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ARE DENDRITIC CELLS A POTENTIAL TOOL FOR MASTITIS VACCINE DEVELOPMENT?

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ABSTRACT

Mastitis is one of the main disease causing big economic losses to dairy farmers. This disease is caused mainly by bacteria. Because of not efficient vaccines, there are necessary to develop new immunotherapy of vaccination strategy to reduce this disease in dairy farms. Dendritic cells are antigen-presenting cells which are able to present antigen to lymphocytes. They are able to induce activation of T naïve lymphocytes. Dendritic cells were used for development of dendritic cell-based anti-tumor vaccines. Development of vaccines against bovine mastitis has many limitations as high number of various pathogens that are able to cause inflammation of mammary gland in cattle; absence of mucus barrier in mammary gland; reduced phagocytic efficiency because of casein and fat globules etc. To this day, it is not available vaccine against bovine mastitis with high efficiency. Development of new immunotherapy or vaccine against mastitis would be very desirable. In this mini review, we are considering possibilities for development of new dendritic cell-based vaccine against bovine mastitis.

Keywords: dendritic cell, lymphocyte, mastitis, vaccine, cattle, mammary gland, immunotherapy

INTRODUCTION

Inflammation of bovine mammary gland (mastitis) is one of the main diseases which cause huge economic losses to dairy farmers in all of the world. This cattle diseases is multifactorial and it is caused by many various bacteria or other microorganisms such as yeasts or fungi. Major pathogens causing mastitis are *Staphylococcus aureus*, *Streptococcus uberis*, and *Escherichia coli* (**Cobirka *et al*., 2020; Zigo *et al*., 2021**).
Dendritic cells are antigen-presenting cells giving the information about antigen to T lymphocytes. For a long time, the function of these cells was not known. In 1868, Paul Langerhans stained a sample of human skin with gold chloride and identified the cells which bear his name. From their appearance, Langerhans believed they were nerve cells. However they are a form of dendritic cells. For more than a hundred years, these cells were considered nerve cells, as described by Paul Langerhans. Then in 1973, Ralph M. Steinman and Zanvil A. Cohn identified this cell type in mice as cells that are almost singularly responsible for commanding the efforts of all other immune cells (**Steinman and Cohn, 1973**). In 1978, Imre Olah and Bruce Glick were first to describe avian dendritic cells in the chicken bursa of Fabricius (**Olah and Nagy, 2013**). In 2011, Ralph M. Steinman won the Nobel Prize in Physiology or Medicine for discovery of the dendritic cell and its role in adaptive immunity.
As mentioned above, dendritic cells are the most efficient antigen-presenting cells. They represent the link between innate and adaptive immunity. Dendritic cells arise like other immune cells from a hematopoietic stem cells and they have the ability to engulf antigen, then they break down the antigen and present the antigen fragment on the cell membrane to T lymphocytes. T helper lymphocytes are able to produce cytokines that activate B lymphocytes or macrophages. T cytotoxic lymphocytes kill cells infected by intracellular pathogens such as viruses or bacteria, they also kill cancer cells and damaged cells. Dendritic cells are divided into several subpopulations: myeloid dendritic cells (also known as conventional dendritic cells), plasmacytoid dendritic cells, and follicular dendritic cells (**Worbs *et al*., 2017; Balan *et al*., 2019**).
Activation of T cytotoxic lymphocytes by dendritic cells is the principal of dendritic cell-based anti-tumor vaccines (**van Willigen *et al*., 2018**). This principle could be used to develop a vaccine against other diseases including mastitis of cattle. However, the development of a bovine mastitis vaccine has many pitfalls.
In this mini review, we tried to show information about vaccines against bovine mastitis. Then, to explain the principle of dendritic cell-based vaccines which are used for cancer treatment and to hypothesize if it is possible to develop dendritic cell-based vaccine against bovine mastitis.

