DNA Vaccines and Immuno-Metabolic Efficiency in Ruminants: Nutritional Perspectives

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ABSTRACT

Infectious diseases lower the productivity of the ruminant production systems not only via morbidity but also by changing nutrient partitioning and efficiency of metabolism. Activation of the immune system decreases glucose, amino acids and micronutrients used in growth and lactation in favor of immune defense leading to lower feed efficiency and performance. Though vaccination plays a crucial role in controlling the disease, traditional vaccine delivery platforms can cause temporary inflammation in the entire body, resulting in decreased feed consumption and metabolic energy balance. A latest method of inducing immunity at low metabolic cost involves DNA vaccines, which are also known as plasmid-mediated expression and endogenous antigen expression. This review combines the present mechanistic understanding of DNA vaccination with the ruminant physiology and animal nutrition with emphasis on their impacts on feed consumption, rumen fermentation, nutrient utilization and immuno-metabolic efficiency. The review has placed DNA vaccination as part of the new immuno-nutritional interventions to revolutionize sustainable production of ruminants and proposed the main research gaps that need to be addressed in the future.

Keywords: DNA vaccine, immune-metabolic efficiency, DNA vaccine as nutrient efficient utilizer in ruminants

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Introduction

Ruminant livestock systems are increasingly challenged to ensure production of milk and meat in an efficient manner against the background of increasing disease pressure, nutritional limitation and sustainability requirements. The impact of infectious diseases on the productivity of animals is not only the direct morbidity and mortality rates, but also significantly changes in the use of nutrients and metabolic priorities in animals [1]. Engagement of the immune system is associated with high nutritional costs and energetics with glucose, amino acids and lipids being diverted to leukocyte generation, synthesis of cytokines and generation of acute-phase proteins, frequently at the cost of growth, lactation and reproductive performance [2]. In ruminants, this nutrient rerouting due to cell-mediated immunity is very important considering that the productivity of ruminants is greatly reliant on the stable feed consumption, efficient rumen fermentation and a constant supply of volatile fatty acids (VFA) to provide energy metabolism [3]. During systemic inflammation, pro-inflammatory cytokines such as tumor necrosis factor-α, interleukin-1β, and interleukin-6 suppress appetite, impair insulin sensitivity and disrupt rumen motility and microbial ecology, leading to reductions in dry matter intake, fiber digestibility, and microbial protein synthesis [4]. All these physiological reactions lower the feed efficiency and nutrient retention, which shows the idea of immune-nutrient competition where nutrient productive functions and immune defense compete with scarce dietary resources [5]. In ruminant production systems, vaccination is also a primary component of disease prevention, but even this technology can cause a temporary inflammation in the entire system, thereby worsening metabolism and lowering milk production by 5.5 to 16 % in dairy cattle [6]. Moreover, the young ruminant infants might be interfered with maternal antibodies that delay immune response to vaccines at sensitive periods of nutritional growth [7]. Consequently, the use of vaccination methods, which prevent disease and maintain metabolic stability and nutritional efficiency has become of interest.

An alternative that is emergent as a vaccine with unique immunological and metabolic properties is DNA vaccines. These are plasmid DNA based vaccines that contain pathogen-specific antigens, which allow the endogenous expression of antigens into host cells and the stimulation of both cellular and humoral immunity without pathogen replication [8]. Significantly, DNA vaccines can induce innate immunity in a regulated way and enhance prolonged immune memory, which requires comparatively low metabolic rates and this aspect can indicate the benefits in terms of nutrient-saving and metabolism efficiency [9]. Although extensive researches have been done on the immunological processes of DNA vaccines but their effects on ruminant nutrition, rumen activity and nutrient distribution are not well examined. The majority of the current literature analyzes vaccine performance in terms of both immunogenicity and protection outcomes, and hardly incorporates nutritional and metabolic performance. This is a vital knowledge gap, in the sense that any immune interventions that interfere with the use of nutrients can unintentionally affect productivity. Thus, the nutrition-based analysis of DNA vaccines should be conducted to comprehend how the immunity protection might be attained without compromising, or even worsening, the immuno-metabolic efficiency of ruminants. This review aims at merging existing mechanistic understanding of DNA vaccines and ruminant physiology and animal nutrition with a focus on their impact on feed consumption, rumen fermentation, nutrient distribution, and productive efficiency. The review will also intend to draw a connection between immune processes and nutritional performance to ensure this places DNA vaccination in a larger immuno-nutritional context, as well as to determine future research needs to enable a sustainable ruminant production system.

