CONTRIBUTE OF C-MYC UPREGULATION TO THE PATHOGENESIS OF CANINE PEMPHIGUS VULGARIS

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SUMMARY

Pemphigus vulgaris (PV) is an autoimmune disease that affects humans and domestic animals. Histologically, PV is characterized by loss of cell-cell adhesion between basal and adjacent suprabasal keratinocytes in mucous membranes and skin. Canine PV resembles human PV in its clinical, pathological and immunological presentation. In both human and canine PV patients, autoantibodies were reported to target the desmosomal protein desmoglein 3 (Dsg3), a glycoprotein that belongs to the cadherin family of adhesion receptors. This has become particularly relevant in view of newly identified signalling events in PV that are pathogenic and thus provides the basis for the development of novel therapeutic strategies.

Two dogs diagnosed with PV and one with coexisting PV/pemphigus foliaceus (PF) were included in the study. For comparison, one dog with clinically and histological typical canine PF and one immunopathologically confirmed human patient with PV were also enrolled in the study. Clinically and histopathologically, the PV dogs presented with typical mucocutaneous and epidermal erosive and ulcerative lesions. In two dogs, PV was further confirmed by direct and indirect immunofluorescence in addition to Western blot analysis on recombinant human Dsg3. Biopsy samples from lesional, perilesional and nonlesional skin in addition to oral mucosa (same sites sampled for diagnosis purposes) of the dogs with PV and coexisting PV/PF were harvested for immunofluorescence analyses.

In control biopsy samples of normal epidermis with one to three vertical rows of keratinocytes, c-Myc expression was not detectable. Control sections with more than four vertical rows of keratinocytes (such as mucocutaneous junctions, thicker epidermis from pet dogs) or oral mucosa showed low levels of c-Myc staining. In canine patients with PV, PV antibody-induced changes in c-Myc were observed in nonlesional skin. This indicates that this event precedes acantholysis and suggests that it might contribute to lesion formation as was shown for human PV using small synthetic c-Myc inhibitors. Mechanistically, high c-Myc expression likely leads to the abnormally prolonged proliferation that in turn delays the strengthening of intercellular adhesion structures in basal keratinocytes. Together with the PV antibody-induced changes at the plasma membrane, this ultimately leads to loss of intercellular adhesion.

In conclusion, PV is the most devastating form of pemphigus and is characterized in dogs by suprabasal blister formation and ulcerations requiring aggressive forms of immunosuppressive therapy. Synthetic inhibitors of c-Myc and GSK3β were effective in preventing loss of intercellular adhesion in both mouse keratinocyte cultures (unpublished data) and neonatal mice exposed to human PV IgG or a mouse monoclonal pathogenic antibody.