Aging increases inflammatory response in cattle

Foucras G[1], Cebron N[1], Walachowski S[1], Chaulot-Talmon A[2], Pontelevoy C[2], Robcis R[1], De Boyer des roches A[3], Ledoux D[3], Richard C[2], Gelin V[2], Kiefer H[2], Jammes H[2]

1. IHAP, Université de Toulouse, ENVT, INRAE, F-31076 Toulouse, France

2. BDR, INRAE, Université Paris Saclay, ENVA, F-78352 Jouy-en-Josas, France

3. UMRH, VetAgro Sup, INRAE, F-63122 Saint-Genès-Champanelle, France

Objectives: Old cows are reputed more sensitive to bacterial infections, developping more severe mastitis than youngest ones. However the biological basis of these observations are not known. Risk factors increase with aging, but inflammation and innate immunity are modified in the long term by previous exposure to microbes. Epigenetic changes of immune cells like monocytes could explain increased severity to infection. Monocytes are central in these mechanisms, and they undergo functional changes upon contact with pathogens or their products, and adapt their response to subsequent challenges. However, the molecular bases of long-term reprogramming are still poorly understood in cattle.

Materials and methods: Twenty-three cows were challenged through an intravenous bolus injection of LPS (0.5 µg/kg BW, ultrapure LPS, InVivogen) to induce a systemic inflammatory response. Fourteen of them were bovine somatic clones originating from the same cell line, in two groups of 5 and 15-years of age, respectively. A genetically-diverse group of 5 years-old cows (n=9) was also included in the study. All cows were raised and housed together as a single group since birth in an experimental farm. Cytokine production was measured sequentially (0, 3, 6, 12, and 24h) in plasma using a newly-developed custom bovine cytokines 15-plex Milliplex assay (MERCK-Millipore). Blood samples were collected twice at 0 and 24 hours after LPS injection. Monocytes were isolated and their genome-wide DNA methylation profile was determined by reduced representation bisulfite sequencing (RRBS) using a dedicated pipeline, in order to assess epigenetic marks according to the age, genetic background, and response to LPS.

Results: LPS exposure was associated with the production of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α). IL-6 and TNF-α production were higher in aged compared to young cows, and clinical signs were more severe in the former, indicating a stronger inflammatory response according to the age. Differentially-Methylated Cytosines (DMCs) targeting genomic regions important to monocyte identity and functions, independently of the genetic background, were identified. LPS stimulation causes hypomethylation in dairy cows whatever the age. Monocytes undergo epigenetic modifications after LPS challenge, indicating that previous exposure to Gram-negative bacteria, may modify the later capacity of the cells to respond to an infection. Comparison of young and old cattle led to identification of epigenetic marks related to aging.

Conclusions: Aged cows have a stronger inflammatory response that correlates with the presence of specific marks that develop during the course of life. Knowledge on epigenetic marks induced by aging may help define new breeding and prevention strategies.