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Invited review article

Plectin-related skin diseases

Ken Natsuga *

Department of Dermatology, Hokkaido University Graduate School of Medicine, North 15 West 7, Sapporo 060-8638, Japan

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ABSTRACT

Plectin has been characterized as a linker protein that is expressed in many cell types and is distinctive in various isoforms in the N-terminus and around the rod domain due to complicated alternative splicing of *PLEC*, the gene encoding plectin. Plectin deficiency causes autosomal recessive epidermolysis bullosa simplex (EBS) with involvement of the skin and other organs, such as muscle and gastrointestinal tract, depending on the expression pattern of the defective protein. In addition, a point mutation in the rod domain of plectin leads to autosomal dominant EBS, called as EBS-Ogna. Plectin can be targeted by circulating autoantibodies in subepidermal autoimmune blistering diseases. This review summarizes plectin-related skin diseases, from congenital to autoimmune disorders.

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1. Introduction

Plectin is a versatile linker protein that is expressed ubiquitously in many tissues, including skin, muscle and tissues of the nervous system. Plectin was originally characterized as an intermediate filament (IF)-linker protein, but it also serves as a binding partner to actin, microtubules and other membranous proteins, including hemidesmosomes and focal contact proteins [1,2]. In studies of plectin, the complexity mostly derives from the diversity of its isoforms. In humans, several splicing transcripts at the 5′ end of *PLEC*, which encodes plectin, lead to plectin 1 and 1a to 1 g isoforms in which the first coding exons are mutually distinct (Fig. 1) (Table 1) [3]. Each isoform tends to have a preference for cell-type-specific or organelle-specific expression: isoform 1 for nucleus/ER membrane [4], 1a for hemidesmosomes in epidermal keratinocytes [5], 1b for mitochondria [4,6], 1c for microtubules [7], 1d for the Z-disk in skeletal muscle [8] and 1f for focal adhesion contacts [4]. It is noteworthy that the nomenclature of *PLEC* mutations is based on the numbering of the coding sequences of transcript variant 1 (NM_000445), which encodes plectin 1c [9], unless the mutations occur in the other isoform-specific first coding exons (e.g., exon 1a, exon 1f) [10,11]. In addition to 5′ splicing diversity, exon 31 of *PLEC*, which encodes the rod domain of plectin, can be spliced out in the rodless transcripts (Fig. 2) [12]. The basic biology of plectin has been recently reviewed from Dr. Wiche's group [1,2], and he and his collaborators have greatly contributed to this field. Accordingly, this review focuses on the pathological aspects of plectin in skin diseases, such as in congenital and autoimmune blistering diseases.

2. Epidermolysis bullosa

Epidermolysis bullosa (EB) is a heterogeneous group of disorders characterized by congenital skin fragility and blister

* Tel.: +81 11 716 1161, ext 5962; fax: +81 11 706 7820.
E-mail address: natsuga@med.hokudai.ac.jp

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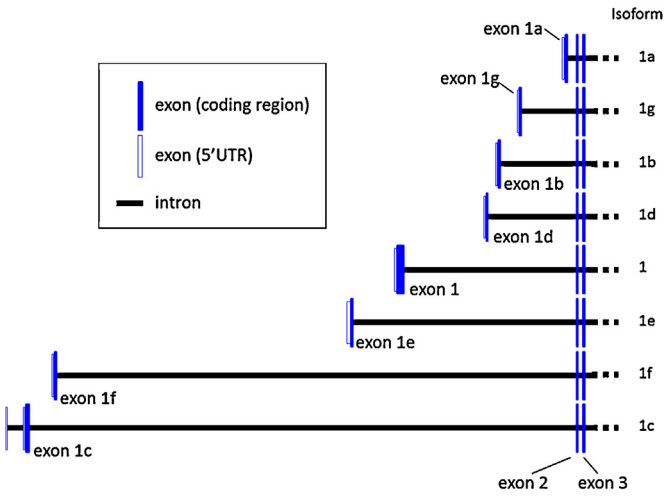

Fig. 1. *5′ End transcript variants of PLEC and isoform-specific first coding exons.* Transcript variants and their encoding isoforms with RefSeq numbers (NM_. . ., NP_. . .) are depicted. See also Table 1 for RefSeq numbers and numbering for transcript variants (1–3, 6–8, 10, 11). The first coding exon is named after its coding isoform (e.g., exon 1a for isoform 1a).

Table 1
Human plectin isoforms and transcript variants listed in NCBI RefSeq.

