biological conditions, including hemostasis-thrombosis, embryogenesis, cancer, and inflammation [2].

STRUCTURE OF THROMBOMODULIN

TM is synthesized from a precursor of signal peptide which is formed of an 18 amino acid. The single chain of mature TM is formed with 557 amino acid residues [2]. Structurally, there are five distinct domains in the mature form of TM: An N-terminal lectin-like domain, epidermal growth factor (EGF)-like domains, an O-glycosylated serine/threonine-rich domain, a transmembrane domain and a short cytoplasmic tail [3] (figure 1).

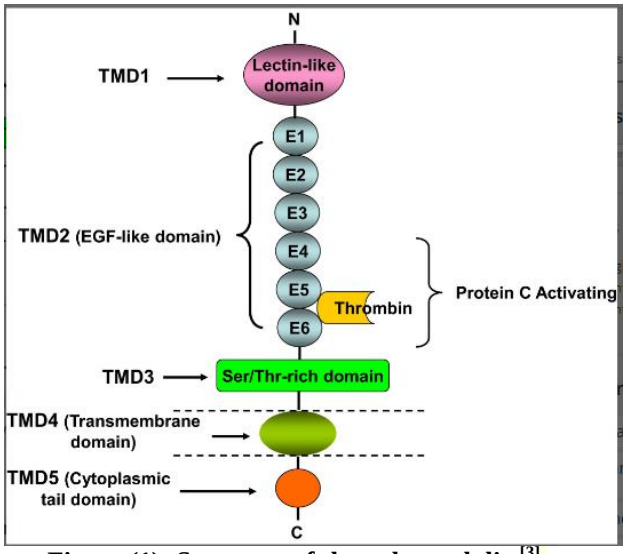

Figure (1): Structure of thrombomodulin [3].

DISTRIBUTION OF THROMBOMODULIN

In all vascular tissues, including lungs, lymphatic vessels, capillaries, and veins, TM is expressed on the surface of vascular endothelium [4]. It has been identified in the gingival epithelium, neutrophils, keratinocytes, monocytes, osteoblasts, dendritic cells, and even platelets. TM has also been found in cultured smooth muscle cells [5]. In plasma and urine, soluble thrombomodulin (sTM) fragments exist. It is produced by proteolysis of TM bound to the cell membrane [2].

FUNCTIONS OF THROMBOMODULIN

- **Anticoagulant function of thrombomodulin**

Tissue factor (TF) initiates the pathway of coagulation and enhances the formation of thrombin through formation of a complex with activated factor VII (FVIIa) [6]. Thrombin plays a crucial role in blood clotting by facilitating the transition of fibrinogen to fibrin. Thrombin also amplifies blood clotting through activation of coagulation factors V and VIII that promote its own generation in a positive feedback manner [7] (figure 2). The epidermal growth factor (EGF)-like domain of TM has a high affinity to thrombin. It forms a complex with thrombin through its 4th and 5th repeats (E45). By binding to thrombomodulin, the affinity of thrombin for FVII, FVIII and fibrinogen, is lost. TM/ thrombin complex also activates protein C (PC), to produce Activated protein C (APC) [8].

