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Mini-Review

The membrane-associated progesterone receptor (MAPR) protein family

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ABSTRACT

The membrane-associated progesterone receptor (MAPR) protein family comprises of four members, progesterone receptor membrane component 1 (PGRMC) 1, PGRMC2, Neudesin, and Neuferricin/ Cytochrome b5 domain containing 2 (CYB5D2), each with a conserved cytochrome b5-like heme-binding domain of ~100 amino acids. The heme-binding domain, which actually binds heme, is required for their activities. However, the members differ greatly in their functions and action mechanisms. PGRMC1 is the original member of the family. PGRMC1 and PGRMC2 are membrane-bound proteins that are mainly located at the endoplasmic reticulum. In contrast, Neudesin and Neuferricin/CYB5D2 are secreted proteins. *PGRMC1* and *PGRMC2* were possibly generated from a common ancestral gene. However, *Neudesin* and *Neuferricin*/*CYB5D2* are not evolutionarily related to the other members. PGRMC1 promotes cell survival and damage resistance in cancer cells. PGRMC1 and PGRMC2 are a target for therapeutic intervention in cancers and a potential biomarker of breast adenocarcinoma staging, respectively. PGRMC1 might play roles in lipid, drug, and hormone metabolism in the liver and neuroprotection in the brain. PGRMC2 might play roles in neuroendocrine functions in the brain. Neudesin promotes neural differentiation and proliferation in cultured neural precursor cells. Neudesin might also play a role in breast tumorigenesis. Neuferricin/CYB5D2 promotes neurogenesis and suppresses proliferation and survival in cultured neuronal cells. Neuferricin/ CYB5D2 also enhances cultured the survival of HeLa cells exposed to etoposide. *Neudesin* knockout mice are protected against high-fat diet-induced obesity, indicating that Neudesin plays roles in energy metabolism. However, as other knockout mice have not been reported, their physiological functions remain unclear.

KEYWORDS: heme, cytochrome b5, MAPR, PGRMC, Neudesin, Neuferricin, CYB5D2, P450

INTRODUCTION

The membrane-associated progesterone receptor (MAPR) protein family comprises of four members, progesterone receptor membrane component 1 (PGRMC) 1, PGRMC2, Neudesin, and Neuferricin/ Cytochrome b5 domain containing 2 (CYB5D2), each with a conserved cytochrome b5-like heme-binding domain of ~100 amino acids [1-4]. The heme-binding domain, which actually binds heme, is required for their activities. However, the members differ greatly in their functions and action mechanisms. PGRMC1 is the original member of the MAPR protein family. However, PGRMC1 does not bind directly to progesterone and has no homology with steroid receptors [1, 2, 5]. PGRMC1 is a membrane-bound protein that is mainly located at the endoplasmic reticulum. PGRMC1 promotes cell survival and damage resistance in cancer cells. PGRMC1 is a target for

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therapeutic intervention in cancers. PGRMC1 might play roles in lipid, drug, and hormone metabolism in the liver and neuroprotection in the brain [1, 2, 5]. Two excellent reviews on PGRMC1 have been published [1, 2]. In this article, we briefly review the MAPR family, focusing on their possible evolutionary history, characteristic structural features, functions, and action mechanisms.

Gene organization and evolutionary history

A BLAST (Basic Local Alignment Search Tool) search of the human genome at the National Center for Biotechnology Information (NCBI) website has indicated that the human MAPR family comprises only of the four members, PGRMC1, PGRMC2, Neudesin, and Neuferricin/ CYB5D2 (Ohta *et al*., unpublished observation). The human *PGRMC1* and *PGRMC2* genes are located at Xq24 and 4q28.2, respectively. No conserved synteny has been observed (data not shown). *PGRMC1* and *PGRMC2* have two and three introns in their coding regions, respectively (Figure 1). The positions of two introns are conserved in the heme-binding domains of *PGRMC1* and *PGMRC2*. *PGRMC2* has an additional intron. These results indicate that *PGRMC1* and *PGRMC2* were generated from a common ancestral gene by a gene duplication event.

Neudesin and Neuferricin/CYB5D2 also have the characteristic b5-like heme-binding domain (Figure 1). The human *Neudesin* and *Neuferricin*/ *CYB5D2* genes are located at 1q32.3 and 17p13.2, respectively (Figure 1). *Neudesin* and *Neuferricin*/ *CYB5D2* have three and four introns in their coding regions, respectively (Figure 1). Their intron positions are not conserved, indicating no evolutionary relationship between *Neudesin* and *Neuferricin*/*CYB5D2*.

PGRMC1 orthologues have been identified in unicellular eukaryotes including *Saccharomyces cerevisiae* to vertebrates including humans and mice [1]. *PGRMC2*, *Neudesin*, and *Nefferricin*/ *CYB5D2* orthologues have also been identified in many vertebrates (Ensemble Genome Browser). However, *PGRMC2*, *Neudesin*, and *Nefferricin*/ *CYB5D2* orthologues in unicellular eukaryotes and invertebrates have not been identified.

