Skin diseases with loss of desmosomal cell-cell adhesion in mammals

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1. Trans-interaction between desmosomal cadherins

Desmosomes are membrane plaques that play an important role in cell-cell adhesion between adjacent cells. The intercellular attachments of desmosomes are formed by two types of desmosomal cadherin-type cell adhesion molecules: desmogleins (Dsgs) and desmocollins (Dscs) [1].

In canine epidermis, Dsg1 is expressed throughout the epidermis, while Dsg3 is expressed in the basal and immediate suprabasal layers [2, 3]. Dsc1 is expressed predominantly in the granular layer of the epidermis. On the contrary, in the canine oral mucous membrane, Dsg3 is expressed throughout the epithelia, while Dsg1 is expressed in the suprabasal epithelia but is minimal or absent in the basal layer. Dsc1 expression is not recognised in oral mucous membranes.

It has been hypothesised that Dsg1 and Dsg3 mediate homophilic trans-interaction when they are expressed in adjacent cells [1]. Therefore, if Dsg1 and Dsg3 are expressed on the same cell (e.g. suprabasal epidermis), loss of adhesive function mediated by either Dsg1 or Dsg3 can be compensated by another Dsg (Dsg compensation theory)[1]. Meanwhile, recent studies indicated that Dsg and Dsc mediate heterophilic trans-interaction in adjacent cells [4, 5]. These findings may provide another theory. If Dsg1 and Dsc1 are expressed on the same cell (e.g. the granular layer of epidermis), loss of adhesive function mediated by either Dsg1 or Dsc1 is sufficient to initiate cell separation.

2. Diseases with loss of desmosomal cell-cell adhesion by autoantibodies

Pemphigus is a group of vesiculopustular or vesiculobullous diseases of the skin and mucous membranes caused by autoantibodies against desmosomal cadherins. Pemphigus is classified into two major subtypes: pemphigus vulgaris (PV), pemphigus foliaceus (PF) and paraneoplastic pemphigus (PNP). PV is further classified into mucosal-dominant type PV, which is characterised by predominant mucosal involvement with minimal skin involvement, and mucocutaneous type PV, in which both skin and mucous membranes are involved[1].

In humans, circulating IgG autoantibodies in mucosal-dominant type PV target Dsg3, while those in mucocutaneous type PV target both Dsg3 and Dsg1. Circulating IgG autoantibodies in human PF target Dsg1 alone [6, 7]. In human PNP, circulating anti-Dsg3 IgG and anti-Dsg1 IgG are detected in conjunction with anti-plakin IgG [8].

To date, the autoimmune targets of the following diseases in companion and domestic animals have been identified:

2.1 PV in dogs

PV is a blistering disease affecting the skin and mucous membranes that consists of stratified squamous epithelia. Most dogs with PV have involvement of the oral mucous membranes, while some cases exhibit lesions in the skin and/or mucocutaneous junctions.

In the early 2000s, circulating IgG autoantibodies against a 130-kDa protein corresponding to Dsg3 in canine PV have been demonstrated by immunoblotting [9] and immunoprecipitation-immunoblotting [10]. Following these studies, it has been reported that circulating IgG autoantibodies against canine Dsg3 were recognised in 3/5 dogs with PV, including two mucocutaneous type PV and one mucosal-dominant type of PV [2]. The two mucocutaneous type PV also have circulating anti-canine Dsg1 IgG [2]. Moreover, the same study reported that the circulating IgG dissociated the cell-cell adhesion of cultured keratinocytes, and depletion of anti-Dsg3 IgG from those sera blocked the dissociation [2]. Furthermore, an enzyme-linked immunosorbent assay revealed that circulating anti-canine Dsg3 IgG autoantibodies were recognised in 11/14 (78.6%) of dogs with PV [11]. These findings suggest that canine PV is homologous to the corresponding human disease, in which circulating anti-Dsg3 IgG autoantibodies lead to the loss of keratinocyte cell-cell adhesion.

2.2 PV in a horse

The autoimmune target of equine PV has been identified in a 9-year-old Welsh pony stallion with blisters and erosions in the skin and oral mucous membranes. Direct immunofluorescence revealed the presence of IgG autoantibodies bound to the plasma membrane of keratinocytes. Immunoprecipitation-immunoblotting revealed that the horse had circulating IgG autoantibodies against a 135-kDa protein labelled by anti-Dsg monoclonal antibody, and against recombinant canine Dsg3 [12]. This was the first evidence of equine PV with anti-Dsg3 IgG autoantibodies, as similarly seen in the corresponding human disease.