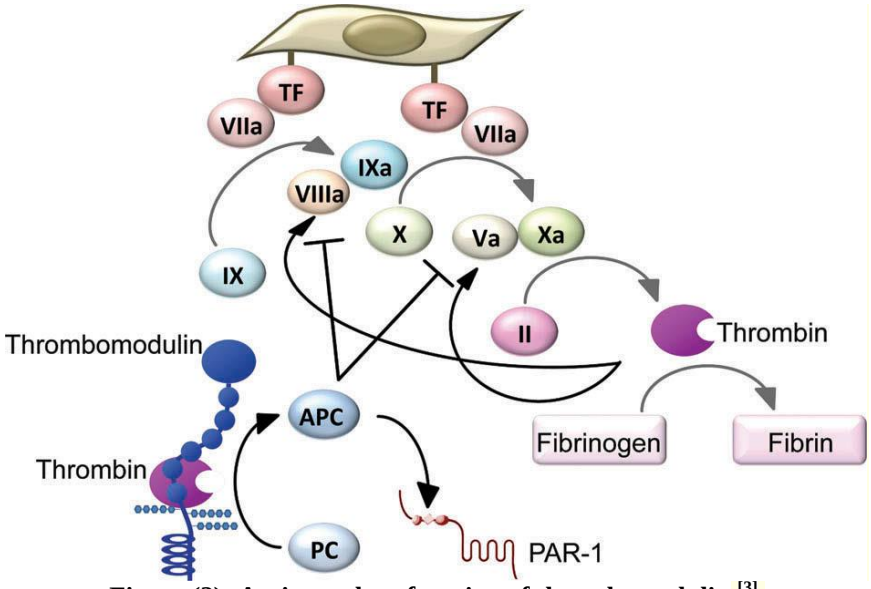

Figure (2): Anticoagulant function of thrombomodulin [3].

APC: Activated protein C; PAR: Protease-activated receptor; PC: Protein C; TF: Tissue factor

- **Anti-inflammatory actions of thrombomodulin**

➢ ***APC-dependent anti-inflammatory actions***

APC cleaves G protein-coupled receptor protease-activated receptor-1 (PAR1) and mediates the pathway of signal transduction, leading to the production of cytoprotective functions independent of its pathway of anticoagulation. Cytoprotective functions include stabilization of epithelial and endothelial barrier, anti-apoptosis, and anti-inflammatory functions [9].

➢ ***APC-independent anti-inflammatory actions***

TM has direct anti-inflammatory activities and Thrombin Activatable Fibrinolysis Inhibitor (TAFI) - based anti-inflammatory functions in addition to its APC-related anti-inflammatory actions. TM can suppress the complements, endotoxin, a representative pathogen- associated molecular pattern (PAMP), and high mobility group Box 1 protein (HMGB1), a prototypical damage associated molecular pattern (DAMP) [3]. Regulation of tm during inflammation:

1. In inflammatory conditions, TM expression on the surface of endothelial cells may be decreased. Via proteolytic cleavage, internalization and transcriptional repression, endotoxin, tumour necrosis factor alpha (TNF-a) and interleukin-1β (IL-1β) all can reduce TM expression [2].
2. ***Transcriptional downregulation of TM:*** Fluid shear stress, low-density lipoprotein (LDL), hypoxia, transforming growth factor beta (TGF-β), free fatty acids and C-reactive protein are factors that transcriptionally downregulate TM [10].
3. ***Transcriptional upregulation of TM:*** TM is transcriptionally upregulated by heat shock. During inflammation and ischemia-reperfusion, stress can cause upregulation of TM that may be significant to counteract forces that can cause reduction of TM expression [2].

ROLE OF THROMBOMODULIN IN SKIN DISEASES

1. **Thrombin/TM complex activates PC, to produce APC** [8].

This conversion is enhanced by endothelial cell PC receptor (EPCR) when binds with PC [11]. APC has the following functions in the skin:

- Protective functions: The normal function of keratinocytes can be reduced by the removal of endogenous PC or APC, with an increase in

programmed cell death and reduction of barrier function. In humans, PC deficiency results in several skin signs, such as ecchymosis and necrosis of skin, as in purpura fulminans. Complete deficiency of PC often results in a life-threatening neonatal fulminant purpura [12].

- Stimulation of Keratinocytes: The proliferation of different cultured cells is stimulated by APC, including keratinocytes. APC shows strong anti-apoptotic properties in accordance with its effects on the cell, as APC stimulates its growth. APC inhibits apoptosis of keratinocytes by reduction of pro-apoptotic factors and activation of anti-apoptotic factors. Migration and proliferation of keratinocytes are important to the normal turnover of the epidermis and maintenance of its function to replace the damaged tissue after injury [13].

- APC promotes the barrier properties of the skin: In cultured keratinocytes, APC reduces paracellular permeability by upregulating and redistributing the tight junction proteins [14].

