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Propolis Potency as an Inhibitory Agent for Regulatory T-Cell Activities in Cancer Conditions

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ABSTRACT

The role of immune system is very important in the process of the occurrence and development of cancer cells. Cancer cells have an ability to avoid and escape from immune response activities. One of them is by activating Treg cells (CD4+, CD25+, FoxP3+) which are suppressor cells for cytotoxic T cells (CD8+). Various monoclonal antibody therapies against Treg cells provide good results against cancer cells, but the side effects that occur cause secondary problems for patients. Exploration of the effect of the activity of propolis extract on Treg cells shows that there is a potential ability of propolis extract to inhibit the activity of Treg cell expression without reducing quantity of Treg cell populations. This paper reviews how Treg cell activity suppresses immune responses to cancer cells as well as the potential ability of propolis extract to inhibit Treg cell activity.

Keywords: Cancer cell, Treg cell, Propolis

INTRODUCTION

The immune system plays an important role in the process of formation and further development of tumor/cancer cells. The human body has a complete defense system that works in an integrated manner to protect itself from various potential hazards including the development of cancer cells. This mechanism is known as immunosurveillance [1]. But on the other hand cancer cells also have various abilities to escape from immunosurveilance activities. Among them is the ability of cancer cells to induce dysfunction and apoptosis of CD8+ T-cells and increase the expansion of regulator T-cells [2], express various immunosuppressive molecules that cause microenvironmental conditions that are beneficial for the development of cancer cells. In this context cancer cells have the ability to attract cells that can inhibit the immune response to the area of tumor/cancer tissue [3], one of the cells with potential immunosuppression is Treg cells (CD4+, CD25+, Foxp3+) [4]. Treg cells are reported to infiltrate tumor tissue in both humans and experimental animals [5]. Treg cells inhibit the effectiveness of the immune response to cancer cells so that it is an important target in cancer immunotherapy. Reducing or inhibiting Treg cells is expected to increase the effectiveness of the immune response to cancer [6,7].

Treg CELLS AND CANCER CELLS

Treg cells in the blood circulation can be pulled towards the breast cancer area through various pathways, including PGE2/EP2 (EP4), CCL22/CCR4, SDF1/CXCR4 and CCL5/CCR1 [8]. Cancer tissue microenvironment also plays an active role in increasing Treg cell differentiation and expansion, CD4+ T-cells can be converted into Treg cells in the presence of induction by TGF-β [9].

Treg cell activity plays a role in influencing many components of the immune system, including CD4+ (Th1, Th2 and Th17), CD8+, macrophage, dendritic cells (DCs), natural killer (NK), NKT cells, mast cells, osteoblasts and B-cells [10], which ultimately decreases and inhibits the immune response in the process of eliminating cancer cells. Activated Treg cells suppress innate and adaptive immune responses through various mechanisms, including: 1) Producing immunosuppressive cytokines IL-10 and TGFβ; 2) Inhibiting maturation APC (in this case dendritic cells) by inhibiting the expression of co-stimulator molecules CD80/86 [11]; 3) Induces cytolysis of T-cells by releasing perforin and granzyme which can kill cells CD4+, CD8+, dendritic cells and monocytes [4,12]; 4) interferes with T-

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cell responder metabolism, Treg cells contain high concentrations of cAMP which can inhibit proliferation, differentiation and synthesis of IL-2 by T-cells [13].

With various immunosuppressive mechanisms, Treg cells are an inhibitor of the success of anti-tumor immunity and immunotherapy, so that Treg cells become an important target in cancer immunotherapy. Reducing or inhibiting Treg cells is expected to increase the effectiveness of the immune response to cancer, various strategies to inhibit Treg cells have been studied in laboratory and clinical studies.

The strategy of inhibiting Treg cells can be carried out on various pathways, including: 1) By depleting Treg cells (quantitatively) with monoclonal antibodies to block IL-2 receptors [14]; 2) Suppress/inhibit the function of immuosuppression through manipulation of the cytotoxic T-lymphocyte antigen 4 pathway (CTLA-4) [15]; 3) Inhibits the homing process [16]; and 4) Inhibits the process of differentiation and conversion of Treg cells [17].

