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TMEM39A and Human Diseases: A Brief Review

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Transmembrane Protein 39A (TMEM39A) is a member of TMEM family. The understanding about this protein is still limited. The earlier studies indicated that TMEM39A was a key mediator of autoimmune disease. TMEM39A seems to be involved in systemic lupus erythematosus and multiple sclerosis in numerous of populations. All of these works stop at insufficient information by using gene functioning methods such as: Genome-wide association studies (GWASs) and/or follow-up study. It is the fact that the less understood of TMEM39A actually is the attraction to the scientist in near future. In this review the current knowledge about TMEM39A and its possible roles in cell biology, physiology and pathology will be described.

***Key words*:** Transmembrane proteins family, Multiple sclerosis, Systemic lupus erythematosus, Mitochondria, Mitophagy

INTRODUCTION

A transmembrane protein (TMEM) is a kind of integral membrane protein that exists in the total biological membrane. TMEM family is characterized by a presence of putative transmembrane domains (1). Many TMEMs works as gateways to allow the transport of specific elements through the biological membrane. TMEMs repeatedly experience important conformational changes to transfer a substance through the membrane. The understanding about functions and localization of this family is still unclear at the present moments.

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TRANSMEMBRANE PROTEIN FAMILY

TMEMs are predicted to be components of cellular membranes, such as mitochondrial membranes, endoplasmic reticulum (ER), lysosomes and golgi apparatus (2). Indeed, the localization of some protein members was proved by biochemical evidences, including TMEM22 (1) and TMEM45A (3). The functions of several TMEMs in cellular processing were also primarily described. TMEM16A, TMEM16F and TMEM16K were identified as the calcium-activated chloride channel (4,5). Remarkably, TMEM45A firstly was identified as effector of hypoxia condition in 2007 (6). Later on TMEM45A was reported to involve in epidermal keratinization (3). These biological functions implicated that TMEM45A may contribute to cancer development. Indeed, TMEM45A is essential for hypoxia-induced chemo-resistance in breast and liver cancers (7). Consistently, downregulation of TMEM45A suppressed many type of cancers by inhibiting the proliferation, migration and cell invasion. The progression of ductal carcinoma xenografts in situ to invasive breast cancer was dramatically increased by suppressing TMEM45A, which may due to its adhesion regulating effect (8). Similar effects were then observed in ovarian cancer (9) and glioma cells (10). Differential regulation of other TMEM members could be also observed in many cancers, such as

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lymphomas (TMEM176) (11), colorectal cancer (TMEM25) (12), meningiomas (TMEM30B) (13), renal cell carcinoma (different TMEMs) (2,14-20), paragangliomas and pheochromocytomas (TMEM127) (21), suggesting that TMEM family is prominent group for further cancer research. However there are vast different characteristic and localization between the members of TMEMs. Thus, the biological functions of each candidate member need to be elucidated in detail.

TMEM39A- THE FURTHER FOCUS

The function of TMEM39A is poorly identified in the member of TMEMs. It contains 488 amino acid and 8 transmembrane helix segments in its sequence (Based on Uniprot database; Fig. 1A). Employing Singer's classification of proteins, TMEM39A is classified as type 3-transmembrane protein (Fig. 1B) (22). The function of TMEM39A was first revealed in 2010 by the international multiple sclerosis genetics consortium (23). TMEM39A was identified as susceptibility loci of multiple sclerosis. This discovery was again confirmed by Varade *et al* (24). Multiple sclerosis is the most common neurological disease among young adults, with onset at a mean age of 30 years. It is an autoimmune condition of the central nervous system affecting over 2 million individuals world-wide (23,24). By also using a genome-wide association (GWA) study, recent studies indicated that TMEM39A involved in Erythematosus, which is considered as autoimmune disease (25-27). These impli-