2.3 PNP in a dog

PNP is a rare autoimmune blistering disease associated mainly with lymphocytic neoplasia. To date, only four PNP cases in companion animals have been reported. Circulating anti-Dsg3 IgG autoantibodies have been reported in one dog with splenic sarcoma. The canine PNP serum also dissociated cultured keratinocytes, and depletion of anti-Dsg3 IgG from the serum blocked this dissociation [2]. Therefore, the anti-Dsg3 IgG in canine PNP may play a primary role in the dissociation of keratinocytes, a histopathological hallmark of the disease.

2.4 PF in dogs

Canine PF is a pustular disease affecting only the skin. In early studies, circulating IgG autoantibodies against 150-160 kDa proteins corresponding to Dsg1 [13, 14]. However, immunofluorescence using a mammalian cell line in which canine Dsg1 is ectopically

expressed revealed that circulating anti-Dsg1 IgG autoantibodies were recognised only in 5/83 (6%) cases of canine PF [15]. Following these studies, Bizikova et al revealed that circulating IgG autoantibodies against canine Dsc1 ectopically expressed in the mammalian cell line were recognised in 64/85 (75.3%) of dogs with PF [16]. These findings suggest that Dsc1 is a major autoantigen in canine PF, although its pathogenicity requires further evaluation.

2.5 PFs in cats

Attempts have been made to detect circulating IgG against the plasma membrane of feline keratinocytes in feline PF. Circulating anti-keratinocyte IgG were detected in 23/30 (76.7%) cats with PF. The majority (21/23, 91.3%) of seropositive PF cats have circulating antibodies against keratinocytes both in the footpad epidermis and buccal mucosa, the latter of which should not express Dsc1 [17]. In contrast, the remaining two cats have antibodies against only the epidermis of the footpad [17]. To date, the exact autoimmune target in feline PF has not been identified. However, these findings suggest that the IgG autoantibodies in the majority of feline PF recognise the cell adhesion molecules expressed both in the epidermis and mucous membrane epithelia.

3. Diseases with loss of desmosomal cell-cell adhesion by bacterial toxins

Besides pemphigus autoantibodies, exfoliative toxins produced in staphylococci also cause loss of desmosomal cell-cell adhesion. In human medicine, *Staphylococcus aureus* exfoliative toxins (ETA, ETB, and ETD) cause loss of keratinocyte cell-cell adhesion, resulting in skin exfoliation in bullous impetigo and staphylococcal scalded-skin syndrome [18-21]. In the early 2020s, Hanakawa and his group first discovered that *S. aureus* ETs are unique serine proteases that selectively digest a single peptide bond in the extracellular segment of Dsg1 [22].

Genetic evidence of exfoliative toxins in *Staphylococcus hyicus* (*exha, exhb, exhc, exhd, and sheta*) [23, 24], *Staphylococcus pseudintermedius* (*expa* and *expb*) [25, 26], and very recently, in *Staphylococcus felis* (*exfa*), has been reported. These toxins digest Dsg1 in a species-specific manner. For example, *S. hyicus* Exhs digest porcine Dsg1 [27, 28]. In contrast, *S. pseudintermedius* Exps digest canine Dsg1[26, 29]. Moreover, *S. felis* ExfA digests feline Dsg1 (manuscript in preparation). These findings suggest that staphylococcal exfoliative toxins facilitate the colonisation of staphylococci in host skin and are involved in the pathogenesis of bacterial skin diseases.

To date, the following exfoliative toxin-associated diseases in domestic and companion animals have been reported:

3.1 Porcine exudative epidermitis (EE)

EE is an acute, contagious, and often fatal bacterial skin disease primarily affecting piglets. Virulent *S. hyicus* or *S. chromogenes* producing exfoliative toxins are frequently isolated in the skin lesions of EE [30]. It has been reported that Exhs cause skin exfoliation, as evidenced by histopathology of superficial epidermal splitting with degradation of Dsg1, when they are injected into pig skin [27]. Also, the Exhs directly solubilise the baculovirus

recombinant extracellular segment of porcine Dsg1 [28]. These findings imply that porcine EE shares identical pathomechanisms of skin exfoliation with generalised bullous impetigo in humans, namely, the digestion of Dsg1.

3.2 Canine impetigo

An *S. pseudintermedius* strain harbouring two *exp* genes has been isolated from a pustule of a dog with impetigo. The recombinant ExpA and ExpB caused skin exfoliation with superficial epidermal splitting, in which Dsg1 is degraded, when they were injected into canine skin [26, 29]. Moreover, the ExpA and ExpB directly solubilised the extracellular segment of canine Dsg1, but not that of canine Dsg3 [26, 29]. The *expa*- and *expb*-harbouring *S. pseudintermedius* strains have been identified in the skin lesions of canine pyoderma, including pustules [26, 29]. Although canine impetigo is not a contagious disease like human impetigo or porcine EE, the canine disease also shares the identical pathomechanisms of skin exfoliation with those human or porcine diseases.

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