Therapy of various monoclonal antibodies that suppress Treg cells shows significant results for the development of cancer, but various side effects related to immunosuppression conditions become a problem in patients. Among the side effects of monoclonal antibody therapy to Treg cells are reported in various publications, including: 1) Treg cell depletion is reported to increase the concentration of circulating IgM autoantibodies [18]; 2) Blocking of CTLA-4 by ipilimumab can cause autoimmune disorders in various organs called immune-related adverse events (IRAEs). IRAEs can attack various organs and organs most affected are the skin and digestive tract. Symptoms of IRAEs include: in the gastrointestinal tract in the form of bowel perforation, enterocolitis, diarrhea, impaired liver function and in the nervous system in the form of Guillain-Barre syndrome, and in the skin in the form of rash and pruritus; 3) Anti-GITR monoclonal antibodies can cause dangerous side effects, namely anaphylactic reactions.

Various side effects of monoclonal antibody therapy require good anticipation efforts to prevent bad things in patients. This encourages the thought of trying to explore natural materials with the potential to inhibit Treg cells. Natural materials in general have a complex composition because there are various components inside which can work synergistically or antagonistically where the activity of an active ingredient can be controlled by other active ingredients so that the use of natural materials in a complex form is generally reported to be relatively safe.

THE EFFECT OF TREATMENT OF PROPOLIS EXTRACT ON Treg CELLS

In past research we explored the effect of giving Indonesian propolis extract to Treg cell populations in mice with breast cancer models both in the number and activity of immunosuppressive molecule expression (IL-10 and TGFβ). The results showed that the treatment of propolis extract had no significant effect on the population of Treg cells in quantity, but significantly affected the Treg cell population that expressed TGFβ (CD4+, CD25+, FoxP3+, TGFβ+) and Treg cell populations that express IL-10 (CD4+, CD25+, FoxP3+, IL-10+) [19].

The effect of propolis extract on the expression of IL-10 and TGFb has a positive immunological benefit in a cancerous state because both are immunosuppressive cytokines synthesized by Treg cells. IL-10 affects several mechanisms, including inhibiting dendritic cell function by suppressing the production of inflammatory cytokines, inhibiting MHC II, and expression of co-stimulator molecules [20,21]. IL-10, known as cytokine synthesis inhibitory factor (CSIF), is an anti-inflammatory cytokine that inhibits gene expression and synthesis of cytokines such as IFNγ, IL-2, IL-4, IL-5, IL-13 and TNFa by T-cells and macrophages, inhibits antigen presentation ability by reducing expression of MHC and B7 costimulatory molecules on APC also inhibiting IFN menghambat synthesis by activated T cells and peripheral blood mononuclear cells (PBMC) [21,22]. TGFβ can suppress the systemic immune system, inhibit immunosurveillance and can affect immune cell populations [23]. TGFβ also inhibits CTL activity, CD4+ T-cells, Macrophages, dendritic cells, and NK cells that have an important role in tumor development, also trigger the formation of Treg cells and Th17 cells [24]. TGF-β decreases transcription of cytolytic and pro-apoptotic factors such as granzyme A and B, perforin, interferon-γ and FAS ligands at both gene and protein levels, also inhibits APC (antigen presenting cells) function which causes a decrease in T-cell activation [25]. The Transforming Growth Factor-β also promotes tumor development by increasing the escape mechanism of immunosurveillance, also in the process of aTreg cell differentiation and conversion [17,26,27]. In serum and breast cancer tissue, high levels of TGF-β are found and this is related to a poor prognosis, in addition to metastatic breast cancer TGF-β expression is higher than in primary tumors [28-30].

CONCLUSION

Propolis extract is a potential agent that is useful for improving immune responses with the ability to reduce Treg cell activity.

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