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MINIREVIEWS

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MINIREVIEWS

Historical evolution, overview, and therapeutic manipulation of co-stimulatory molecules

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Abstract

Co-stimulatory molecules are key mediators in the regulation of immune responses and knowledge of its different families, structure, and functions has improved in recent decades. Understanding the role of co-stimulatory molecules in pathological processes has allowed the development of strategies to modulate cellular functions. Currently, modulation of co-stimulatory and co-inhibitory molecules has been applied in clinical applications as therapeutic targets in diseases and promising results have been achieved.

Key Words: Co-stimulatory molecules; Immune modulation; Monoclonal antibodies; Biological therapy; Autoimmune diseases; Oncological diseases

Core Tip: Several reviews of co-stimulatory molecules have been published, however, this review summarizes the historical aspects, the cellular and molecular mechanisms of the different families of costimulatory molecules implied in processes of health and disease. All of this knowledge has been applied to develop different drugs targeting costimulatory molecules in different diseases like cancer and autoimmune diseases.

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INTRODUCTION

Regulation of the immune response is a crucial process in the initiation and control of inflammatory phenomena. Various mechanisms capable of regulating T cell activation have been described. Co-stimulatory molecules were initially described as accessory signals present in antigen-presenting cells (APCs) that interacted with T cells during the immunological synapse[1]. They comprise a diversity of glycoproteins expressed in the membrane of APCs, and they interact with other glycoproteins that function as their receptors on T cells, modulating in a positive or negative way the activation, proliferation, differentiation, and function of T cells[2]. In recent decades, advances in the knowledge of co-stimulatory molecules and the development of biological drugs allowed a therapeutical targeting of co-stimulatory molecules in distinct diseases[3].

A BRIEF HISTORY OF CO-STIMULATORY MOLECULES

A two-signal model of T cell activation was first proposed in the second half of the 1960s. The two signals were antigen recognition by an antigen receptor and the interaction with co-stimulatory molecules. Although the mechanisms were not known, the model proposed that in the absence of a second signal or "co-stimulation," the T cell would enter a state of paralysis or inactivation[4,5]. By the second half of the 1980s, a series of investigations had experimentally demonstrated the existence of co-stimulatory molecules and their participation in T cell activation[6-9]. The findings resulted in the description of a diversity of molecules and the investigation of their function in different disease models, which led to therapeutic applications. One example is the 2018 Nobel Prize in Physiology and Medicine, awarded to Tsuku Honjo and James P Alisson, for their contributions to the discovery of cytotoxic T lymphocyte–associated antigen (CTLA)-4 and programmed death (PD)-1 protein and the development of methods of molecular blockade for the treatment of oncological diseases[10-12].

OVERVIEW OF ANTIGEN PRESENTATION AND INVOLVEMENT OF CO-STIMULATORY MOLECULES

APCs are part of the innate immune system and act as an interface between antigen recognition and the adaptive response of T cells during antigen presentation[3]. Activation of T cells requires the appropriate activation and integration of three signals. The first signal is the antigen, which is presented in the context of the major histocompatibility complex, and its recognition by the T cell receptor (TCR). The first signal is not sufficient to activate T cells. Activation continues with a second signal that involves the participation of surface molecules expressed on dendritic cells that interact with their respective receptors on the T cell. The third signal involves the production of cytokines, which not only favor the activation state but also promote the polarization of T cells into their various helper/cytotoxic subpopulations[3,13] (Figure 1). In that dynamic microenvironment, the spatiotemporal expression of various co-stimulatory molecules on dendritic cells and T cells, as part of the second signal, is the key to regulating T cell activation, inhibition, survival, and polarization.

Activating and inhibitory signals

Co-stimulatory molecules are transmembrane glycoproteins that induce activation or inhibition cascades that enhance or diminish TCR signaling[14,15]. Stimulatory, or activating signals (co-stimulation by CD28 or CD40), lead to the production of growth factors, cell expansion, and survival. Inhibitory signals (co-inhibition by PD1 or CTL-4) attenuate TCR-induced signals, resulting in decreased cell activation, inhibition of growth factor production, inhibition of cell cycle progression, and in some cases, promotion of cell death[14].

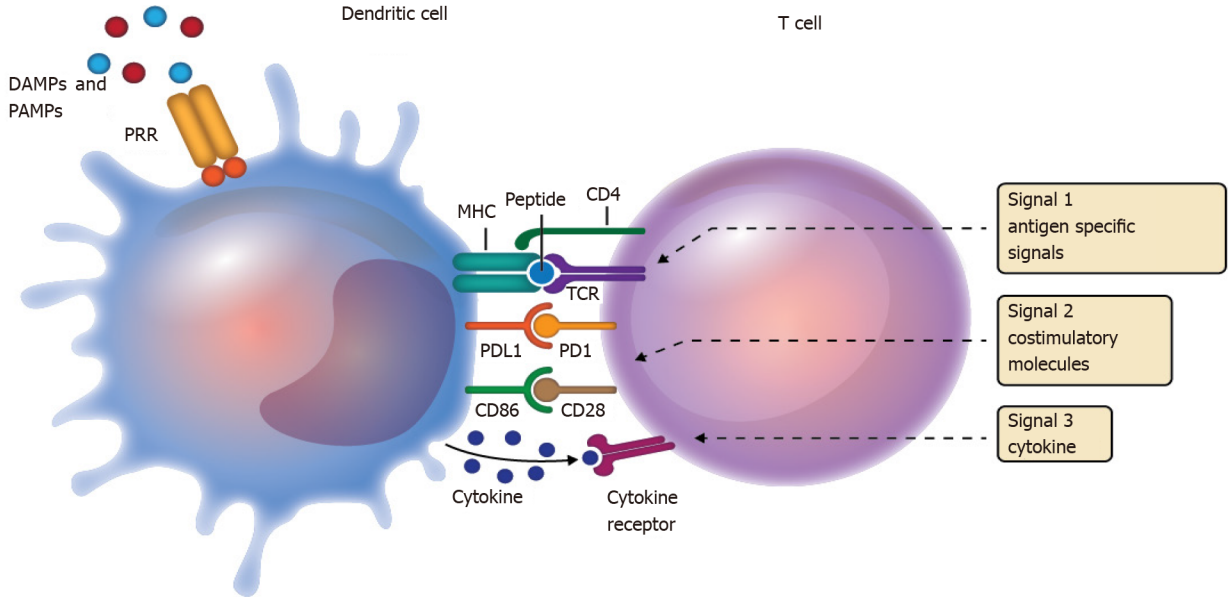

Figure 1 Overview of antigen presentation and the three-signal model. The three-signal model proposes: (1) Antigen presentation to the T cell receptor by the major histocompatibility complex; (2) Interaction of co-stimulatory molecules with their receptors; and (3) Cytokine production and recognition by the cytokine receptors of T cells. DAMPs: Damage-associated molecular patterns; PAMPS; Pathogen-associated molecular patterns; PD1: Programmed death-1; PDL1: Programmed death ligand 1; PRR: Pattern recognition receptor.

