

How to Regulate for Human Physiological Functions by Fermented Material

Yuma Katoh¹, Isao Horiuchi¹, Hisako Izumi² and Nobuo Yamaguchi^{2,3*}

¹Department of Respiratory Medicine, Tohkai Central Hospital, Gifu, Japan

²Ishikawa Natural Medicinal Products Research Center, Ishikawa, Japan

³Department of Fundamental Research for CAM, Kanazawa Medical University, Ishikawa, Japan

***Corresponding Author:** Nobuo Yamaguchi, Department of Fundamental Research for CAM, Kanazawa Medical University, Ishikawa, Japan.

Received: November 29, 2019; **Published:** December 12, 2019

Abstract

Background: There are many fermented foods either botanical or vertebrate source everywhere in the world. We have been investigated the mechanism of action by these products why these are good for many physiological functions. However, the focus of the products seem to attract as nutritional point of view such as taste and flavor, but few was for biomedical point of view.

Introduction: Fermentation process are close to digestive process by enzymes in digestive tract. However, we have found that there are difference between stating molecular weight for select to their destiny, digestion by the cleavage enzyme or pass through intestinal tube without attack by the digestive enzyme. The latter one is the fate of fermented material but full molecular original/natural food is not.

Material and Method: A malted rice were prepared by the microorganisms from plum flower (*Enterococcus faecalis*, MPF). This products were exhibited by safe in animal safety test. The trial was made to investigate the relation between the molecular styles and complement activation.

Results: Our results in animal model showed that MPF was the safe for the animal safety test. Four weeks after the administration, granulocyte and lymphocyte ratio was regulated as modulate and neutral.

Conclusion:

1. A multi-molecular saccharide are attacked by digestive enzyme in digestive tract.
2. However, middle molecular saccharide, such as oligo-saccharide made by fermentation escape from digestive enzyme, when that introduced in digestive tract.
3. The molecular size less than oligo-saccharide could pass through intestinal barrier to the lymph.
4. A multi-chained saccharide can activate alternative complement pass way.
5. The activated complement fragments can augment many physiological function including craniological system.
6. The activated fragment of alternative pathway Bf was proved by the immuno-precipitin method after electrophoresis of human serum.

Keywords: Complement; Alternative Pathway; Multi-Molecular Sugar Chain; Fermentation; Digestive Tract; Malted Rice; Mono-Saccharide; Disaccharide; Oligo-Saccharide; Poly-Saccharide

Introduction

There are many famous ancient cultural area known to five major civilization. Each area succeeded an original letter, cultural ceremony combined by religious activity. A fermented food include wine was a common incidences in their capitals. These fermented foods were reentry focused on the effect on the digestive tract, such as intestinal flora [1]. However, the effects were limited in local site, intestinal flora and appendix for immunological point of view. These custom also succeed in each civilization up to recent period. The typical food was wine, made of fermentation [2]. However, the effects were limited in local site, intestinal flora and appendix for immunological point of view. Today we would like to prove more systematic analysis through the agent beside of cytokine. We have been investigated the mechanism of action by these products why these are good for many physiological functions by evidence based manner by digital technique [3-5]. The interest of the products seem to attract as nutritional point of view such as taste and flavor, but few was for biomedical point of view for human physiology. A recent excessive report was found for as biochemical mechanism such as complement pathway. The purpose of this report was to try to review how are the real effect of fermented material on the human physiological function such as immune-modulatory effect on both young and elderly.

The efficacy of molt rice has traditionally been established but the scientific mechanism on the traditional health food. We had reported the molt rice was augmented complement component and lead to the activation of the cell that exhibited complement receptors.

Materials and Methods

Preparation of and fermented products

The fermented specimen was prepared at commercially available decoction. The specimen, Molted Lunch, made by yeast and plum blossom (*Enterococcus faecalis*) was prepared and used in these reports (IMPACT, Co. Ltd., Hita, Ohita, Japan). As a control, the fermentation was carried out for 5 days at 40°C by *Lactobacillus leuteria*.

Fermentation and GABA generation

There followed the method of quantification of γ -aminobutyric acid, which comprises the steps of producing reduced nicotinamide adenine dinucleotide phosphate using a specific aminotransferase and a dehydrogenase which use oxidized nicotinamide adenine dinucleotide phosphate as a coenzyme and must deactivate the enzymes thereby removing any amino acid having a similar structure to that of GABA is removed and an electron carrier acts on NADPH produced in the above step in the presence of a tetrazolium salt which can produce a water-soluble formazan dye and the water-soluble formazan dye is measured and reported in References [13,14].