Isoform (RefSeq no)	Transcript variant (Tv) (RefSeq no)
Isoform 1 (NP_958782)	Tv 6 (NM_201380)
Isoform 1a (NP_958786)	Tv 11 (NM_20384)
Isoform 1b (NP_958784)	Tv 8 (NM_201382)
Isoform 1c (NP_00436)	Tv 1 (NM_00445)
Isoform 1d (NP_958783)	Tv 7 (NM_201381)
Isoform 1e (NP_201379)	Tv 3 (NM_201379)
Isoform 1f (NP_958780)	Tv 2 (NM_201378)
Isoform 1 g (NP_958785)	Tv 10 (NM_201383)

formation. Mutations in the genes encoding basement-membrane-zone (BMZ) proteins or other junctional proteins are responsible for EB phenotypes. EB has three major types and one minor type, depending on the ultrastructural level of skin detachment: EB simplex (EBS; cell lysis of basal or spinous layers), junctional EB (JEB; skin separation at the lamina lucida), dystrophic EB (DEB; skin separation under the lamina densa) and Kindler syndrome (mixed pattern) [13]. EBS is further subcategorized into basal and suprabasal EBS, based on the level of skin split. The newest classification of EB lists five genes (*KRT5*, *KRT14*, *EXPH5*, *DST* and *PLEC*) that are responsible for basal EBS [13]. Mutations in *PLEC* cause three distinct subtypes of basal EBS: EBS with muscular dystrophy (EBS-MD), EBS with pyloric atresia (EBS-PA) and EBS-Ogna.

2.1. EBS-MD

The cutaneous manifestations of EBS-MD are congenital skin fragility and nail dystrophy. The skin fragility can be so subtle that it is sometimes overlooked until muscular symptoms develop. The onset of the MD varies among patients, from birth until their forties. Respiratory complications due to MD can be fatal in those patients. In addition to MD, myasthesia syndrome (MyS) has been documented in a few EBS cases [14,15]. In patients with EBS-MD-MyS, defects of neuromuscular transmission have been demonstrated. However, the EBS-MD-MyS subtype was not included in the newest EB classification [13]. MyS symptoms might be often overlooked due to the MD manifestations [15]. Whether EBS-MD-MyS is really a specific phenotype should be determined by further case descriptions in the future.

In 1996, several groups reported *PLEC* mutations in EBS-MD cases [16–20]. Since then, more than 30 patients have been described in the literature (Table 2). Of note, most of the EBS-MD patients harboured heterozygous or homozygous truncation mutations in exon 31 of *PLEC*, which encodes the rod domain of plectin (Fig. 2) [21–23]. Hence, the rodless plectin isoform is generally expressed in the tissues of EBS-MD patients whereas full-length plectin is deficient. The ratio of full-length to rodless transcripts is estimated at 10:1 in skin, although it is possible that the amount of rodless plectin isoform is comparable to that of the full-length isoform in human skeletal muscle [22]. This quantitative difference in rodless plectin between skin and muscle might account for the relatively delayed onset of MD symptoms, whereas skin fragility is typically found in infancy.

However, a few EBS-MD cases were found not to harbour any *PLEC* mutations in exon 31 [22]. All these cases harboured heterozygous or homozygous in-frame amino acid deletions/insertions in the N-terminal domain of plectin, where the actin-binding domain (ABD) and spectrin repeats are conserved [19,24,25]. ABD and spectrin repeats of plectin bind to integrin β4 and type XVII collagen (COL17) [26,27]. It is possible that the binding deficits with plectin partners may underlie the skin fragility in these cases. Otherwise, it may be that in-frame deletions/insertions of plectin cause protein instability or aggregation [24].

It has been hypothesized that plectin isoform-specific mutations cause phenotypes in the tissues that express the isoform [9]. This was true in one case of limb-girdle muscular dystrophy (LGMD) with mutations in exon 1f of *PLEC*, which encodes the plectin 1f isoform (Fig. 1), that are mainly expressed in muscle [10]. Exome sequencing on EB patients whose mutations were not detected by conventional Sanger sequencing identified an EBS patient with homozygous mutations in exon 1a of *PLEC*, which encodes the N-terminus of the plectin 1a isoform (Fig. 1) [11]. Intriguingly, the patient was described as being hypotonic, even

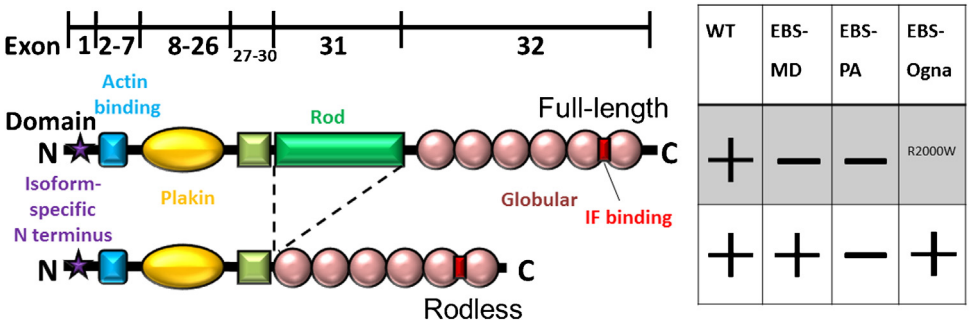

Fig. 2. *Full-length and rodless plectin structure and plectin expression patterns in EBS.* The rodless isoforms are produced through alternative splicing of exon 31, which encodes the rod domain. In the wild type (WT), the tissue expresses full-length and rodless plectin. EBS-MD typically lacks full-length plectin with the maintenance of the rodless isoform, whereas EBS-PA has neither full-length nor rodless plectin. EBS-Ogna is heterozygous for p.Arg2000Trp (R2000W) in the rod domain.