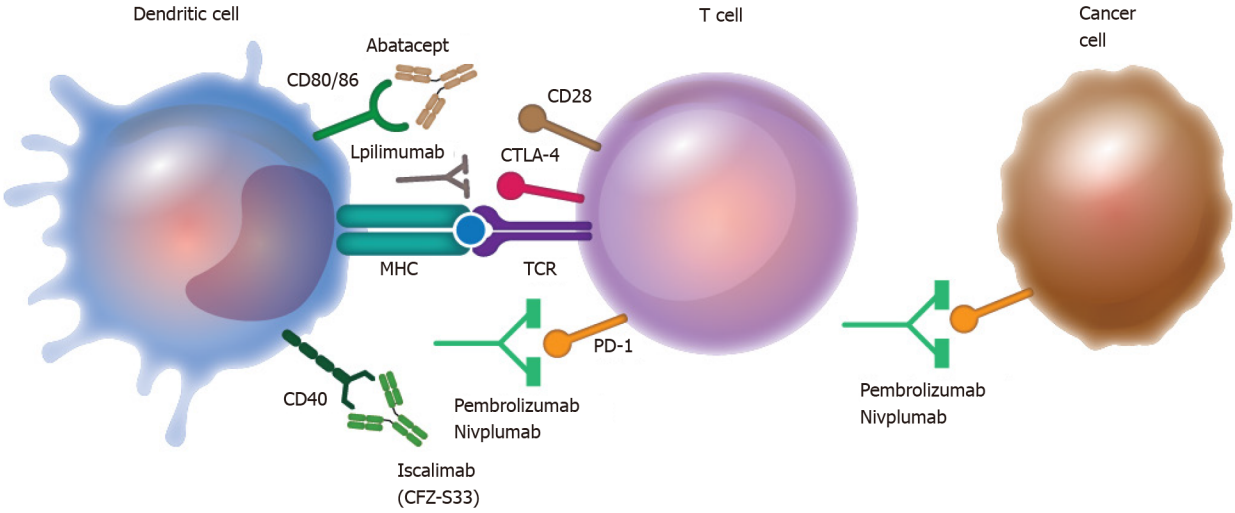

Figure 2 Therapeutical manipulation of co-stimulatory molecules. Biological drugs have been developed to target co-stimulatory molecules and promote or inhibit their functions in distinct diseases. For example, the fusion protein abatacept blocks CD80/CD86 to prevent interaction with CD28; mAb iscalimab blocks CD40, ipilimumab blocks cytotoxic T lymphocyte antigen-4, and pembrolizumab blocks programmed death-1 (PD-1). These strategies have been implemented to modulate co-stimulatory molecule functions in immune and cancer cells. MHC: Major histocompatibility complex; TCR: T cell receptor.

Families of co-stimulatory molecules

Co-stimulatory molecules are divided into two main families by their molecular structure. The first (Table 1) is the immunoglobulin superfamily which includes CD226, the CD2/signaling lymphocytic activation molecule family, T cell immunoglobulin and mucin (TIM) family, butyrophilin (BTN) family, and leukocyte-associated immunoglobulin-like receptor (LAIR) family. Because of its historical relevance, the most studied is the B7 family, which includes CD80, CD86, and its receptor CD28. The second (Table 2) is the tumor necrosis factor superfamily (TNFR SF), which includes three subfamilies, the divergent type (OX-40, CD27, glucocorticoid-induced TNFR-related protein), the S-type (CD267), and the conventional type [FAS, herpes virus entry mediator, receptor activator of nuclear factor kappa-B (RANK), and CD40]. CD40 and its ligand CD40L are the most investigated co-stimulation molecules of the TNFR SF[3].

Table 1 Immunoglobulin super family co-stimulatory molecules

IgSF co-stimulatory molecules	Function	Cells expressing the receptor	Ligand	Cells expressing the ligand
CD28	Activation	Constitutive in T cells	CD80, CD86	CD80: Inducible in dendritic cells, monocytes, B and T cells. CD86: Constitutive in dendritic cells, monocytes, B and T cells
ICOS (CD278)	Activation	Inducible in T, B, and NK cells	ICOSL	Constitutive in macrophages, dendritic cells, B and T cells
CTLA-4 (CD152)	Inhibition	Inducible in T cells	CD80, CD86	CD80: Inducible in dendritic cells, monocytes, B and T cells. CD86: Constitutive in dendritic cells, monocytes, B and T cells
PD-1 (CD279)	Inhibition	Inducible in T, and B cells, macrophages	PD-L1, PD-L2	PD-L1: Constitutive in dendritic cells, B and T cells. PD-L2: Inducible in dendritic cells and monocytes
PD-1H (VISTA)	Inhibition	Monocytes, neutrophils, T cells	Unknown	Unknown
BTLA (CD272)	Inhibition	B and T cells	HVEM, UL144	Monocytes, B and T cells
B71 (CD80), B72 (CD86)	Activation/Inhibition	CD80: Inducible in dendritic cells, monocytes, B and T cells. CD86: Constitutive in dendritic cells, monocytes, B and T cells	CD28, CTLA-4	CD28: Constitutive in T cells. CTLA-4: Inducible in T cells
B7H1 (CD274, PDL1)	Inhibition	Constitutive in dendritic cells, monocytes, B and T cells	PD-1, B71	PD-1: Inducible in macrophages, B and T cells. CD80: Inducible in dendritic cells, monocytes, B and T cells

BTLA: B- and T lymphocyte attenuator; CTLA: Cytotoxic T lymphocyte antigen; HVEM: Herpes virus entry mediator; ICOS: Inducible T cell co-stimulator; ICOSL: Inducible T cell co-stimulator ligand; PD-1: Programmed death-1; PD-L: Programmed death ligand; PD-1H: Programmed death-1 homolog; VISTA: V domain Ig suppressor of T cell activation.

Co-stimulatory molecules and their study in human disease

The involvement of co-stimulatory molecules in clinical conditions has been explored. Mutations in ICOSL, CD40, or C267 have been associated with immunodeficiencies; increased expression of CD86, CD28, CD27, and CD70 has been reported in autoimmune diseases and allergies[16-23]. Some of the most interesting findings are summarized in Tables 3 and 4.

Therapeutic application of co-stimulatory or co-inhibitory molecules

Numerous scientific studies have shown the involvement of co-stimulatory molecules in the regulation of the inflammatory process[3]. Subsequently, both experimental trials in various disease models and preclinical trials have demonstrated promising results achieved by the therapeutic manipulation of these molecules[24,25]. The preclinical results support their application at the clinical level either by inhibiting the function of activating co-stimulatory molecules to promote tolerogenic functions or by inhibiting inhibitory co-stimulatory molecules to promote pro-inflammatory functions.

Blockade of the co-inhibitory molecules PD1 and CTLA-4 by the monoclonal antibodies pembrolizumab, ipilimumab, and nivolumab is a therapeutic indication in cancer treatment, particularly melanoma. On the other hand, therapeutic approaches for autoimmune diseases have exploited the blockade of the co-stimulatory molecules CD80/CD86 by abatacept or CD40 by iscalimab. In both cases, co-stimulatory molecule-targeted therapies have shown promising results[26-32] (Figure 2 and Table 5).

CONCLUSION

Challenging limitations need to be overcome before these therapeutical tools are approved for clinical use[33]. Nevertheless, understanding the function and the possibility of therapeutic manipulation of co-stimulatory molecules represents a milestone for immunology and pharmacology. The knowledge gained from the study of co-stimulatory molecules has allowed a deeper understanding of the pathophysiology of many diseases. The therapeutic use of these molecules has been

Table 2 Tumor necrosis factor receptor super family co-stimulatory molecules

TNFR SF co-stimulatory molecules	Function	Cells expressing the receptor	Ligand	Cells expressing the ligand
OX40 (CD134)	Activation	Activated and regulatory T cells	OX40L	T cells, macrophages, endothelial cells, vascular smooth muscle cells, dendritic cells, tumor cells
CD27 (TNFR SF7)	Activation	T and B cells, NK cells	CD70	NK, T and B cells
GITR (CD357)	Activation	T cells	GITRL	T cells
CD30 (TNFR SF8)	Activation	T and B cells	CD30L	T cells
HVEM (CD270)	Activation	Monocytes, T and B cells	LIGHT, BTLA, CD160, LTα3, HSV1gD	Monocytes and APCs
FAS (CD95)	Activation	NK and T cells	FASL	Dendritic cells, NK, T cells, neutrophils
CD40 (TNFR SF5)	Activation	All B-cell lineages except plasma cells, macrophages, activated monocytes, follicular dendritic cells, interdigitating dendritic cells, endothelial cells, fibroblasts	CD40L	Activated CD4+ T cells, some CD8+ T cells, γδ T cells, basophils, platelets monocytes and mast cells
RANK (CD265)	Activation	Osteoclast and dendritic cells	RANKL	Osteoblasts, T cells
TACI (CD267)	Inhibition	B and plasma cells	BAFF, APRIL	Stromal cells, dendritic cells, and macrophages

APCs: Antigen-presenting cells; APRIL: A proliferation-inducing ligand; BAFF: B-cell activating factor; BTLA: B- and T lymphocyte attenuator; FASL: FAS ligand; GITR: Glucocorticoid-induced TNFR-related protein; HSV1gD: Herpes simplex virus-1 glycoprotein D; HVEM: Herpes virus entry mediator; LIGHT: TNFR14; LT3: Lymphotoxin-alpha 3; RANK: Receptor activator of nuclear factor kappa; TACI: Transmembrane activator and calcium-modulator and cyclophilin ligand interactor; TNFR SF: Tumor necrosis factor superfamily.