Mechanistic Integration of DNA Vaccines with Ruminant Nutrition

DNA vaccines on administration, are taken into host myocytes and antigen-presenting cells (APC), into which plasmid DNA is transcribed and translated into antigenic proteins through host cellular machines. The result is this endogenous expression of antigens facilitating antigen presentation in both MHC class I and class II pathways which cause equal cellular and humoral immune responses [10]. Nutritionally, this process is important as it restricts over processing of the antigens by the extracellular pathway and systemic inflammation, thus decreasing the cost of immune activation. Excessive immune activation in ruminants is linked with higher use of glucose by the immune cells and more acute-phase protein synthesis with the use of amino acids. Reducing these processes with the aid of DNA vaccination, molecular energy and amino acid consumption of the diet remain unused, which means that the energy could go to milk production, muscle building, and basic requirements [11]. Simultaneously, CpG motives that have not been methylated in the plasmid DNA stimulate the activation of Toll-like receptor 9 on the dendritic cells and B lymphocytes, leading to regulated innate immune reaction. This activation is both localized and short lived in contrast to inflammation caused by pathogens and it improves antigen presentation without leading to prolonged cytokine release or anorexia. Maintaining voluntary feed intake is of particular importance in ruminants, in which any lasting decreation in intake leads to a rapid impairment of rumen microbial activity and the generation of volatile fatty acids. DNA vaccination contributes to sustained acetate, propionate, and butyrate supply by maintaining stable rumen fermentation, therefore, maintaining energy supply to gluconeogenesis, milk fat synthesis and epithelial integrity. This regulated immune activation thus, directly relates molecular immune signalling to entire animal nutritional efficiency [12].