VACCINE AGAINST BOVINE MASTITIS

The excessive use of antibiotics not only in human medicine, but also in veterinary medicine, leads to a major problem which is antibiotic resistance. In dairy cattle there are also used antibiotics for treatment of mastitis. Therefore, it is highly desirable that new methods of prevention or treatment of these diseases in cattle be created. There were developed some vaccines against bovine mastitis but the effectiveness of that is not satisfactory till now (**Rainard *et al*., 2021; Rainard *et al*., 2022**). Why are bovine mastitis vaccines not successful? There are many reasons why this is so. Here, there are some of them. Mastitis is caused by various microorganisms, mainly by bacteria. It is known about one hundred of various bacteria which are able to cause bacteria. If we create a vaccine against one species of bacteria, other bacteria have the possibility to cause mastitis. Moreover, milk is a very good growth medium for bacteria which is conditions that contribute to high bacterial load. Milk is also diluting antimicrobial agents that reduce their effectivity. In mammary gland, there are absence of mucus barrier which cause decrease of efficiency of secretory IgA or antimicrobial peptides. There is also reduced phagocytosis of bacteria by neutrophils because neutrophils phagocyte fat globules leading to reduction of phagocyte capacity of those cells (**Rainard *et al*., 2022**). In mastitis caused by *S. aureus*, neutrophils phagocytosis is less effective because some strains of this bacteria is able to survive in phagosomes and they are able to avoid the process of fusion of phagosomes and lysosomes (**Peyrusson *et al*., 2020**). *S. uberis* is able to attach to epithelial cells of cavity system of the mammary gland using *S. uberis* adhesion molecule (SUAM). These bacteria penetrate the epithelial cells and survive inside of them (**Almeida *et al*., 2015**). Those bacterial survival mechanism is another factor which reduce effectivity of mastitis treatment and vaccine development.
In next paragraphs, we would like to shortly explain bovine mastitis vaccines or vaccine antigens that are used or tested for reduction mastitis cases and severity of mastitis.

E. coli J5 bacterin with killed S. aureus (StartVac, Hipra) is known as the vaccine which is able to decrease severity of mammary gland inflammation but it has no effect on incidence of mastitis. The mechanism of this vaccine is not revealed very well (**Bradley et al., 2015**, **Rainard *et al*., 2022**).

Klebsiella siderophore receptors and porin proteins (KlebVax) are able to increase production of milk and it has just small decrease in coliform mastitis. There was published that effect of this vaccine is variable in different experiments (**Tomazi *et al*., 2021**).

S. uberis slime preparation (UBAC, Hipra). Efficacy of this vaccine is limited but in the literature we are able to find information that this vaccine reduces milk yield losses and incidence of clinical cases of mastitis (**Collado *et al*., 2018**).

E. coli J5 bacterins has low effect in experimentally induced mastitis. It decreases severity of coliform mastitis in farm experiments. But we can find different results in different herds of cattle and in different experiments (**Vangroenweghe *et al*., 2020**).

E. coli enterobactin FepA or siderophore receptor FecA. This system was tested in *in vitro* conditions. FepA was not tested *in vivo* (**Lin *et al.*, 1999**). FecA had just low effectivity in experiments (**Takemura *et al*., 2002**).

S. aureus bacterins and and toxoid or bacterial lysate. Incidence of mastitis was reduced and it was also noted reduction of severity of mastitis. It was described little effectivity in prevention of chronic mastitis but with variable results in various studies (**Middleton *et al*., 2006; Middleton *et al*., 2009**).

S. aureus protein A is another in a series of tested vaccine antigens but with unknown mechanism of action. It was not tested on dairy farm till now (**Pankey *et al*., 1985; Rainard *et al*., 2022**).

S. aureus FnBP and ClfA were not tested in field conditions. After experimentally induced infection, it was noted spontaneous clear up (**Shkreta *et al*., 2004**).

S. uberis live bacteria and surface extract. As the previous one, it was not tested in dairy farms and the mechanism of action is still not known (**Hill *et al*., 1994; Rainard *et al*., 2022).**

SUAM is a potentially promising agent for the development of a new vaccine against mastitis. Unfortunately, there are still not enough results to show us the sufficient effectiveness of this vaccine antigen used in this way (**Siebert *et al*., 2017**).

DENDRITIC CELL-BASED VACCINES

Dendritic cell-based vaccine in cancer therapy

Dendritic cell-based vaccine are able to induce specific immune response eliminating cancer cells. Many studies was done to examine efficacy of this type of vaccine in various cancer disease such as acute myeloid leukemia, myelodysplastic syndromes, and other nonleukemia malignancies (**Yu *et al*., 2022**). Dendritic cells are capable to activate NK cells as the part of non-specific immunity and activate the specific immunity based on memory cells (**Durai and Murphy, 2016**). Dendritic cells are also in contact with T lymphocytes through immunological synapses which leading to T lymphocyte activation against the presented antigens (**Reuther *et al*., 2013**). Dendritic cells allow CD4 positive T lymphocytes to activate B lymphocytes and CD8 positive T lymphocytes (cytotoxic T cells). They are also able to activate T regulatory lymphocytes to endeavour essential immunosuppressive functions (**Wang *et al*., 2020**).
Monocyte derived dendritic cells are typical source for dendritic cell-based vaccines. These dendritic cells are developed from CD14 positive peripheral blood cells (monocytes) in autologous or allogeneic system using interleukin-4 (IL-4) and granulocyte-macrophage colony-stimulating factor (GM-CSF) as a growth factors (**Yu *et al*., 2022**). Mature dendritic cells are loaded by antigens and then administrated into lymph nodes. In the lymph nodes, dendritic cells present antigens to CD8 positive T lymphocytes (cytotoxic T cells). Cytotoxic T lymphocytes then perform their functions, i.e. these cells destroy tumour cells (**van Willigen *et al*., 2018**).