Table 3 Immunoglobulin super family co-stimulatory molecules studied in various diseases

Molecule	Disease	Alteration	Ref.
CD86	Rheumathoid arthritis	Increased expression in B cells	[16]
ICOSL	Combined immunodeficiency	Mutation	[17]
CTLA-4	Mycosis fungoides	Increased expression in T cells	[18]
CD28	Tuberculosis	Decreased expression in CD8+ and CD4+ T cells	[19]
CD28	Graves' disease	Increased expression in T cells	[20]

CTLA: Cytotoxic T lymphocyte antigen; ICOSL: Inducible T cell co-stimulator ligand.

Table 4 Tumor necrosis factor superfamily co-stimulatory molecules studied in various diseases

Molecule	Disease	Alteration	Ref.
CD27	Lupus erythematosus	Increased expression in plasmablasts	[21]
CD70	Lupus erythematosus	Increased expression in plasmablasts	[21]
CD40	Hyper IgM Syndrome	Mutations	[22]
CD30	Vernal Keratoconjunctivitis	Increased expression in T cells	[23]
CD267	Common variable immunodeficiency	Mutations	[24]

well exploited in autoimmune diseases and oncology, where they serve as effective adjuvants to conventional therapy. However, we should not exclude the potential that these molecules have in many other contexts. They will undoubtedly continue to be an area of great interest for research and drug development.

Table 5 Co-stimulatory molecule manipulation in various diseases

Disease	Therapeutic target	Manipulation	Outcome	Ref.
Brain metastases melanoma	PD-1 and CTLA-4	Blockade with mAbs (nivolumab + ipilimumab)	55% of treated patients reduced tumor size. 21% showed full response	[27]
Melanoma	PD-1	Blockade with mAbs (pembrolizumab or nivolumab)	19% of treated patient reduced tumor size	[28]
Melanoma	PD-1	Blockade with mAbs (pembrolizumab)	33% of treated patient reduce size tumor	[29]
Rheumatoid arthritis	CD80/CD86	Blockade with soluble receptor (abatacept)	Reduction in the disease index	[30]
Psoriatic arthritis	CD80/CD86	Blockade with soluble receptor (abatacept)	Musculoskeletal clinical improving	[31]
Sjögren syndrome	CD40	Blockade with recombinant antibody (CFZ533 or iscalimab)	Reduction in the disease index	[32]
Kidney graft	CD40	Blockade with recombinant antibody (CFZ533 or iscalimab)	Transplant success rate similar to tacrolimus treatment, but with a lower probability of adverse effects and infections	[33]

CTLA: Cytotoxic T lymphocyte antigen; PD-1: Programmed death-1.

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EDITORIAL

Vaccines and autoimmunity during the COVID-19 pandemic

Tsvetelina Velikova

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Abstract

To control the pandemic, efficient vaccines must be applied to the population, including patients with autoimmune diseases. Therefore, one can expect that coronavirus disease 2019 (COVID-19) vaccines may influence the underlying autoimmune processes in these patients. Additionally, it is essential to understand whether COVID-19 vaccines would be effective, safe, and provide long-lasting immunological protection and memory. However, the currently available and approved COVID-19 vaccines turned out to be safe, effective, and reliable in patients with autoimmune inflammatory and rheumatic diseases. Furthermore, most patients said they felt safer after getting vaccinations for COVID-19 and reported enhanced overall quality of life and psychological wellbeing. In general, the COVID-19 vaccines have been highly tolerated by autoimmune patients. Such findings might comfort patients who are reluctant to use COVID-19 vaccines and assist doctors in guiding their patients into receiving vaccinations more easily and quickly.

Key Words: SARS-CoV-2; COVID-19; Immune response; COVID-19 vaccine; Immune memory; Autoimmunity; Autoimmune diseases; Relapse

Core Tip: Coronavirus disease 2019 (COVID-19) vaccines have created concerns about their efficacy and safety, notably in autoimmune patients. Which vaccine adverse events are related to the underlying autoimmunity is unclear. Additional data is needed to evaluate the immunological impact of COVID-19 vaccines in terms of effectiveness and immune-driven adverse effects that might provoke a disease flare in individuals with a history of autoimmune-related symptoms. However, the risk of autoimmune disease flare after vaccination was considered low, while the immune responses after vaccination showed great immunogenicity for these patients. In addition, vaccination will considerably decrease related morbidity and mortality from COVID-19 in autoimmune patients.

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INTRODUCTION

We still do not know all the mechanisms involved in the immune system - severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) interaction during coronavirus disease 2019 (COVID-19) infection. However, it was demonstrated that the virus possesses a tremendous ability to inhibit the immune mechanisms, both innate and adaptive[1]. Nevertheless, there are still controversial data on which immunity is better - naturally acquired or vaccine[3].

There are concerns regarding people living with autoimmune diseases as well. In patients with autoimmune diseases, the body's immune system is overactive and destroys its own cells through various mechanisms, including autoantibodies and immune cells[4,5]; therefore, one can expect that COVID-19 vaccines may influence the autoimmune processes in these patients. Additionally, it is essential to understand whether COVID-19 vaccines would be effective and safe in patients with autoimmune diseases and whether vaccines will provide long-lasting immunological protection and memory[6]. However, in order to take control of the pandemic, the medical community has stressed that efficient vaccines must be applied to the population. This approach includes vaccinating patients with autoimmune diseases.

CAN THE COVID-19 VACCINES CAUSE AUTOIMMUNITY?

Data showed that the immune hyperactivation and cytokine-excessive release in patients with COVID-19 resulted in multi-organ failure and death[7]. In line with this, patients with already activated immune system could be more prone to severe SARS-CoV-2; however, this was not proven for patients with autoimmune diseases. The main concerns are severe outcomes for patients on immunosuppressive therapy or developing severe clinical complications[8]. Indeed, it was shown that SARS-CoV-2 could induce a robust immune response in immunocompromised patients[9,10].

On the other hand, COVID-19 vaccines have also created concerns about their efficacy and safety, notably in autoimmune patients. We recently published a paper addressing the known pros and cons of vaccinating patients with autoimmune disorders, stressing the absence of data on the advantages and disadvantages of newly discovered COVID-19 in patients with autoinflammatory and rheumatic diseases[11]. Various pathways that contribute to the increase in acute autoimmune responses have been suggested[12]. For example, molecular mimicry, *i.e.*, antibodies against SARS-CoV-2 spike glycoproteins, has the theoretical potential to trigger autoimmunity, as Vojdani and Kharrazian[13] recently demonstrated. Talotta[14] further suggested that an injectable nucleic acid vaccination might put young women in danger of undesired, unexpected immunological side effects, especially those already susceptible to autoimmune or auto-inflammatory disease. However, even in the autoimmune population, serious adverse events are rare[15,16].

Akinosoglou *et al*[7] further hypothesize that immunization with COVID-19 is not the cause for *de novo* immune-mediated adverse events. In contrast, the immunological reaction might lead to dysregulation of the pre-existing underlying pathways. This might result from the polyclonal expansion of the B cells leading to the development of immunological features of autoimmunity. It should be noted that autoimmune disorders can be provoked in genetically sensitive individuals through various autoimmune mechanisms, including epitope spreading and bystander activation[17]. Which vaccine adverse events are related to the underlying autoimmunity is unclear. An unsolved issue remains whether to provide a second dosage after such reactions in patients with rheumatic diseases. Additional data is needed to evaluate the immunological impact of COVID-19 vaccines in terms of effectiveness and immune-driven adverse effects that might provoke a disease flare in individuals with a history of

autoimmune-related symptoms[7].

COVID-19 VACCINES AND PATIENTS WITH AUTOIMMUNE DISEASES

As demonstrated previously, elderly populations with chronic disorders such as diabetes, asthma, and cardiovascular disease are especially susceptible to severe SARS-CoV-2[18]. The same concerns were raised regarding patients with autoimmune inflammatory rheumatic diseases (AIIRDs)[19,20]. However, recent studies demonstrated that patients receiving immunosuppressive therapy for AIIRDs produced sufficient and protective immune response after SARS-CoV-2 mRNA vaccination without experiencing severe side effects or flares[21].