Characteristic structural features

PGRMC1 and PGRMC2 are intracellular membrane-bound proteins with a transmembrane domain. In contrast, Neudesin and Neuferricin/CYB5D2 are secreted proteins with a typical N-terminal secrected signal sequence (Figure 1). Amino acid sequences of the heme-binding domain of PGRMC1 and PGRMC2 are highly conserved

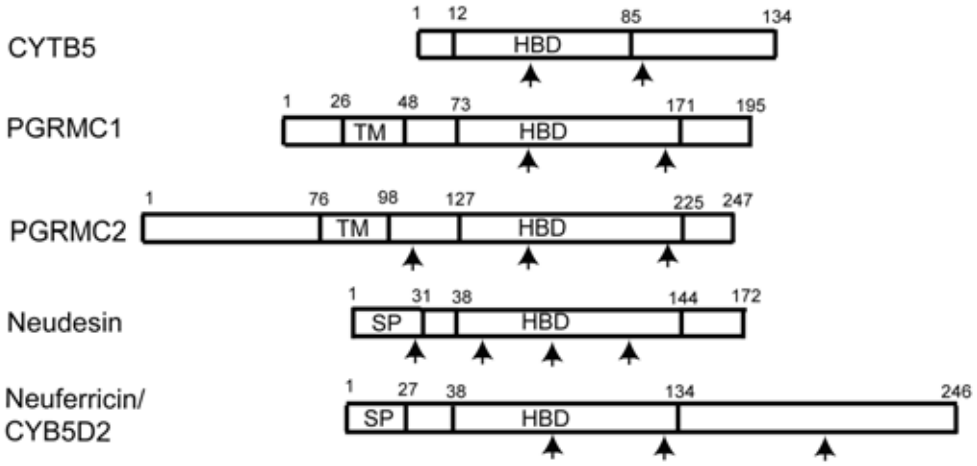

Figure 1. Schematic representations of human cytochrome b5 and the human MAPR family. PGRMC1, PGRMC2, Neudesin, and Neuferricin/CYB5D2 but not cytochrome b5 (CYTB5) are members of the MAPR family. TM, HBD, and SP indicate a transmembrane domain, a heme-binding domain, and a cleavable secreted signal sequence peptide, respectively. The numbers refer to amino acid positions. Arrows indicate the positions of introns.

(73% identity) (Figure 2). Amino acid sequences of the heme-binding domains of human Neudesin and Neuferricin/CYB5D2 are also significantly conserved (36% identity). In addition, the amino acid sequence of human Neudesin is also significantly similar (40% identity) to that of human PGRMC1. In contrast, the amino acid sequence of the heme-binding domain of cytochrome b5 is not significantly similar (15~22% identity) to those of the MAPR family proteins. Cytochrome b5 has two conserved heme-coordinating histidine residues. In contrast, the MAPR family members lack these histidine residues (Figure 2) [5]. These results indicate that cytochrome b5 is not a member of the MAPR family. However, the MAPR proteins bind heme. The heme-binding of the MAPR family is required for their biochemical activities [1-4].

Localization and function

PGRMC1 and PGRMC2

PGRMC1 and *PGRMC2* are ubiquitously expressed in various tissues [6, 7]. The potential functions of PGRMC1 have been extensively described in two excellent reviews [1, 2]. PGRMC1 and PGRMC2 are mainly located at the endoplasmic reticulum [1]. *PGRMC1* expression is increased in cancer cells. PGRMC1 promotes cell survival and damage resistance in cancer cells. PGRMC1 is a target for therapeutic intervention in cancers [2]. Hepatic PGRMC1 also might play roles in lipid, drug and hormone metabolism. *PGRMC1* in the brain is induced by progesterone after brain injury. PGRMC1 might play roles in neuroprotection [2]. The neuroanatomical expression profiles of *PGRMC2* in the brain indicate its potential roles in neuroendocrine functions [8]. *PGRMC2* is also expressed in breast adenocarcinoma. PGRMC2 is a potential biomarker of breast adenocarcinoma staging [9].

Neudesin and Neuferricin/CYB5D2

Neudesin and *Neuferricin/CYB5D2* are expressed in neural tissues at embryonic stages and widely expressed in adult tissues [3, 4, 10]. Neudesin promotes neuronal differentiation and proliferation in neural precursor cells [10, 11]. Neudesin also suppresses adiogenesis in 3T3-L1 cells [12]. *Neudesin* knockout mice, which are apparently normal and fertile, are protected against high-fat diet-induced obesity, indicating that Neudesin