- APC enhances the immunological properties of the Epidermis. In culture, APC inhibits the inflammatory mediators secreted by keratinocytes. The NF-κB pathway is essential for the induction of different inflammatory genes, including TNF-alpha and cell adhesion molecules. APC inhibits NF-κB activation triggered by calcium and lipopolysaccharide in keratinocytes [15]. A defective epidermal barrier is found in inflammatory skin conditions, such as atopic dermatitis, chronic wounds, and psoriasis, and bullous skin diseases, such as pemphigus and the debilitating and frequently lethal toxic epidermal necrolysis. Thus, APC's cytoprotective properties on keratinocytes position it as an important new treatment for skin diseases related to barrier function disruption and inflammation [16]. Evidence indicates that APC is also successful in the treatment of chronic venous ulcers, diabetic wounds, resistant orthopaedic injuries, pressure sores, and ulcer of pyoderma gangrenosum. APC has also been suggested as a possible treatment for skin diseases, as it can induce re-epithelization, maintenance of the barrier function of the skin and reduce inflammation [17].

2. Thrombomodulin enhances the healing of diabetic wounds

In 15% of diabetic patients, chronic limb ulcer may occur and precede amputations in 84% of diabetic patients [18]. Impaired cutaneous wound healing is one of the important causes of such complication. To date, wound healing remains difficult for diabetes. It is necessary to understand the potential causes of deficient wound healing, and this can contribute to the development of successful treatment [19].

TM has an important role in the differentiation of keratinocytes and the healing of skin injuries [20]. Also, in the initial stage of healing of skin wounds, Toll-like receptors (TLR4) plays a significant role [21]. TM expression increases most obviously after injury in the hyperproliferative epithelium, improving wound healing by increasing the expression of TLR4 on keratinocytes. [19].

High-glucose conditions induce TNF-alpha upregulation through an unexplained mechanism that can lead to a reduction of TM and TLR4 and decrease the production of sTM, resulting in delayed wound healing in diabetic patients [19].

3. TM and Buruli Ulcer

Buruli ulcer (BU) is a subcutaneous infection caused by *Mycobacterium ulcerans* [22]. Various presentations of the disease can occur, including edema, indurated subcutaneous nodules, plaques, and ulcers. The existence of widespread subcutaneous necrosis, because of the cytotoxic action of mycolactone, a macrolide toxin produced by bacteria, is the hallmark of BU disease. Mycolactone may cause a reduction of TM by different mechanisms. The TM/ thrombin complex is internalized by endocytosis in the presence of thrombin and free TM is returned to the surface of the cell [23]. Mycolactone is suggested to cause inappropriate polymerization of actin that could dampen this process [24].

4. TM and psoriasis

There is evidence that the interface between inflammation and coagulation primarily contributes to a variety of diseases [25]. One of these disorders is psoriasis, which is a long- lasting immune-mediated inflammatory disorder (IMID) of the skin that affects around 3 % worldwide [26]. Although it originally affects the skin, researches implicate its relationship with systemic inflammation. This can explain the high incidence of atherosclerosis and cardiovascular disease (CVD) among psoriatic patients [27].

The risk of myocardial infarction (MI) was found to be substantially increased in patients with mild psoriasis, indicating that the risk of CVD was not limited to those with severe disease [28]. A longer period of psoriasis is also associated with an elevated risk of CVD [29]. These data collectively provide proof of psoriasis as an independent risk factor for CVD [30].

Detailed pathophysiological mechanisms leading to atherosclerosis in patients with psoriasis remain uncertain but shared pathophysiological pathways between psoriasis and CVD can explain the increased risk of psoriasis-related CVD [30]. Endothelial cell dysfunction (ED) is one of these pathways [31]. Impairment of endothelial function has already been suggested as a link between chronic systemic inflammatory processes and increased CVD in psoriasis [32].

In the general population, ED has been postulated to represent an initial stage in the pathogenesis of atherosclerosis [33]. ED has also been documented in psoriatic patients by elevated levels of soluble markers of ED or impaired flow-mediated vasodilatation [34]. ED in psoriatic patients may be hypothesized to be a result of the existence of traditional cardiovascular risk

factors. However, there is growing a proof that inflammatory conditions in psoriasis cause systemic effects and lead to ED and pathogenesis of atherosclerosis [32].