Since AIIRD patients are usually not included in phase III clinical trials of vaccines, immunological response to COVID-19 vaccination in AIIRD patients under the immunosuppression treatment remains unknown. Although the COVID-19 vaccine efficacy was demonstrated between 60%-95% with acceptable safety, uncertainty in AIIRD patients for the COVID-19 vaccines, especially the novel RNA and viral vector vaccines, led to hesitancy in both physicians and patients[22,23]. However, the currently available and approved COVID-19 vaccines turned out to be safe, effective, and reliable in patients with AIIRD. Furthermore, unless contraindicated for medical conditions, such as previous allergy/anaphylaxis to the COVID-19 vaccine or its ingredients, any patient with AIIRD should receive one of the available COVID-19 vaccines.

Patients have to continue immunosuppressive therapy for their underlying AIIRD, which may include biological and selective synthetic disease-modifying anti-rheumatic medications. Korean College of Rheumatology issued guidelines recommending limiting corticosteroids to the lowest possible dosage without exacerbating AIIRD. Methotrexate may be deferred for 1-2 wk following each injection to increase vaccine response. The duration of rituximab and abatacept infusions may also be adjusted[21]. The overall vaccine benefits exceed possible vaccine dangers, as the study showed. Additionally, the risk of disease flare of AIIRD after vaccination is low. However, the currently accepted surrogate markers for the immune response after vaccination (*i.e.,* antibodies against SARS-CoV-2 and activated T cells) showed great immunogenicity of the vaccines in these patients[21].

Another concern that must be discussed is assessing vaccine effectiveness in the IV phase, a.k.a. the real-world studies. Clinical studies investigating high-risk for infection people, *i.e.,* healthcare workers, showed that the absolute risk of testing positive for SARS-CoV-2 after vaccination with mRNA vaccine in a cohort of healthcare workers was 0.97%-1.19%[24]. One must consider that the healthcare staff was younger and more susceptible to SARS-CoV-2 than the clinical trial participants. As stated above, hesitancy in autoimmune patients may have arisen because these individuals were mainly omitted from vaccination studies of COVID-19. Boekel *et al*[18] have already shown that more than one-third of autoimmune patients are reluctant to get vaccinations against COVID-19. The primary concerns are the anticipated side effects and the lack of long-term studies.

Additionally, there are currently very little data on the safety of COVID-19 vaccines in patients with autoimmune disorders, and no research available can compare the impact of different types of vaccinations between patients and healthy controls. For example, worldwide vaccination recommendations for COVID-19 for autoimmune illness patients is based on experts' opinion[25]. In their previous study, Boekel *et al*[26] presented the results from a survey that evaluated the adverse events following COVID-19 vaccinations in systemic AIIRD patients and healthy control (Netherlands Trial Register, trial ID NL8513 and NCT04498286). Of all participants, 1780 patients and 660 controls filled out the questionnaire, whereas 46% and 41% of patients received ChAdOx1 nCoV-19 (AstraZeneca) and BNT162b2 (Pfizer/BioNTech), respectively. Thirteen percent of patients were vaccinated with Moderna. Half of the patients and controls reported at least one mild adverse event, and about 20% of all participants had moderate adverse events. Severe adverse events remained below 1%, with no serious adverse events. Complaints of joints and bones were stated more frequently by patients with AIIRD than controls (10% *vs* 1%, respectively). Fortunately, only 2% of patients reported flare or deterioration of the disease up to 2 mo after COVID-19 vaccination[26].

The results from the survey show that, regardless of the kind of vaccine, adverse effects of immunization with COVID-19 in patients with autoimmune disorders are equivalent to controls. The adverse effects included also predicted local or systemic hyperreactivity responses, which were largely self-limiting. The incidence of individuals who reported adverse events in the clinical trials was lower than the number stated[15], similar to the national study of COVID-19 adverse events in the United Kingdom general population[27]. In conclusion, the survey demonstrated that the vaccines against COVID-19 do not tend to induce autoimmunity flares, as shown in previous limited studies that evaluated mRNA vaccines' impact on patients with autoimmune diseases[20,28].

Known pathophysiological effects mRNA may be both immunostimulatory and immunosuppressive to the innate immune system as COVID-19 vaccines are the first to be widely applied, and prospective, monitored studies of the long-run effects of COVID-19 vaccines on their activities require robust conclusions[11]. Nevertheless, most participants said they felt safer after getting vaccinations for COVID-19, and 20% of individuals with autoimmune disorders reported enhanced overall quality of life

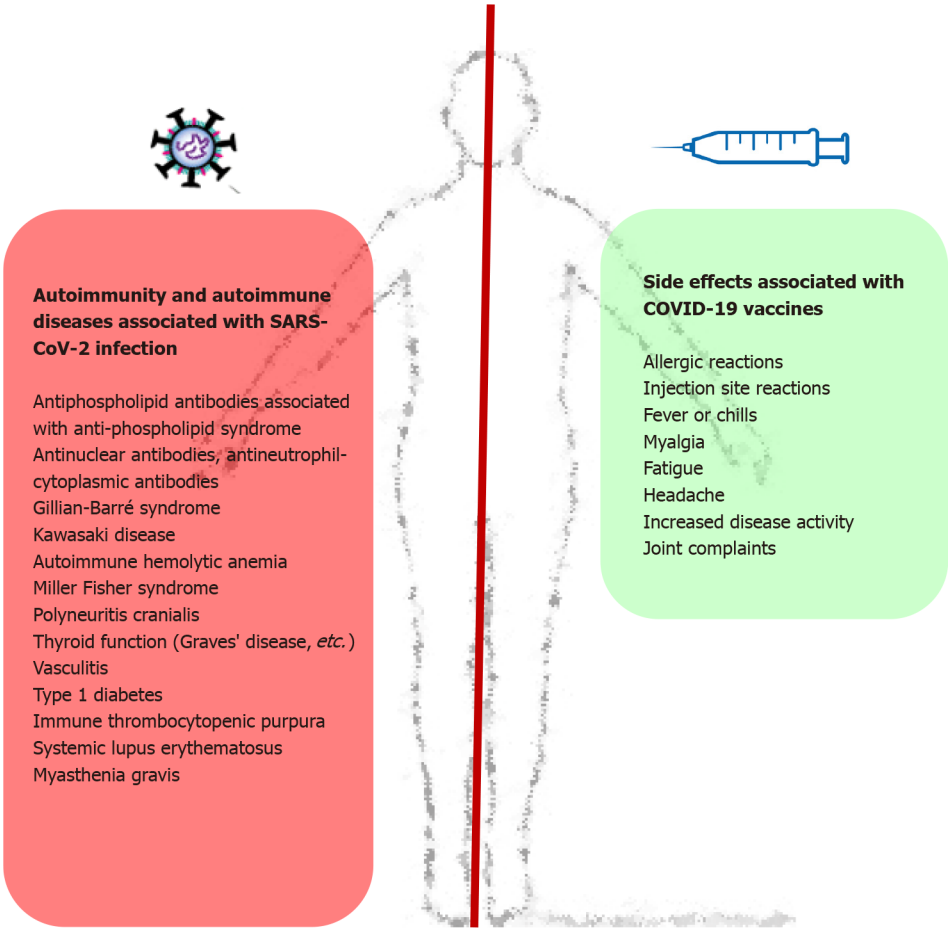

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Figure 1 Many features and characteristics of severe acute respiratory syndrome coronavirus-2 are associated with the development of autoantibodies and autoimmune phenomena. In some patients, autoimmune disease is developed after coronavirus disease 2019 (COVID-19). On the other hand, COVID-19 vaccines proved their efficacy, effectiveness and safety in patients with autoimmune diseases. SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2; COVID-19: Coronavirus disease 2019.

and psychological wellbeing[26]. If we compare these adverse effects associated with the application of COVID-19 vaccines with autoimmune complications during SARS-CoV-2 infection[29], the benefits of vaccines significantly outweigh the side effects of vaccination. This comparison is presented in Figure 1.

CONCLUSION

In general, the COVID-19 vaccines have been highly tolerated by autoimmune patients. Such findings might comfort patients who are reluctant to use COVID-19 vaccines and assist doctors in guiding their patients in vaccination timely. Therefore, the therapy and management of COVID-19 should be given priority to reduce the catastrophic effect of COVID-19 in autoimmune patients, and SARS-CoV-2 immunization is one of the most effective protection against infection. Additionally, significant research with the acquisition of new data is required to assess the safety and efficiency of COVID-19 vaccines in immunocompromised patients. In addition, medical practitioners should counsel their immunocompromised patients to support SARS-CoV-2 vaccinations, as this might considerably decrease related morbidity and mortality from COVID-19.

