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Expression of Natural Resistance Associate Macrophages Protein One (NRAMP1) in Ruminant Neutrophils

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Abstract

Developing genetic resistance is an ideal approach to control infectious diseases in ruminants. Natural Resistance Associated Macrophages Protein one (NRAMP1) is a phagosomal membrane protein. It is ubiquitously expressed in macrophages and neutrophils, and plays an important role in the host's innate resistance/susceptibility to diseases. This mini review focuses on the expression of NRAMP1 in neutrophils of ruminants and its possible role in host innate immunity.

Introduction

The pattern of constitutive and inducible expression of genes associated with the inflammatory response is important in defining innate (natural) resistance/susceptibility to diseases. The gene for Natural Resistance Associated Macrophages Protein one (NRAMP1), also known as solute-like carrier family 11 A1 (SCLC11A1) encodes a trans membrane protein that regulates divalent cation transport in phago some membranes, transporting ions out of the phago some that are essential for growth of bacteria. NRAMP1 has been found in diverse organisms from, bacteria to man. Studies have reported NRAMP1 expression in ruminants such as cows [1] and goats [2].

NRAMP1 is expressed in many different cells including macrophages, polymorphonuclear leukocytes in the blood, lung, spleen and liver in humans. It is expressed in cells of the myelomonocytic linkage and also in the duodenum. NRAMP1 was first identified in macrophages but polymorphonuclear leukocytes (PMN) are the major site of NRAMP1 expression. Studies in human neutrophils identified the sub cellular localization of NRAMP1 in tertiary granules which are positive for gelatinase and ATPase enzymes [3]. NRAMP1 provides natural resistance against intracellular pathogens such as Leishmania, Salmonella, and Mycobacterium [4].

In humans, polymorphism in Nramp1 gene is associated with several disease conditions like inflammatory bowel disease, multiple sclerosis and diabetes mellitus. Other studies in humans have shown that polymorphism in Nramp1 gene is also associated with a decrease in macrophage activation. In ruminants, there are evidences indicating expression and polymorphism of NRAMP1 in bovine neutrophils. Furthermore, the effect of different forms of LPS in inducing the expression of Nramp1 in bovine neutrophils has been reported [1].

Expression of Nramp1 has been found to be induced in macrophages upon exposure to lipopolysaccharide (LPS) and the cytokine IFN-γ [1]. Lipopolysaccharide is a major component of the outer wall of gram negative bacteria and is responsible for causing mastitis and acute inflammation associated with bacterial infection. Studies in porcine tissue have shown that Nramp1 expression is induced upon treatment with LPS in a dose dependent manner in different cell types like macrophages and neutrophils. Cytokines like TNF-α and IL-1β also induced NRAMP1expression in macrophages and neutrophils.

Increased expression of NRAMP1 in response to LPS is dependent upon CD14 receptor and expression of NRAMP1 decreased to basal levels on treatment with monoclonal antibodies to CD14. In goat blood CD14 expression was not related to NRAMP1 expression or coccidian infection [2]. In a study by Worku & Morris [1], NRAMP1 gene expression increased in cow neutrophils treated with LPS in vitro; expression was dose-dependent and neutrophils expressed polymorphic transcripts for the Nramp1. Their study findings demonstrated the high expression of Nramp 1 following LPS exposure of blood bovine neutrophils and that indicate its significant role in pathogen destruction.

Cells of innate immunity especially Neutrophils play a key role in the acute inflammatory process. Pro-inflammatory cytokines like IL-1β and IL-8 play a crucial role in the inflammatory

process. A detailed understanding of the Neutrophil's response to LPS exposure and evaluation of Nramp1 expression may help to give clues regarding disease susceptibility associated with E. coli infections. The neutrophil is a major effect or cell of innate immunity. Exocytosis of granules and secretory vesicles plays a pivotal role in most neutrophil functions from early activation to the destruction of phagocytosed microorganisms. Neutrophil granules contain a multitude of antimicrobial and potentially cytotoxic substances that are delivered to the phagosome or to the exterior of the cell following degranulation.

NRAMP1 and innate immunity

Natural Resistance associated macrophage protein1 (Nramp1) is associated with susceptibility to several diseases in farm animals. Natural resistance-associated macrophage protein one regulates intracellular pathogen proliferation and inflammatory responses. The NRAMP1 protein is a phosphor protein and the extent of phosphorylation changes in response to inflammatory cytokines and plays a role in host innate immunity. Studies in goats indicated that cytokines may be a factor in the pathogenesis of goat coccidiosis. NRAMP1 has been associated with innate resistance to unrelated intracellular pathogen infections, up-regulation of pro-inflammatory phagocyte functions, and susceptibility to diseases.

Several studies performed on intracellular organisms such as Mycobacterium, Salmonella, Brucella and Leishmania in human and mouse and in cows infected with Staphylococcus aureus, revealed that resistance against these bacteria was dependent on high activity of NRAMP1 in macrophages [5] confirmed the association between SLC11A1 (NRAMP1) and tuberculosis susceptibility. Ahmed et al. [2] reported NRAMP1 expression in goats infected with coccidiosis: Infections with Eimeria species have been observed to result in differential cytokine gene expression including production of Interferon gamma, IL-10 and IL-8 in cattle. Ahmed et al. [2] have reported that NRAMP1 may serve as a molecular marker and therapeutic target against coccidia in goats. More studies on the association between the NRAMP1 gene and innate immune response to pathogens may aid in understanding and enhancement of genetic resistance to pathogens in ruminants.

NRAMP1 polymorphism in ruminants

Natural resistance-associated macrophage protein one (NRAMP1) exhibits a natural polymorphism with alleles termed resistant and susceptible. Alleles restrict or allow the proliferation of intracellular pathogens. Polymorphisms in the human NRAMP1 gene and mycobacterial diseases have been explored, including INT4 (single nucleotide G>C change in intron 4, 469+14G/C, rs3731865), D543N (conservative single base G>A substitution at codon 543, resulting in a change to asparagine from aspartic acid), and 3'UTR TGTG (a deletion in the 3' untranslated region, 1729+55del).

In ruminants NRAMP1 polymorphism has been observed in cow and goat cells. Polymorphisms have been associated with diseases in man and cattle including bovine brucellosis [6], tuberculosis [7], and Mycobacterium bovis [8]. Qu et al. [9] reported that polymorphism in the intron 4 region contribute to NRAMP1 mediated bovine tuberculosis (bTB) susceptibility. In bovine studies, a genomic region of the 3'UTR of the SLC11A1 cDNA gene sequence is associated with natural resistance against bTB. Polymorphisms in this region (alleles 211, 215 and 217) were associated with a significantly lower incidence of bTB in Zebu (Bosindicus) cattle. Moreover, recent findings have shown different levels of susceptibility to bTB among various cattle breeds.

Natural resistance-associated macrophage protein polymorphism identification could be used selected for immunity. Hu et al. [10] have reported studies on cow milk somatic cells associated with S. aureus which is an intracellular organism and the main cause of bovine mastitis. Resistant cows produced more NRAMP1 mRNA than the susceptible ones, and ratios of NRAMP1: β-actin expression was higher in resistant cows with or without LPS activation [5,10-12]. These studies did not evaluate NRAMP1 in neutrophils [13,14]. Studies on the expression and identification of the role of polymorphisms in NRAMP1 genes in bovine neutrophils might help to give a better understanding of differences in innate immunity and aid in the definition of the impact of differential activation of neutrophils in response to infectious organs in ruminants and thus warrants further study [15,16].

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