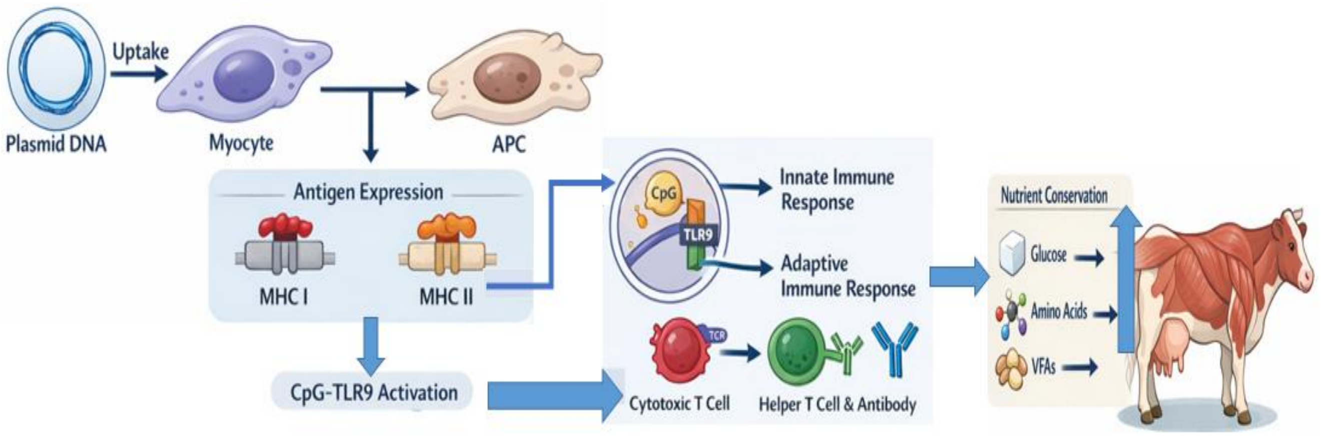

Figure 1:Mechanistic integration of DNA vaccination with nutrient utilization

A further advantage of DNA vaccines is their capacity to induce long-lived memory T and B cells with relatively low metabolic demand [13]. The memory immune cells are more dependent on oxidative phosphorylation over glycolysis, and they use fewer nutrients to maintain their functions as opposed to actively growing effector cells [14]. Such metabolic programming decreases the number of times an immune response is activated after exposure to a pathogen, and decreases the number of times that dietary protein and energy is diverted off productive activities. During the productive life of ruminants, this efficiency is reflected into better nitrogen retention, greater feed conversion efficiency and more consistent growth and lactation performance. All these processes support the assertion that DNA vaccines are not immunologically neutral interventions but they influence nutrient use and metabolic priorities in ruminants [15].

Table 1. Immunological mechanisms of DNA vaccines and their implications for ruminant nutrition and metabolism

Immune mechanism	Physiological effect	Nutritional consequence	Production relevance	References
Endogenous antigen expression	Reduced systemic inflammation	Conserved glucose & amino acids	Improved feed efficiency	[10]
CpG–TLR9 activation	Transient innate response	Stable feed intake & rumen VFAs	Sustained milk production	[12]
Memory T/B cell formation	Low metabolic demand	Reduced nutrient diversion	Long-term productivity	[13]
Early-life efficacy	Protection despite maternal antibodies	Improved early nutrient utilization	Enhanced growth performance	[15]

System-Level Integration with Rumen Function and Nutrient Partitioning

Immune activation, rumen functioning, and nutrient partitioning are closely linked in ruminants at the systems level. Chronic inflammation has been known to alter ruminal motility, microbial communities as well as fiber digestibility [16] which results in decreased VFA generation and suboptimal energy provision [17]. DNA vaccination indirectly stabilizes rumen microbial ecosystems by decreasing systemic inflammatory load, which maintains protein synthesis by microorganisms and fiber degradation [16]. This stabilization increases the efficacy of the transformation of the dietary nutrients into the absorbable energy and amino acids and supports the connection between immune protection as well as nutritional performance [18]. In addition, proper state of micronutrients, especially zinc, selenium and omega-3 fatty acids, enhances immune competence and antioxidant defense and indicates that the effect of DNA vaccines can be maximized by specific nutritional interventions [19].

Practical Implications and Future Directions

Practically, the incorporation of DNA vaccination into ruminant production systems will have the potential of enhancing the feed efficiency by improving immune diverted nutrient and the stability of feed intake. This might be especially useful in young animals that have a higher likelihood of being affected by maternal antibody and thus vaccine downstream targeting is better in young animals when they are more vulnerable to infections in their nutritionally sensitive periods. Moreover, vaccination programs should be brought into agreement with nutritional management such as sufficient energy, protein, and trace minerals which may help to boost the immuno-metabolic efficiency further. Despite these benefits there is a limited amount of direct experimental evidence that has been able to confirm the connection of DNA vaccination to feed intake, rumen fermentation, nitrogen retention and production performance in ruminants. In the next generation of study, integrated research methods should be focused on vaccinations and nutrient intake measurements, rumen dynamics, and metabolic analysis. Metabolomics and transcriptomics could be used to further understand immuno-nutritional processes that are affected by DNA vaccines to facilitate the creation of specific immuno-nutrition methods to promote sustainable livestock production.

Conclusion

The DNA vaccines are not just a disease-controlling method but a biologically effective intervention, which is compatible with the immune protection and ruminant nutritional physiology. DNA vaccination promotes immuno-metabolic efficiency and effective nutrient utilization by reducing systemic inflammation, maintaining feed consumption, stabilizing rumen activity and diversion of nutrients to immune reactions. Incorporating DNA vaccines into nutrition-based management systems presents an exciting direction to strong, effective and sustainable production systems of ruminant.

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