FOOTNOTES

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MINIREVIEWS

Probiotic treatment of inflammatory bowel disease: Its extent and intensity

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Abstract

Free radicals (reactive oxygen species, superoxides and hydroxyl radicals) lead to the development of oxidative stress because of imbalance in the amount of antioxidants. Continued development of oxidative stress leads to chronic diseases in humans. The instability in the antioxidant activities and accumulation of oxidative stress due to free radicals may occur in diseases like inflammatory bowel disease (IBD). Antioxidants are substances that inhibit or delay the mechanism of oxidation of molecules mediated by free radicals and also transform into lesser-active derivatives. Probiotics are defined as live microorganisms that show beneficial effects on inflamed intestine and balance the inflammatory immune responses in the gut. Probiotic strains have been reported to scavenge hydroxyl radicals and superoxide anions that are abundantly produced during oxidative stress. The most widely studied probiotic strains are *Streptococcus, Bifidobacterium* and *Lactobacillus*. Probiotics cultured in broth have shown some amount of antioxidant activities. Fermented milk and soy milk, which possess starter microorganisms (probiotics), tends to increase the antioxidant activities many-fold. This review aims to discuss the *in vivo* and *in vitro* antioxidant activities of specific probiotics with various assays with respect to IBD.

Key Words: Oxidative stress; Inflammatory bowel disease; Probiotics; Therapy; Anti-oxidative activity

Core tip: Inflammatory bowel diseases (IBDs) are degenerative diseases that cause chronic inflammation in the intestine. The most prevalent therapy for IBD is conventional antibiotic therapy. Keeping the adverse effects of antibiotics in mind, researchers have shown that *Streptococcus, Lactobacillus* and *Bifidobacterium* are some of the most efficient antioxidative agents with respect to *in vitro* and *in vivo* activities. Probiotics individually or in combination play an important role in regulating superoxide dismutase activity, which is always dysregulated due to oxidative stress caused in IBD. The mechanism of antioxidation of probiotics using NRf2-antioxidative response element pathway, nuclear factor-B and protein kinase C pathway may be activated to contribute to the reduction of oxidative-stress-induced IBD. The review focuses on the antioxidative activities of the specific bacterial strains as therapeutic molecules in IBD. Multiple combinations of probiotic strains have still not been adequately studied. We are currently researching the antioxidative effect of *Streptococcus thermophilus*, *Lactobacillus acidophilus* and *Bifidobacterium bifidum*in combination.

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INTRODUCTION

Inflammatory bowel disease (IBD) is an umbrella term used to describe chronic inflammation in the human digestive tract. IBDs are characterized by diarrhea, rectal bleeding, abdominal pain, fatigue and weight loss. IBDs are prevalent in western countries, although they are on the rising track in the Asian countries, which mimics the prevalence in American and European countries. When the burden of IBD is compared between eastern and western countries, the prevalence of IBD in India, which is one of the eastern countries, is found to be the highest. The imbalance in pro-oxidants and antioxidants in the gut leads to inflammation. Despite having antibiotic medication, the prevalence of IBD is still high worldwide. Thus, there is a need to investigate small molecule therapeutic approaches to stop the increase in the number of cases of IBD. In humans, reactive oxygen species (ROS) function as regulators and mediators to ensure correct cell functioning[1,2]. Overproduction of ROS can easily induce damage to proteins, nucleic acids or lipids through free radical reactions. Therefore, in the event of excess ROS production, protective antioxidant mechanisms are required to prevent oxidative stress[1,2]. ROS include superoxides, nitric oxides (NO), hydroxyl radicals, singlet oxygen and hydrogen peroxide (H_2O_2) that contributes to cellular damage, leading to inflammation. IBD is known for the occurrence of oxidative stress. Ulcerative colitis (UC), which is one type of IBD, leads to the increased generation of highly toxic ROS that exceeds the capacity of the limited intestinal antioxidative defense system[3,4]. Oxidative stress in IBD is the key factor for progression of inflammation and is identified by the increased production of ROS, decreased antioxidant molecules and enzymes (beta-carotene, vitamin C and vitamin E) and enhanced lipid peroxidation in the intestine[5].

In the inflammatory processes, intestinal cells of inflamed tissue in response to chemical agents or pathogens, produce high levels of ROS and superoxide anions[6]. Exposure to antigens for a short period of time does not cause any harm because of the adequate first-line defense system producing antioxidative enzymes for protection[6]. However, in chronic intestinal inflammation, there is persistent high ROS production. This process damages the intestinal epithelial barrier, enhances inflammation and injures the intestinal epithelium[6]. Lipid peroxidation is another process that involves a source of secondary free radicals, which directly interact with other biomolecules. The lipid peroxidation depends on the number of double bonds; therefore, polyunsaturated fatty acids are the most susceptible to oxidation. Lipid peroxidation occurs on polyunsaturated fatty acids located on the cell membrane[7]. Superoxide anion radicals, H_2O_2 and hydroxyl radicals secreted by neutrophils and other phagocytes, causes cell membrane to be impaired, eventually leading to cell death by lipid peroxidation[6]. Enhanced free radicals in the gut can exert peroxidation of membrane phospholipids of intestinal epithelial cells, resulting in the release of toxic products like malondialdehyde (MDA) that can cause damage and cellular stress. MDA is the key breakdown product of lipid peroxides, which is present in the plasma of IBD patients[6]. Increased level of MDA in plasma of Crohn's disease (CD) patients is considered to be anoxidative stress marker[6]. Decreased superoxide dismutase (SOD)-2 expression is one of the identification markers in colitis-induced mice.

The current preferred therapies for IBD include 5-aminosalicylate, steroids, corticosteroids and azathioprine[8]. The limitations of IBD therapy include the clinical adverse effects of antibiotics, corticosteroids and immunomodulators, which revolves around nausea, vomiting, stomach pain, diarrhea, headaches, respiratory infections, acne, weight gain, insomnia, dizziness, muscle or joint cramps and pathological side effects, causing some pathogenic bacteria to become resistant in IBD.

Surgery is generally costly and unaffordable to many people in remote areas. Also it can cause harm to many organs. Thus, the literature reviews have confirmed the apparent need for improvised treatment using small molecules, like probiotics[9]. Nowadays, 60%–80% of the world population relies on alternative medication to cure IBD. Probiotics are preferably of human origin: they have to be safe for the host, genetically stable and capable of surviving throughout the gastrointestinal tract. Probiotics are generally applicable for viable cells, whereas, postbiotics are soluble factors (either secreted by live bacteria or released after bacterial cell lysis), which are beneficial to human hosts. Probiotics have recently been emerged as one of the powerful novel therapeutic small molecules against IBD. They have been shown to have a positive effect on oxidative stress by promoting the potency of the antioxidative defense system, and in turn may lower the risk of several inflammatory disorders such as IBD. Various known probiotics play an important role in antioxidative activity. Probiotics could be a possible intervention for reducing ROS and lipid peroxidation and thereby increasing SOD activity. Our goal was to review on the *in vivo* and *in vitro* antioxidative activities of probiotics. Antioxidative activities of probiotics like *Streptococcus*, *Bifidobacterium* and *Lactobacilli* against oxidative stress in IBD are the main focus of the review.

MECHANISM OF OXIDATIVE REACTION INSIDE A CELL

Oxidative stress occurs due to an imbalance between free radical production and antioxidant defense, resulting in hydroxylation of DNA, denaturation of proteins, peroxidation of lipid, and apoptosis, ultimately compromising cell viability[10]. An excess of oxidative stress can lead to the oxidation of lipids and proteins, which is associated with changes in their structure and function. H_2O_2 is formed by dismutation of superoxides or direct reduction of oxygen. H_2O_2 can penetrate most of the cell membranes and react with iron in the cell to form hydroxyl radicals. Therefore, hydrogen peroxides are more cytotoxic than superoxide anion radicals. The oxidative modification of lipids, proteins, nucleic acids and carbohydrates is induced and mediated by both free radicals and nonradical activities of reactive species[7,11]. Superoxides are unreactive molecules but undergo dismutation or enzymatic catalysis to form H_2O_2[7,11]. Hydroxyl radicals are thought to initiate ROS and remove hydrogen atoms. This form of radical is extremely reactive and attack most cellular components[7,11] (Figure 1).