The adhesive properties of endothelial cells (ECs) may be impaired by pro inflammatory cytokines and proteases generated by granulocytes, leading to ED causing an increase in the incidence of CVD in psoriasis [34]. Also, IL-12 and IL-17 are of critical significance in the inflammatory microenvironment present in psoriasis [35]. Interestingly, IL-17 has been shown to promote the aggregation of platelets [36], thereby promoting the dissemination of the thrombus. They are known to trigger ED as well [37].

An intact endothelium also offers anti-inflammatory defenses, in addition to an anticoagulant function. Both actions are regulated by PC pathway, which consists of TM /EPCR, abundantly presented on vascular endothelium, and PC, produced in the liver but circulating systemically [8].

Cytoprotective functions of the pathway of protein C are antagonized by ED, caused by inflammation. The development of TM/EPCR/PC complexes is inhibited in different inflammatory conditions due to release of TM and EPCR in a soluble form. This inhibits the anti-inflammatory functions of this pathway [38].

In inflammatory conditions, TM expression on vascular endothelium may also be reduced. Tumor necrosis factor alpha (TNF-α), Endotoxin, and Interleukin-1β (IL-1β) can reduce TM expression via proteolytic release, internalization, and transcriptional expression [2]. Considering the previous data, local tissue hemostasis including TM may play a role in the pathogenesis of psoriasis [39].

5. TM and Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder of unknown etiology, affecting various organs. A complex combination of genetics, hormones, and environment, contributes to dysregulation of the immune system, resulting in the development of autoantibodies, inflammation, and end-organ involvement [40]. Multiple organs affection in SLE is due to inflammation of the blood vessels. This active vasculitis in SLE can be indicated by serum sTM, which is an indicator of endothelial cell damage [41].

Yehia et al., study indicated that SLE patients have higher levels of serum sTM in comparison to control. The highest levels of serum sTM were indicated in those patients with both lupus cerebritis and nephritis. This suggests that sTM was released from vascular endothelial cells via immunologically mediated inflammatory injuries [41].

CONCLUSION

TM has diverse and complex functions other than its role as an anticoagulant protein making it a target in the future for various approaches to the treatment of several inflammatory, proliferative, and immune-mediated disorders.

Conflict of interest: No direct or indirect conflict of interest

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الملخص العربي

دور الثرمبوموديولين فى الأمراض الجلدية

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ملخص البحث

الخلفية: الثرومبومودولين عبارة عن بروتين موجود كجزيء عبر غشاء سطح الخلية وقد تم التعرف عليه في الأصل في بطانة الأوعية الدموية. ويعد الثرومبومودولين وبروتين سي أحد آليات مضادات التخثر الطبيعية كما ان له وظائف مضادة للالتهابات بالإضافة إلى وظيفته كمضاد للتخثر. ويعد الثرومبومودولين عامل مساعد مهم له تأثير على الظروف البيولوجية المختلفة.كما ان الاضطرابات الالتهابية والتخثرية قد تحدث تغييرات في تعبير TM والبروتينات الشريكة له. من ناحية أخرى ، فان العديد من الدراسات السابقة قد اثبتت ان الثرومبومودولين عامل مساعد في العديد من اضطرابات الالتهاب المناعي الذاتي. بالاضافة الى وجود الثرومبومودولين على جدار البطانة الوعائية فقد تم التعرف عليه أيضًا في أنواع أخرى من الخلايا بما في ذلك الخلايا الكيراتينية للجلد. ومع ذلك ، فإن وظيفته في الجلد ودوره في بعض الامراض الجلدية لم يتم البحث فيه الا في دراسات قليلة فقط.

الهدف: تسلط الضوء على النتائج الأخيرة ذات الصلة بدور الثرومبومودولين في الجلد وبعض الأمراض الجلدية بما في ذلك مرض الصدفية.

الأستنتاجات: الثرومبومودولين له وظائف متنوعة ومعقدة بخلاف دوره كبروتين مضاد للتخثر مما يجعله هدفًا في المستقبل لمختلف الطرق لعلاج عدد من الاضطرابات الالتهابية والتكاثرية والمناعة.

كلمات مفتاحية: الصدفية، الامراض الجلدية، مرض الزئبقة الحمراء، الثرومبومودولين

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