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DIFFERENCES BETWEEN CHONDRODYSSTROPHIC AND NON-CHONDRODYSSTROPHIC DOGS ON CARTILAGE LEVEL: A GENETIC BASIS FOR OSTEOARTHRITIS?

Chondrodystrophy causes abnormal short limbs and is a characteristic for several dog breeds (figure 1). It has been shown that the canonical Wnt signaling pathway in intervertebral discs is downregulated in chondrodystrophic (CD) dogs when compared to non-chondrodystrophic (NCD) dogs⁽¹⁾, causing early disc degeneration. Similarly, loss of Wnt signaling has also been related to osteoarthritis (OA)⁽²⁾. Therefore, the aim of this study was to explore whether NCD and CD cartilage differ on a molecular level and thereby relate it to OA predisposition.

Healthy cartilage from 11 donors, NCD and CD, was cultured in an explant setup for 14 days in the presence of control (chondrogenic) medium or a pro-inflammatory stimulus (Tumor Necrosis Factor α (TNF- α)). Read-out parameters were histology, immunohistochemistry, qPCR, and biochemical assays (glycosaminoglycan- (GAG) and DNA content).

Dickkopf-3 (DKK3) and Wnt Inhibitory Factor-1 (Wif1), both negative regulators of the Wnt signaling pathway, were significantly downregulated in CD cartilage compared

to NCD explants. Furthermore, Low-density lipoprotein Receptor-related Protein-5 (LRP5) and Fibroblast Growth Factor-2 (FGF2), both involved in the pathogenesis of OA, were significantly downregulated in CD compared to NCD cartilage. Notably, CD cartilage was more capable in retaining GAGs than NCD cartilage, when exposed to an inflammatory environment.

Altogether, there seems to be a difference at the biomolecular and biochemical level between CD and NCD cartilage providing a possible explanation for the higher prevalence of OA in NCD dogs. Upregulation of DKK3 has been associated with osteoarthritis. Lower expression of DKK3 may have a protective effect on the integrity of cartilage by preventing the loss of proteoglycans in CD cartilage⁽³⁾. Therefore, genes involved in the Wnt signaling pathway may prove valuable as a target for the treatment of OA and cartilage regeneration.

References

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Figure 1. Left an example of a non-chondrodystrophic (NCD) breed (labrador retriever) and right an example of a chondrodystrophic (CD) breed (shorthaired dachshund). Source: Beeldbank UKG