MECHANISM OF ANTIOXIDANT MOLECULES

To neutralize the damaging effect of oxidative stress, we need supplements that possess some antioxidative activities. Antioxidants are proteins or enzymes in nature. Antioxidants inhibit cellular damage mainly through their radical scavenging properties[12]. The principle micronutrients that can scavenge free radicals are vitamin E, Vitamin C and beta-carotene. Humans cannot produce these antioxidant micronutrients. So, they must be supplied through the diet[7]. SOD catalyzes the breakdown of superoxide anions into oxygen and H_2O_2 using Zn/Cu, Fe/Mn and Ni as cofactors[10,13]. Only a few species of *Lactobacillus*, *Lactobacilluscasei*, *Lactobacillusparaplantarum*, *Lactobacillusbucneri* and *Lactobacillussakei* exhibit SOD activity. Catalases are the common enzymes found in all living organisms, which are frequently used by cells to catalyze the decomposition of $H_2O_2$to water and less reactive gaseous oxygen[10].

The nicotinamide adenine dinucleotide phosphate (NADP) oxidase/NADP peroxidase enzyme system prevents oxygen accumulation in bacterial cells by formation of H_2O_2 followed by water. This maintains an intracellular redox balance[10,14]. Antioxidants work by scavenging free radicals, preventing production of free radicals and improving levels of endogenous antioxidants. Scavenging antioxidants remove active species rapidly, before they react with biologically essential molecules in the body. This antioxidants function by scavenging active free radicals before they attack biologically essential molecules by donating hydrogen atoms to give stable compounds.

PROBIOTICS AS ANTIOXIDANT SMALL MOLECULES

When the antioxidant capacity of damaged mucosa is compromised, various natural substances can act as antioxidant molecules to inhibit ROS generation, cell damages and improve the activity of antioxidative enzymes in cells. A food can be considered as functional, when it is demonstrated to provide nutritional effects for health and well-being and reduction of the risk of disease. Ingredients that make foods functional are: dietary fibers, vitamins, minerals, antioxidants and essential fatty acids. One of the novel approaches as therapy against oxidative stress are the development of probiotics[16,17]. Probiotics are the functional foods that possess antioxidant properties[7,15]. Several studies have highlighted that the ability of probiotics are to enhance antioxidant properties. For probiotics growth, milk can be used as a substrate for starter microorganisms. Naturally, milk has its own antioxidant activities due to the

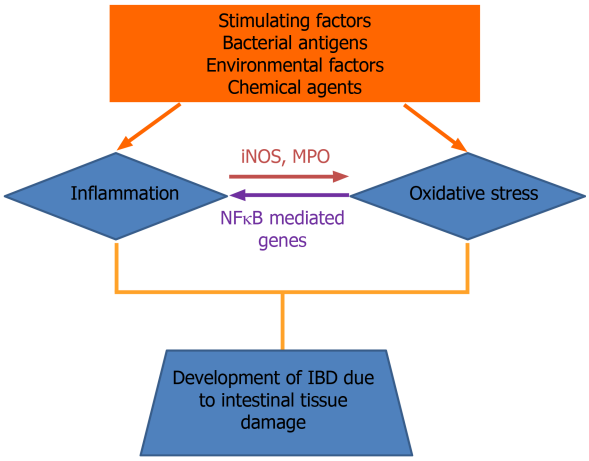

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Figure 1 Illustration of the role of oxidative stress and inflammation in the pathophysiology of inflammatory bowel diseases. Inflammation enhances the oxidative stress by stimulating inducible nitric oxide synthase and myeloperoxidase from inflammatory cells. Simultaneously, oxidative stress involves in the secretion of the inflammatory cytokines, like nuclear factor-B and other cytokines developing IBDs. IBD: Inflammatory bowel disease; iNOS: Inducible nitric oxide synthase; MPO: Myeloperoxidase.

presence of bioactive compounds of whey proteins, caseins, lactoferrin, urate, ascorbate, alpha-tocopherol, beta-carotene as well as enzymes like SOD, catalase and glutathione peroxidase. Fermented milk with probiotic microorganisms has further improved antioxidant potential[18]. Furthermore, the fermentation of soyabean extract using probiotic cultures of lactic acid bacteria possesses superoxide radical scavenging and reducing activities. Soybeans contain SOD, which possesses the superoxide anion scavenging effect. Soymilk obtained from soybean is also expected to possess SOD. The fermented soymilk has an increased superoxide-anion-scavenging effect due to the production of secretory byproducts in the presence of lactic acid bacteria[19].

MODES OF ANTIOXIDATIVE ACTIONS OF PROBIOTICS

Probiotics can directly act to neutralize oxidants by the production of antioxidant enzymes. The antioxidant mechanism of probiotics could be assigned to ROS scavenging, chelation of metal ions, enzyme inhibition and their reducing ability. Probiotics have an antioxidant effect by scavenging of oxidants or by prevention of generation of free radicals in the intestine. Probiotics can upregulate the intracellular activity of SOD, catalase and glutathione peroxidase to protect the cells from intracellular damage. Pro-oxidative metal ions are capable of initiating decomposition of H_2O_2 into radicals and triggering lipid peroxidation. Certain chelators are normally detected in probiotics, stating the chelating capacity of probiotics[8,18]. According to reviews, *Lactobacillus rhamnosus* and *Lactobacillus paracasei* have significantly inhibited the production of hydrogen peroxide, whereas, *L. casei* also possess high antioxidant activity *via* chelating Fe^{2+}[10,21]. Different *in vitro* and *in vivo* studies have reported that probiotic bacteria can protect against oxidative stress through regulation of the Nrf2 (Nuclear factor erythroid 2-related factor 2)–Keap1–antioxidant response element (ARE) pathway, protein kinase C (PKC) pathway and nuclear factor (NF)-B pathway[7,10,22].

The Nrf2–Keap1–ARE system transmits signal into the nucleus. Under normal conditions, Keap1 is associated with Nrf2. However, in ROS infiltration in cells, the bond between Keap1 and Nrf2 is cleaved and Nrf2 eventually enters the nucleus and binds to ARE and enhances the production of the antioxidative enzymesproduction[7,10,23]. ROS activates NF-B, entailing expression of inflammatory cytokines. NF-B responds to oxidative stress. Thus, the probiotic formulations (*Lactobacillussp.*, *Bifidobacteriumsp.* and *Streptococcussp.*) are able to inhibit NF-B activation in colonicepithelial cells[10,24] (Figures 2 and 3). PKCs are the family of protein kinases that are the target for redox modifications. Administration of *L. plantarum*improved the oxidative stress in a rat model of obstructive jaundice by strengthening the expression and activity of the PKCpathway[10,24,25].

IN VITRO AND *IN VIVO* ANTIOXIDATIVE ACTIVITY

Not all the probiotics have antioxidant activity due to high strain heterogeneity. *Bacillus proteolyticus* shows the highest 1-diphenyl-2-picrylhydrazyl (DPPH) and hydroxyl radical scavenging activity[26]. Zeng *et al*[26] reported that *Bacillus amyloliquefaciens* could significantly increase the antioxidative

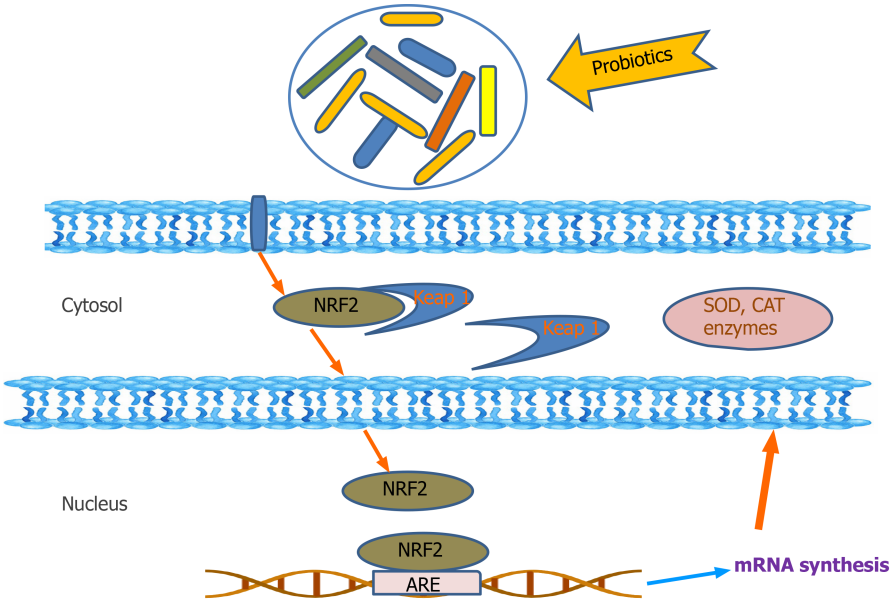

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Figure 2 Cellular antioxidative regulations of probiotics. Antioxidative effect of probiotic on cellular receptor and regulation of cellular cascade is portrayed. SOD: Superoxide dismutase; CAT: Catalase; ARE: Antioxidant response element.