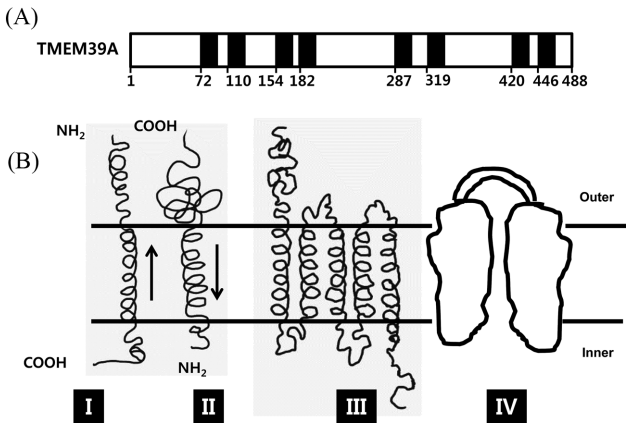

Fig. 1. TMEM39A is predicted as type III membrane protein. (A) Schematic of TMEM39A topology analyzing in Uniprot database. TMEM39A contains eight transmembrane domains starting at residues: 72, 110, 154, 182, 287, 319, 420, 446. (B) The topography of the four main types (I-IV) of integral membrane proteins. The external and cytoplasmic surfaces of the membrane are designated by outer and inner respectively. (Adopted from (22)).

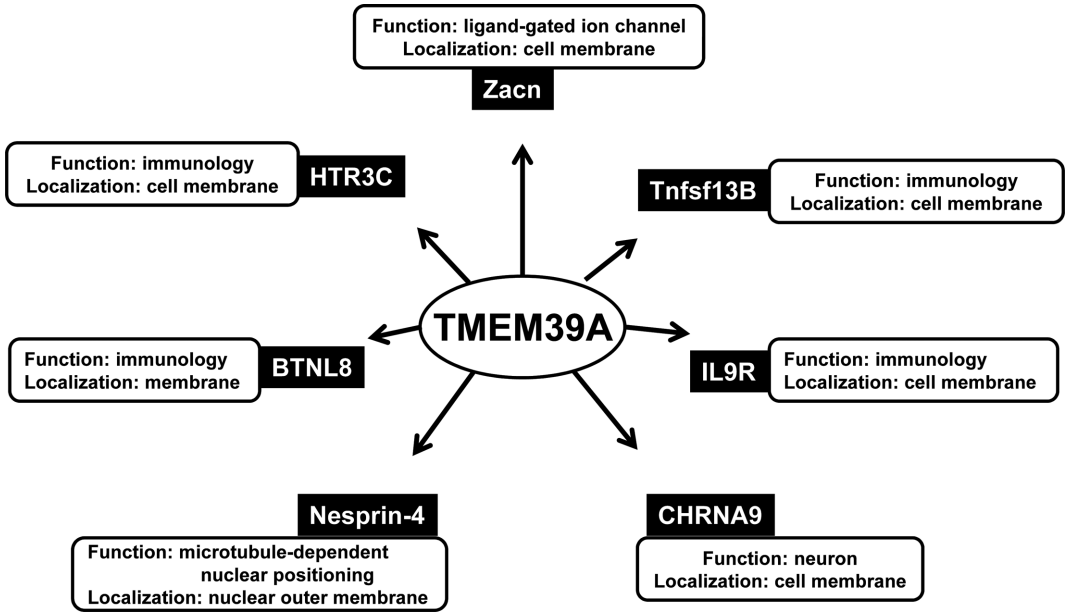

Fig. 2. The network showing interactions of TMEM39A with its interactors. TMEM39A was found to be interacted with several protein baits (28). The major function and localization of each interactor were also investigated. Among seven interactor, five proteins including Zacn, Tnfsf13B, IL9R, CHRNA9 and HTR3C are located in cell membrane. Nesprin-4 locates to nuclear outer membrane and BTNL8 is just predicted to be in membrane. Regarding to the functions of those interactors, there are 4 proteins involved in immunology includingTnfsf13B, IL9R, BTNL8, and HTR3C. Other proteins have the following function; Zacn - ion channel, CHRNA9 - neuron development, Nesprin-4 - nuclear positioning. (BTNL8: Butyrophilin-like protein 8, CHRNA9: Neuronal acetylcholine receptor subunit alpha-9, HTR3C: 5-hydroxytryptamine receptor 3C, IL9R: Interleukin-9 receptor, Tnfsf13b: Tumor necrosis factor ligand superfamily member 13B, Zacn: Zinc-activated ligand-gated ion channel).

