

Let-7 Mirnas Regulate Inflammatory Cytokine Production in Bovine Endometrial Cells after Lipopolysaccharide Challenge by Targeting TNF α

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Abstract : Bovine endometrial cells appear to have a key role in innate immune defense of the female genital tract. A better understanding of molecular changes in microRNAs (miRNAs) and their target genes expression may identify reliable prognostic indicators for cows that will resolve inflammation and resume cyclicity. In the current study, we hypothesized that let-7 miRNAs family has a primary role in the innate immune defence of the endometrium tissue against bacterial infection, which is partly achieved via regulating mRNA stability of pro-inflammatory cytokines at the post-transcriptional level. Therefore, we conducted two experiments. In the first experiment, primary bovine endometrial cells were challenged with clinical (3.0 μ g/ml) and sub-clinical (0.5 μ g/ml) doses of lipopolysaccharide (LPS) for 24h. In the 2nd experiment, we have investigated the potential role of let-7 miRNAs (let-7a and let-7f) using gain and loss of function approaches. Additionally, tumor necrosis factor alpha (TNF α), transforming growth factor beta 1 induced transcript 1 (TGFB1I1) and serum deprivation response (SDPR) genes were validated using reporter assay. Here we addressed for the first time that let-7 miRNAs have a precise role in bovine endometrium, where LPS dysregulated let-7 miRNAs family expression was associated with an increased pro-inflammatory cytokine level by directly/indirectly targeting the TNF α , interleukin 6 (IL6), nuclear factor kappa-light-chain enhancer of activated B cells (NF κ B), TGF β 1I1 and SDPR genes. To our knowledge, this is the first study showing that TNF α , TGF β 1I1 and SDPR were identified and validated as novel let-7 miRNAs targets and could have a distinct role in inflammatory immune response of LPS challenged bovine endometrial cells. Our data represent a new finding by which uterine homeostasis is maintained through functional regulation of let-7a by down-regulation of pro-inflammatory cytokines expression (TNF α and IL6) at the mRNA and protein levels. These findings suggest that LPS serves as a negative regulator of let-7 miRNAs expression and provides a mechanism for the persistent pro-inflammatory phenotype, which is a hallmark of bovine subclinical endometritis.

Keywords : bovine endometrial cells, let-7, lipopolysaccharide, pro-inflammatory cytokines

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