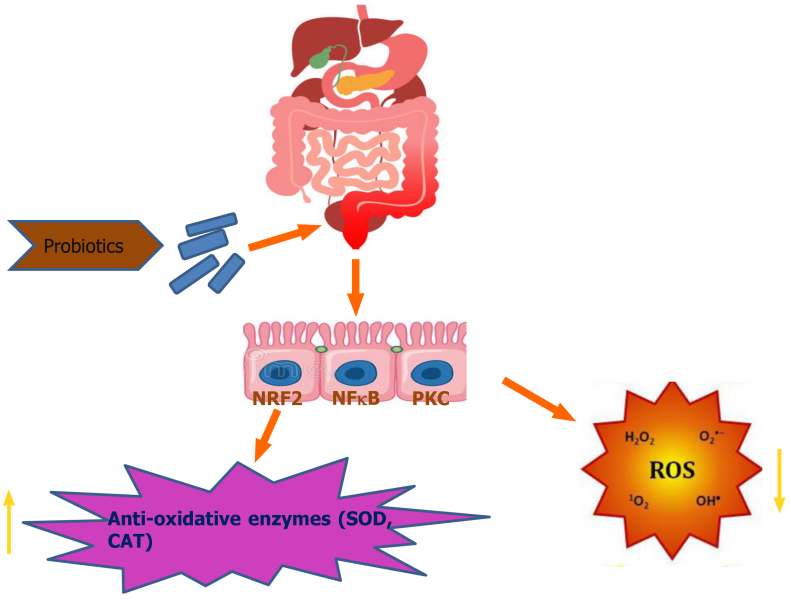

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Figure 3 Modulation of antioxidation by probiotics. SOD: Superoxide dismutase; CAT: Catalase; ROS: Reactive oxygen species; PKC: Protein kinase C.

capacity of epithelial cells to reduce induced oxidative stress in pigs. *Bacillus subtilis* and *L.casei* can scavenge free radicals (*in vitro*) and reduce oxidative damage by improving lipid metabolism followed by reduction in lipid peroxidation. *Streptococcus thermophilus* (YIT 2001) showed the highest *in vitro* antioxidative activity against lipid peroxidation[27]. *Lactobacillus* and *S.thermophilus* showed the highest TAA_{LA} (total antioxidant activity against linoleic acid oxidation) and TAA_{AA} (total antioxidant activity against ascorbate auto-oxidation). The cell-free extracts and intact cells of *Lactobacillus acidophilus* (ATCC4356) demonstrated an increased inhibition of linoleic acid peroxidation from 38% to 48%. This indicates astrongantioxidativeactivity[14]. *Bifidobacterium longum* was also investigated for inhibition of lipid peroxidation activity.

In-vitro cell based antioxidative activity

Stress induced HT29 cells, *i.e.*, H_2O_2-stimulated HT29 cells showed a reduced amount of intracellular SOD, catalase and increased ROS activity. The cultured cells were treated with probiotics for 24 h. The

supernatant of the cells was collected to study the presence of the antioxidative enzyme activity of SOD and catalase[28]. The *Bifidobacterium bifidum* treated cell line showed increased catalase activity. SOD and catalase production by *B. bifidum* can decrease oxidative stress. Moreover, *in vitro* studies have showed that strains like *L. acidophilus* and *Lactobacillus delbrueckii* displayed highest superoxide anion radical dismutation. *L. plantarum* showed increased ability to degrade chemically pure H_2O_2 and demonstrated the highest catalase activity[29]. SOD activity was found in *Lactococcus, S. thermophilus* and *Bifidobacterium*, with significantly higher activity in *Lactococcus* than in *S. thermophilus*[14]. SOD activity of cell-free extracts of the above-mentioned probiotics was studied by the amount of inhibition of reduction of nitrobluetetrazolium[14]. Greatest SOD activity was demonstrated by *Lactococcus* strains. Glutathione was analyzed in deproteinized bacterial cell-free extract using a commercial kit that showed that the *Lactococcus* group had the highest inhibitory effect[14]. However, *S.thermophilus, Lactococcus lactis* and *Bifidobacterium animalis* also contained relevant amounts of intracellular reduced and oxidized forms of glutathione. Total glutathione measurement was carried out in presence of glutathione reductase and NADP[14].

In vivo probiotic antioxidative activity

In an animal model of IBD, it was observed that *L. acidophilus* with dismutase-like activity was more effective than *L. plantarum* in suppressing the inflammatory process[29]. *In vivo* studies have also revealed that *L.plantarum* 0B and *L. acidophilus* has the highest catalase activity and highest dismutase-like activity respectively. Male Wister rats were administered with probiotic formulation (mixture of *B.animalis, L. acidophilus* DSMZ 23033 and *Lactobacillus brevis* DSMZ 23034) after acclimatization of rats in cages. After 18 d of probiotics supplementation, blood plasma was collected to study the antioxidant status[14]. Reactive oxygen metabolite (ROM) concentration of plasma was evaluated as studied by d-ROM test. Plasma total antioxidant activity (TAA) was spectrometric ally measured in the presence of 2-binamine-di-3-ethylbenzothiazolin-6-sulfonic acid (ABTS) radical by evaluating the decoloration and reduction of radical cations of ABTS[14]. Plasma ROM concentration was inversely related to the dose of administered probiotics[14]. TAA was significantly related to the dose of administered probiotics. In another study, oral administration of *Bifidobacterium breve* yakult appeared to prevent transepidermal water loss and significantly suppress oxidation of lipids, proteins and H_2O_2 levels[31].

The antioxidant activity of buffalo milk fermented with *B.bifidum* and *L.acidophilus* was evaluated. Control groups included mice fed with standard dahi without probiotic enrichment and another with fermented milk. Catalase and SOD activity in blood was analyzed[27,31]. SOD activity in red blood cells increased exclusively after probiotic dahi administration. Dahi supplemented by *L.casei* NCDC19 and *L.acidophilus* NCDC14 inhibited lipid peroxidation and maintained the activity of glutathione peroxidase, SOD and catalaseinstreptozotocin-induced oxidative stress inrats[32,33]. *Lactobacillus fermentum* (Lf1) was studied to assess its antioxidative properties, and confirmed the enhanced expression of NRF2 and MDA inhibition in HT29 cells under stress[34]. In another study it was shown that *S.thermophilus* YIT2001 decreased the amount of lipid peroxide in colonic mucosa and improved the symptoms of DSS-induced colitis in mice[27].

QUANTIFIABLE PARAMETERS THAT INDICATE ANTIOXIDATIVE ACTIVITY

Scavenging activity of ROS is one of the antioxidative properties of probiotics. The Reactive Oxygen Species are used to include both oxygen centered radicals and nonradical derivatives of oxygen. There is the scavenging activity of probiotics occurs in conditions where there is abundance of ROS, hydroxyl radicals and H_2O_2.