cated that TMEM39A had an important contribution in immune system such as: inflammation, dysregulated type 1 interferon responses, and autoantibodies directed to the nuclear compartment which were characteristics of erythematosus. TMEM39A was found to be bound to seven baits (Fig. 2) (28). Among all the baits, Tumor necrosis factor ligand superfamily member 13B (Tnfsf13B), Butyrophilin-like protein 8 (BTNL8) and 5-hydroxytryptamine receptor 3C (HTR3C), Interleukin-9 receptor (IL9R) were involved in immune system. Thus the further study is required to demonstrate the molecular mechanism of TMEM39A in immune response.

TMEM39A was significantly changed in sclerosis-a neurological disease. Cholinergic receptor nicotinic alpha 9 subunit (CHRNA9), an interactor of TMEM39A (29), also functioned in neuronal activity. In brain, the functions, dynamics and homeostasis of mitochondria are really important and associating with several neuronal disorder diseases. Mitochondria dose not only provide ATP but also perform a variety of roles in processes such as the transduction of metabolic and stress signals. Thereby mitochondria was a factor deciding the cell fate. The quality and quantity controls of mitochondrial thus were highlighted. Mitophagy, a key process to remove damaged mitochondria, was well known to be regulated by Pink/Parkin pathway which linked to the neurodegenerative diseases. Mutations in these protein encoded-genes defected mitophagy leading to accumulation of damage mitochondria, resulting in neuronal cell death (30). Taken these evidences raised a question that: is there any contribution of TMEM39A in mitochondria, mitophagy and other molecular signaling in neuron? Indeed, image-based genome-wide siRNA screen study showed that TMEM39 was potential factor involved in Parkin-mediated mitophagy (31). However the molecular mechanism for this phenomenon has not been provided yet. In addition, it has been found that TMEM39A was mutated in breast cancer (32). Moreover, mitophagy and mitochondria were considered as the important modulators of tumorigenesis and development (33-35). Note that in TMEM family, TMEM59 was known as regulator of neuron stem cell during differentiation (36) as well as an Alzheimer's related protein (37,38). Interestingly, Emilio et al. showed that TMEM59 binds to ATG16L and promotes local activation LC3 (39). This indicated for a connection between a trans-membrane protein with autophagy and neuronal disease that can also be happened in case of TMEM39A. From these all information, the relationship between TMEM39A and brain tumor-GBM, autophagy may become a good point for further study.

In other aspect, the discovery of TMEM39A role in mitochondria pointed that intracellular location of TMEM39A is now also in needed and mitochondria might be a possibility. However five of seven interactors identified by Huntlin *et al*. (28) were cell membrane proteins or were predicted to be cell membrane proteins (Fig. 2). This implicates that TMEM39A may be in cell membrane and thus may have more change to interact with those interactors.

CONCLUSION REMARKS

The function of TMEM39A is poorly understood. There is no biochemical evidence to bring this protein into the brightness. However, the genetic studies have discovered that TMEM39A may contribute to Multiple Sclerosis and Erythematosus, the autoimmune diseases. Base on all of our knowledge about TMEM39A, this review has described and connected its characteristics with cellular biology topics, therefore providing some promising points for TMEM39A study in future:

1. The molecular mechanism of TMEM39A in regulating the autoimmune diseases. Investigation of some of TMEM39A interactors such as Tnfsf13B, BTNL8 and HTR3C, IL9R might provide the interesting results with TMEM39A in autoimmune diseases.
2. The function of TMEM39A in mitochondria and mitophagy has been suggested. Thus, the further study on the effects of TMEM39A on mitophagy in neurobiology and brain cancer will be required.
3. The exact localization of TMEM39A is urgently required to investigate the function of TMEM39A. TMEM39A might localize to plasma membrane since most of its interactors are plasma membrane proteins. However mitochondrial localization of TMEM39A is also possible, due to the effects of TMEM39A on mitophagy.

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