

# Understanding the Skin Immune and Healing Response in Bovine Digital Dermatitis to Create Therapeutic Alternatives

Kaitlyn M. Watts, Priyoshi Lahiri, Rakel Arrazuria, Jeroen De Buck, Cameron G. Knight, Karin Orsel, Herman W. Barkema and Eduardo R. Cobo

Dept. of Production Animal Health, Faculty of Veterinary Medicine, University of Calgary, Calgary, Alberta, Canada

Digital dermatitis (DD) commonly associated with *Treponema* spp. infection is a prevalent infectious bovine foot disease characterized by ulcerative and necrotic lesions. Current treatments utilizing antimicrobials or chemical footbaths are often ineffective and rarely cure DD lesions. In our study, the expression of the local innate host defense peptides cathelicidins and  $\beta$ -defensins was investigated in cows with DD and associated with the presence of treponemes and inflammatory reactions. Samples from active ulcerative DD lesions (M2) had considerable epidermal neutrophilic infiltration and increased gene expression of  $\beta$ -defensin tracheal antimicrobial peptides compared to control skin, along with elevated local Cxcl-8 and TLR4 gene expression and abundant treponemes as identified by direct visualization, immunohistochemistry, and culture. Conversely, the anti-inflammatory peptide IL-10 was elevated in skin from chronic (M4) lesions, whereas bovine cathelicidin myeloid antimicrobial peptide 28 (Bmap-28) was increased in skin from oxytetracycline-treated M2 lesions. These findings indicate that neutrophil influx, Cxcl-8, and  $\beta$ -defensin are key markers of active DD. Next, we explored the comparative effects of topical application of vitamin D<sub>3</sub> and oxytetracycline on M2 DD lesions and its effects on innate immune responses. DD M2 lesions characterized across a 5-day period showed elevated Tlr2 gene expression indicating its importance for progression to healing stages of DD. Topical oxytetracycline resulted in elevated Tlr2 gene expression and decreased Cxcl-8 gene expression compared to untreated lesions. Oxytetracycline promoted the formation of hyperplastic scab tissues and reduced the local burden of *T. pedis* bacteria after 5 days. Topical vitamin D<sub>3</sub> induced the gene expression of a main  $\beta$ -defensin in cattle, tracheal antimicrobial peptide (Tap). These findings indicate that oxytetracycline proved successful as macroscopically the lesion became less ulcerated, was associated with lowered inflammatory markers, as well as reduced the amount of pathogenic treponemes within the lesion. Vitamin D<sub>3</sub> seems to be relevant promoting the expression of local host defense peptides. Both therapeutics, combined or individually, might provide clinical benefits in the resolution of DD, providing welfare and economic benefits for the cattle industry.