2. Survey of Related Literature

Atopic dermatitis (AD) is a common allergic skin disease recognized in dogs (Hillier and Griffin 2001) and humans (Rothe and Grant-Kels 1996). Canine atopic dermatitis (CAD) is defined as 'genetically predisposed inflammatory and pruritic allergic skin disease with characteristic clinical features associated with IgE antibodies most commonly directed against environmental allergens' (Halliwell 2006). CAD prevalence seemed to be increasingly in the past decade to approximately 15% of the dog population (Hillier and Griffin 2001). Diagnosis of CAD is based primarily on history, clinical signs, the exclusion of other pruritic dermatose (Olivry 2010) and the diagnostic criteria proposed by Favrot et al. (2010). Intradermal skin test and laboratory evaluation, including allergy tests and histopathology of skin biopsy specimens, also support the diagnosis (DeBoer and Hillier 2001; Hillier and DeBoer 2001; Olivry et al 2010). CAD is considered to be a spontaneous model of human atopic dermatitis (HAD) since both have similar clinical features and immunological profiles, including familial occurrence, early age of onset, recurrent pruritus, skin lesions typically located at flexor and extensor sites of extremities, skin xerosis and the presence of Th2-dominated immune response against environmental allergens. Moreover, the similarity in impaired skin barrier function, reflecting in increased transepidermal water loss (TEWL) and in histological lesion with spongiotic dermatitis and eosinophil and IgE+CD1c+ infiltrates, supported the role of dogs as an appropriate model to study pathogenesis of human disease (Willemse 1988; Olivry et al 1997; Lian and Halliwell 1998; Griffin and DeBoer 2001; Hill et al 2001;

Olivry and Hill 2001; Olivry et al 2001; Marsella and Olivry 2003; Vickery 2007; Marsella and Girolomoni 2009).

Epidermal barrier is important to prevent allergen from penetrating into the skin. Epidermal keratinocytes (KCs) move from the basal layer to the spinous layer, granular layer and eventually corneum layer which is the outermost layer of the epidermis. The stratum corneum plays a crucial role in the permeability barrier of the skin since the cornified envelop (CE) proteins, which are transglutaminase cross-linked proteins deposited under the plasma membrane of keratinocytes, are formed in this layer. The CE functions to keep skin moisture. The proliferation and differentiation of KCs are important for cornified envelope associated protein formation in the S. corneum (Ekanayake-Mudiyanselage et al 1998; Marekov and Steinert 1998). A number of CE proteins are coordinatedly expressed, including IVL, FLG, S100 proteins, etc. Most of them are transglutaminase substrates, used to assemble a cross-linked scaffold beneath the keratinocyte plasma membrane (Hitomi 2005).

Ki-67, a nuclear protein expressed in cycling cells, is widely used in routine pathology as a cell proliferation marker not only in human but also in canine. The Ki-67 antigen is detected within the cell nucleus during interphase but in mitosis it is relocated to the surface of the chromosomes. Ki-67 protein is found during active phases of the cell cycle (G_1, S, G_2, and mitosis), but is absent from postmitotic cells (G_0) (Kawahira 1999; Schlozen and Gerdes 2000; Sapuntsova et al 2002; Jensen et al 2004; Bovenschen et al 2005). In the epidermis, basal cells undergo differentiation and maturation, moving into the suprabasal compartment. During this differentiation process, cytokeratins, a major

component of the intracellular cytoskeleton of epidermal cells, are synthesized. Several keratins and CE proteins are associated with the keratinocyte proliferation and differentiation programs, in particular keratin 5 (K5) and K14 which are the main keratins in the basal layer, K1, K2 and K10 in the suprabasal layer, involucrin, loricrin and filaggrin which are CE proteins and terminal differentiation markers (Fuchs and Green 1980; Cline and Rice 1983; Watt 1983; Moll et al 1984; Wertz et al 1989; Mehrel et al 1990; Hohl 1993; Ekanayake-Mudiyanselage et al 1998; Candi et al 2005; Proksch et al 2008; Proksch et al 2009). Disturbed differentiation and epidermal hyperproliferation lead to a defect of skin barrier permeability that enhanced the penetration of environmental allergens (Hudson 2006; Proksch et al 2009). Humans with AD have decreased expression of filaggrin and involucrin in skin (Cline and Rice 1983; Watt 1983; Seguchi 1996; Ekanayake-Mudiyanselage et al 1998). CAD was associated with impaired epidermal barrier, evaluating from increased transepidermal water loss (TEWL) and defect of lipid lamellae in atopic dogs compared with normal controls, (Hightower et al 2008; Inman et al 2001; Shimada et al 2009). The expression of FLG and IVL proteins in CAD were studied but the association to CAD was still unclear (Marsella et al 2009; Chervet et al 2010).

The lymphoepithelial Kazal-type-related inhibitor (LEKTI), encoded by the serine protease inhibitor Kazal-type 5 (SPINK5) gene (Mägert et al 1999), is involved in regulation of proteolysis in epithelia formation and keratinocyte terminal differentiation (Chavanas et al 2000). SPINK5 polymorphism has been reported to be associated with HAD (Walley et al 2001; Kato et al 2003; Namkung et al 2010). LEKTI protein inhibited