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# Modulation of the Innate Immune Response in Bovine Udder Tissue by Epigenetic Modifiers

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**Abstract :** Mastitis is among the most important production diseases in cows. It accounts for large parts of antimicrobial drug use in the dairy industry worldwide. Due to the imminent normative to reduce the use of antimicrobial drugs in livestock, new ways for therapy and prophylaxis of mastitis are needed. Recently epigenetic regulation of inflammation by chromatin modifications has increasingly drawn attention. Currently, some epigenetic modifiers have already been approved for the use in humans, however little is known about their actions in the bovine system. The aim of our study was to investigate whether three selected epigenetic modifiers (Vitamin D3, SAHA and S2101) influence the initial immune response towards mastitis pathogens in bovine udder tissue in vitro. Tissue explants of the teat cistern and udder parenchyma were collected from 21 cows and were incubated for 36 hours in the absence and presence of epigenetic modifiers. Additionally, the tissue was stimulated with heat-inactivated particles of Escherichia coli and Staphylococcus aureus, which are regarded as two of the most important mastitis pathogens. After incubation, the explants were tested by RT-qPCR for transcript abundances of immune-related candidate genes. Gene expression was validated in culture supernatants by an AlphaLISA assay. Furthermore, the culture supernatants were analyzed for their chemotactic capacity through a chemotaxis assay. Statistical analysis of data was performed with the program 'R' version 3.2.3. Vitamin D3 had no effect on the immune response of udder tissue in vitro after stimulation with mastitis pathogens. The epigenetic modifiers SAHA and S2101 however significantly blocked the pathogen-induced upregulation of CXCL8, TNFα, S100A9 and LAP ($P < 0.05$). The regulation of IL10 was not affected by treatment with SAHA and S2101. Transcript abundances for CXCL8 were reflected by IL8 contents and chemotactic activity in culture supernatants. In conclusion, these data show the potential of epigenetic modifiers (SAHA and S2101) to block overshooting inflammation in the udder. Thus epigenetic modifiers may serve in future as immune modulators for the treatment and/or prophylaxis of clinical mastitis. (Funded by Deutsche Forschungsgemeinschaft PE 1495/2-1).

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