DPPH RADICAL SCAVENGING ACTIVITY

To evaluate the antioxidative activity of probiotics, DPPH solution was mixed with methanol and probiotic sample and incubated at 37 degree Celsius for 30 min in the dark. The DPPH radical scavenging activitywascalculated by measuring the absorbance of the sample and blank at 517 nm.The radical scavenging activity was calculated as follows: [1-(A_{517}(sample)/A_{517}(blank)]× 100%. According to Das and Goyal, DPPH radical scavenging activity was higher in *L. plantarum* and *L. acidophilus*. Scavenging activity of *Bacillus* ranged from 46% to 190%. *B. proteolyticus* showed the highest DPPH radical scavenging activity, whereas, *B. amyloliquefaciens* had the weakest DPPH radical scavenging activity[36]. Probiotic strains such as *S. thermophilus* and *L. delbrueckii* can scavenge ROS, hydroxyl radicals and H_2O_2[37]. Cell-free supernatants of *Lactobacillus* exhibit strong DPPH radical scavenging activity[37]. Moreover, the crude peptides extracted from *L. acidophilus, L. casei* and *L. paracasei*have radical scavenging activities for DPPH *in vitro.*

LIPID PEROXIDATION INHIBITION

To study the effectiveness of antioxidants, inhibition of lipid peroxidation is commonly studied. Bacterial strains (*L. acidophilus and B. longum*) and the intracellular cell-free extract indicated an inhibitory rate on linoleic acid peroxidation that ranged from 33% to 46%[38]. *L. acidophilus* and *B. longum* demonstrated a high antioxidative activity for inhibiting lipid peroxidation. Inhibitory rate of different strains of *L. acidophilus* ranged from 34.9% to 46.3%[37]. Cell-free supernatants of *Lactobacillus* show higher inhibitory effect than MRS broth cell culture. Intact cells or intracellular cell-free extracts of *L. acidophilus* and *B. longum* were investigated for their antioxidative effects, which demonstrated that inhibition of linoleic acid peroxidation ranged from 38% to 48%[34,39]. *Levilactobacillus brevis* exhibited greater radical scavenging activity and lipid peroxidation inhibitory activity than *Pediococcus pentasaceus* [35]. Many studies related to lipid peroxidation have chosen linoleic acid as the source of unsaturated fatty acids. Unsaturated fatty acids such as linoleic acid, methyl linoleate and arachidonic acid are typically used. The protocol forlipid peroxidation assay using linoleic acid has been standardized to study the inhibition of linoleic acid peroxidation. Egg homogenate is generally not used for lipid peroxidation inhibition studies in the presence of probiotics. Thus, lipid peroxidation assay using egg homogenate can be used to investigate the inhibition of lipid peroxidation by probiotics.

REDUCING ACTIVITY

Reducing power is based on the kinetics of reduction of Fe^{3+} to Fe^{2+} to prevent the oxidation reaction [37]. Ferric-reducing antioxidant power allows estimation of the ability to reduce pro-oxidant metal ions. The fermented black soybean broths of *B. subtilis* have shown a potent reducing power as compared to positive controls *i.e.*, -tocopherol and Butylated hydroxytoluene[39]. Cell-free supernatants of *Lactobacillus* strains showed significantly higher reducing power than MRS broth containing *Lactobacillus*[38]. Ferric ion reducing antioxidant power assay was performed for the fermented milk with *Lactobacillussp*., *S.thermophilus* and *Bifidobacteriumsp*. in the presence of green tea supplementation[15]. Fermented milk with 15% green tea infusion (GTI) shows the highest anti-oxidative power as compared to 10% or 5% GTI[15].

SUPEROXIDE ANION SCAVENGING ACTIVITY

Superoxides are radicals with free electrons located on oxygen[16]. These radicals initiate lipid oxidation as the superoxides and H_2O_2 are precursors of singlet oxygen and hydroxyl radicals[17]. Assays can measure the ability to scavenge superoxide anion radicals. *S. thermophilus* containing fermented milk accounts for the highest superoxide anion scavenging effect as compared to *L. acidophilus*. Archibald and Fridovich showed that *S. thermophilus* was able to produce SOD, while *L.acidophilus* was not. Fermented soy milk with *L. acidophilus+Bifidobacterium infantis*, *L. acidophilus+B. longum*, *S. thermophilus+B. infantis*, or *S. thermophilus+B. longum* shows higher superoxide anion scavenging activity than reducing activity [17]. The cell-free supernatant of *L.plantarum* and *L.acidophilus* showed a potent inhibitory superoxide radical scavenging activity with increasing concentration compared to ascorbic acid[40]. Xing *et al*[36] had studied an enhanced superoxide radical scavenging activity in co-fermentation conditions in milk (with *B.infantis*, *L. plantarum*, *B. animalis* and *S. thermophilus*). *S. thermophilus* exhibited only 58.34% activity, whereas co-fermentation increased the superoxide scavenging activity to 65%.

SCAVENGING OF HYDROGEN PEROXIDE ACTIVITY

H_2O_2 can be generated in biological system in oxidative stress conditions. Being a non-radical oxygen containing reactive agent, it can form hydroxyl radicals (the most highly oxygen radical known). Soymilk fermented with *Bifidobacterium* alone accumulated the largest amount of H_2O_2, whereas, fermented soymilk with *Bifidobacterium* and lactic acid bacteria simultaneously reduced H_2O_2[17].

HYDROXYL RADICAL SCAVENGING ACTIVITY

Among reactive oxygen species, hydroxyl radicals are the most reactive species. It can react with polyunsaturated fatty acid moieties of cell membrane phospholipids and causes damage to the cells. Venkatesan *et al* stated that different concentrations of probiotic species of *Bifidobacterium* and *Lactobacillus* showed strongest radical scavenging activities. The hydroxyl radical scavenging activity of cell-free supernatant of *L.plantarum* and *L. acidophilus* showed potent hydroxyl radical scavenging activity

when compared to positive control ascorbic acid. These two specific strains have shown a better DPPH and hydroxyl radical scavenging activity. The radical scavenging activity was calculated as follows: [A(sample)-A(control)/A(blank)-A(Control)]× 100%.Cell-free supernatants of various *Lactobacillus* strains (*L. rhamnosus, L. casei, L. plantarum, L. reuteri, L. acidophilus, Lactobacillus fermenti* and *Lactobacillus parciminis)* were studied through *invitro* cell-free hydroxyl radical assay. It was concluded that all the *Lactobacillus* strains showed a better scavenging than hydroxyl radical scavenging activities.

ASSESSING THE POTENCY OF PROBIOTICS AS ANTIOXIDANTS

Generally, antioxidants are molecules that interact with the free radicals generated in the cells and terminate the chain reaction before damage is done to the vital molecules. In recent years, researchers have witnessed a beneficial effect of probiotics, especially in regulating the oxidative stress in IBD[32]. *Lactobacillus*, *Streptococcus* and *Bifidobacterium* have been shown to have antioxidative activity that can easily scavenge oxidative stress inducing molecules inside a cell.

CONCLUSION

From this review, it can be concluded that, in IBD, high levels of oxidative stress induce intestinal tissue damage. Oxidative stress is defined as an imbalance between pro-oxidants and antioxidants, and is tightly associated with the exacerbation of IBD. This disturbs the cellular homeostasis by causing cell injury and increased permeability of the mucosal barrier. Probiotics are equipped with antioxidative defense mechanisms, not only to protect their own survival but also to confer protection to the host cell against oxidative stress during colitis. Probiotics are used to combat IBD by reducing ROS generation and lipid peroxidation and by increasing production of antioxidant enzymes (SOD, catalases and peroxidases)[40]. The most common strains studied, *Bifidobacterium* and *Lactobacillus* are reported to secrete SOD and antioxidant molecules that can alleviate oxidative stress in inflamed intestine[41]. Accumulation of probiotic strains in inflamed colon results in some protective effects like, metal-chelating activities, antioxidant enzymes (SOD), eventually showing free-radical scavenging activities by restoring the gut microbiota during colitis. Different *in vitro* studies have suggested that combination of probiotics in fermented milk improve its antioxidative activity[40]. An enhanced superoxide radical scavenging activity of soy milk containing *Bifidobacterium* was observed. Multiple *in vivo* and *in vitro* studies have demonstrated that *Lactobacillus*, *Streptococcus* and *Bifidobacterium* possess outstanding antioxidant activities like DPPH, hydroxyl, superoxide radical scavenging and reducing activities. The important mechanism of antioxidant activities used by probiotics is to reduce oxidative stress, which includes, redox signaling of Nrf2 leading to increase in antioxidant enzyme levels and scavenging of Reactive Oxygen Species. Moreover, it can also be concluded that multiple probiotic strains in combination is much more effective than single probiotic strain with respect to antioxidative studies. Antioxidant probiotic strains can be selected and investigated as promising candidate against IBD. Thus, to develop a novel probiotic combination product with the potential for preventing the oxidative stress, there remains a need to search for particular probiotic strains that can be effective in mitigation of oxidative stress in IBD. The molecular mechanism of the reviewed probiotic strains (*Streptococcus, Lactobacillus* and *Bifidobacterium*) by which they regulate the oxidative stress based cellular cascade in IBD conditions needs to be investigated in detail and validate these antioxidative properties in specific *in vivo* models. Likewise, our novel combination probiotics (*S. thermophilus*, *L. acidophilus* and *B. bifidum*) are under investigation with respect to their antioxidative properties.

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FOOTNOTES

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