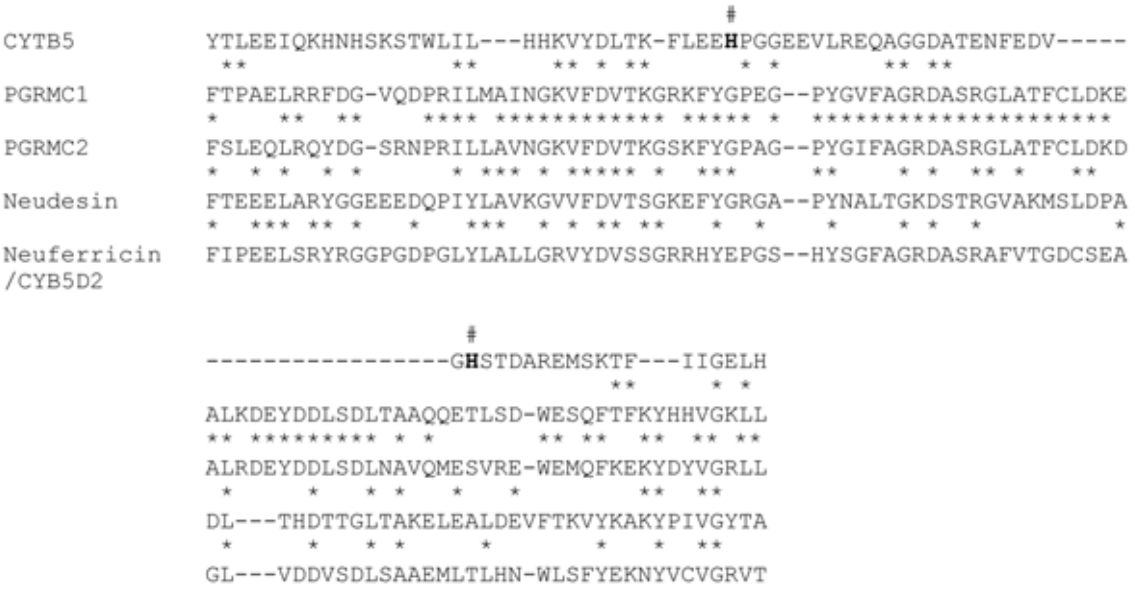

Figure 2. Comparison of amino acid sequences of the b5-like heme-binding domains of human cytochrome b5 and the human MAPR family. Dashes indicate gaps introduced to align sequences. Asterisks indicate identical amino acid residues in the sequences. Sharps indicate two conserved heme-coordinating histidine residues in CYTB5.

plays roles in energy metabolism (Ohta *et al*., unpublished observation). *Neudesin* is also over-expressed in primary breast tumors. The ectopic expression of *Neudesin* in MCF7 cells promotes the invasiveness. These indicate that Neudesin might play a role in breast tumorigenesis [13]. Neuferricin/CYB5D2 promotes neurogenesis in neural precursor cells and suppresses cell survival in Neuro2a cells [4]. Neuferricin/CYB5D2 also enhances the survival of HeLa cells exposed to etoposide [14].

Action mechanism

PGRMC1 and PGRMC2

Heme-binding is thought to be the sole biochemical activity of PGRMC1. PGRMC1-associated progesterone binding is functionally important in cancers [2]. Epidermal growth factor receptor (EGFR) is associated with cancer progression. PGRMC1 increases plasma membrane EGFR levels and co-precipitates with EGFR. PGRMC1 promotes several cancer phenotypes at least in part by binding and stabilizing EGFR [15]. PGRMC1 directly binds to P450 proteins. By the direct binding, PGRMC1 plays roles in lipid, drug and hormone metabolism [2]. The 3'-untranslated region of *PGRMC1* contains conserved binding sites for the microRNA let-7/miR-98. *PGRMC1* expression is regulated by let-7/miR-98 [16]. In contrast, the mechanism of action of PGRMC2 remains unclear.

Neudesin and Neuferricin/CYB5D2

The activity of Neudesin is significantly enhanced by the binding of heme [3, 4] (Kimura *et al*., 2008; Kimura *et al*., 2010). Neudesin activates the protein kinase A (PKA), phosphatidylinositol-3 kinase (PI-3K), and mitogen-activated protein, kinase (MAPK) pathways [10-12]. The activity of Neuferricin/CYB5D2 is also significantly enhanced by the binding of heme [4]. However, its action mechanism remains unclear.

Frontier

The MAPR family has a conserved b5-like heme-binding domain. The binding of heme is required for their activities. However, the mechanism of action of PGRMC1 and PGRMC2 is quite distinct from that of Neudesin and Neuferricin/CYB5D2 as described above. With further study, PGRMC1 and PGRMC2 should become useful targets for therapeutic intervention in cancers or useful biomarkers of cancers. Neudesin activates intracellular signaling pathways by activating its cell-surface receptor. Identification of the Neudecin receptor will greatly facilitate elucidation of its action mechanism. Studies with *Neudesin* knockout mice indicate that Neudesin plays roles in energy metabolism. Other knockout mice have not been reported. The generation and analysis of relevant knockout mice will reveal their physiological functions.

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