Dendritic cell-based vaccine against COVID-19

Coronavirus Disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is one of the biggest public health emergencies in human history (**Roychoudhury *et al*., 2021**). SARS-CoV-2 was firstly detected in December 2019 in Wuhan (China). This virus is highly contagious and in December 2020, SARS-CoV-2 infections were confirmed in almost 70 million people worldwide (**Roychoudhury *et al*., 2020**). There were developed more types of vaccines against COVID-19: mRNA vaccine, viral vector vaccine, protein subunit vaccine, and whole virus vaccine (**Fiolet *et al*. 2022**). Nowadays, it is discussed the possibility of using of dendritic cells for development of vaccine against COVID-19. **Jonny *et al*. (2022)** explained possible use of *ex vivo* loaded dendritic cells for vaccination against COVID-19. At the same time, however, they are considering the obstacles that hinder the development of such a vaccine and its launch on the market. The chapter on the use of dendritic cells as a vaccine against the disease COVID-19 is included here to emphasize the importance of the use of these cells and their functionality in other diseases, such as in the treatment of cancer. This mastitis vaccine may expand the portfolio of uses of dendritic cells and suggests their wider use than before. We would like to keep this chapter in the manuscript.

DENDRITIC CELL-BASED VACCINE AGAINST MASTITIS

Obstacles in development of vaccines against mastitis mentioned above is the reason why it is necessary to create a new system of vaccination in that disease. It could be possible to use similar principal of vaccination like dendritic cell-based vaccine in cancer therapy. The following is a process by which a vaccine could be developed:
1. Isolation of monocytes from peripheral blood. This isolation is based on centrifugation of blood to get buffy coat. From buffy coat, there are isolated peripheral blood mononuclear cells (PBMC = lymphocytes and monocytes) by density gradient centrifugation. Monocytes can be obtained from PBMC by adherent method (monocytes are able to adhere on the wall of cultivation flask or well of cell culture plate) or by magnetic sorting using magnetic microbeads (**Kratochvilova *et al*., 2019; Cuncha *et al*., 2022**).
2. Monocytes are cultivated with growth factors as IL-4 and GM-CSF for developing of dendritic cells for about 5 to 6 days **(Kratochvilova *et al*., 2019; Yu *et al*., 2022**).
3. Mature dendritic cells are loaded by bacteria or bacterial fragment, for example *S. uberis* or *S. aureus* as main Gram-positive bacteria that are able to cause inflammatory response of bovine mammary gland.
4. Administration of antigen loaded dendritic cells into regional lymph nodes of mammary gland.
These dendritic cells are able to present antigen to T lymphocytes inside of lymph nodes. The contact between T lymphocytes and dendritic cells are ensured by major histocompatibility complex (MHC) molecule (at the side of dendritic cell) and T cell receptor (TCR) at the side of T lymphocyte. Activation of naive T lymphocytes by dendritic cells leads in their clonal expansion and differentiation into effector and memory T lymphocytes (**Bousso, 2008**).
One of the main problem of developing vaccine like that in cattle is the financial difficulty. This procedures is expensive. Another difficulty is that preparing of antigen loaded dendritic cells takes about one week and if we can use it for treatment by activating T lymphocytes, it can be late for inflammation of mammary gland. But as we mentioned previously, activation of naïve T lymphocytes by dendritic cells leads to differentiation not just effector cells but also memory cells. Therefore, it could be used preventively.

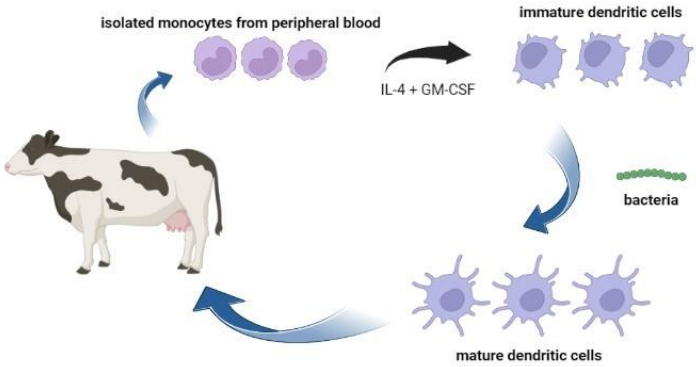

Figure 1 Schematic representation of dendritic cell-based vaccine preparation.

CONCLUSION

The title of this review is the question that should be answered in the conclusion. "Are dendritic cells a potential tool for mastitis vaccine development?" Despite the many mentioned obstacles in the development of a bovine mastitis vaccine based on dendritic cells, we consider these cells to be an interesting alternative to traditional vaccines. Of course, a large amount of experimentation and optimization of the method of vaccine creation against mastitis will still be required.

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