Results

Digestive System against high-molecular to Low-molecular one

Original high-molecular material

When polysaccharide materials were mixed with lactobacilli and/or East and cultured in a microorganism system, a polysaccharide was cleaved into a low molecular weight sugar chain (Figure 1). The sugar chains were called oligosaccharide, disaccharide and monosaccharide. This low molecular weight saccharide can enter the intestinal wall of the lymph (Figure 2). It is really nice to know that the further processing by microorganisms can lead to wine, further to CO₂, H₂O and energy.

Fate for the low-molecular/fermented material

When polysaccharide materials were mixed with lactobacilli and/or East and cultured in a microorganism system, a polysaccharide was cleaved into a low molecular weight sugar chain (Figure 1). The sugar chains were called oligosaccharide, disaccharide and monosaccharide. This low molecular weight saccharide can enter the intestinal wall of the lymph (Figure 2). The fate of these low molecular weight saccharides was different, where they chose the last organ. One has worked for the functional cell for the energy source. However, if they remain in lymphatic fluid, they may come into contact with the complement component. You can enable the complement component that is specified in the square marked in figure 3.

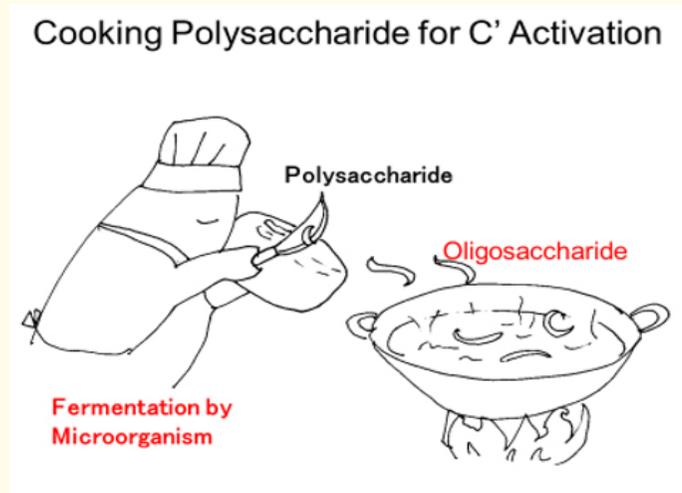


Figure 1: Illustrative imaging for degradation of polysaccharide by microorganism.

When a poly-saccharide materials mixed with *Lactobacilli* and/or *East* and culture in a system for microorganisms, a polysaccharide were digested into low molecular saccharide chain. The sugar chains were called poly-saccharide, oligo-saccharide, di-saccharide and mono-saccharide. These low molecular saccharide except poly-saccharide can enter into the intestinal wall for the lymph. It is really nice to know that further processing by microorganism, they may turn to wine, further to CO_2 , H_2O and energy.

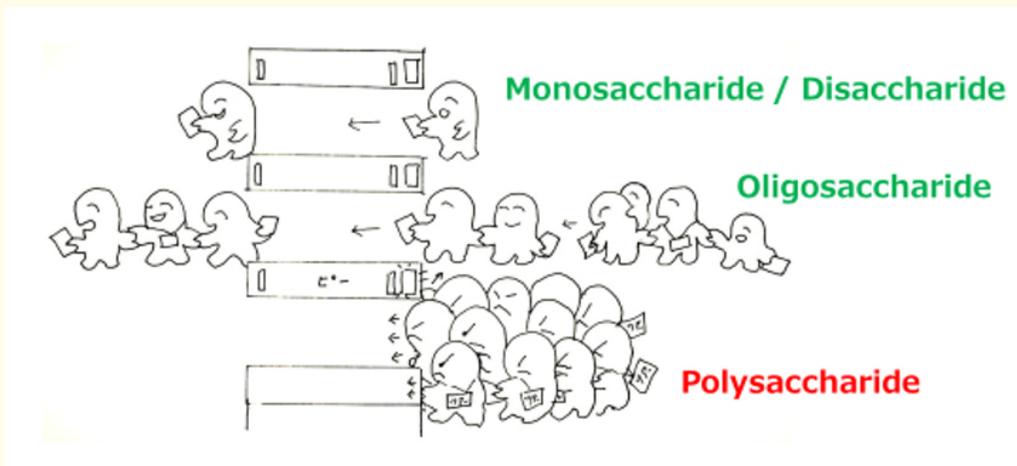


Figure 2: Glycoside size and permeability.

The bone marrow-suppressed mice were administered fermented materials 1 g/kg dairy for 30 days, and one week later, their blood was withdrawn from their tail vein. The cell count of the peripheral blood is showed in the text. Figure shows that the marker decreased to half of normal control after 5mg/kg of MMC was injected. However, all the markers recovered to about 70% of the control.

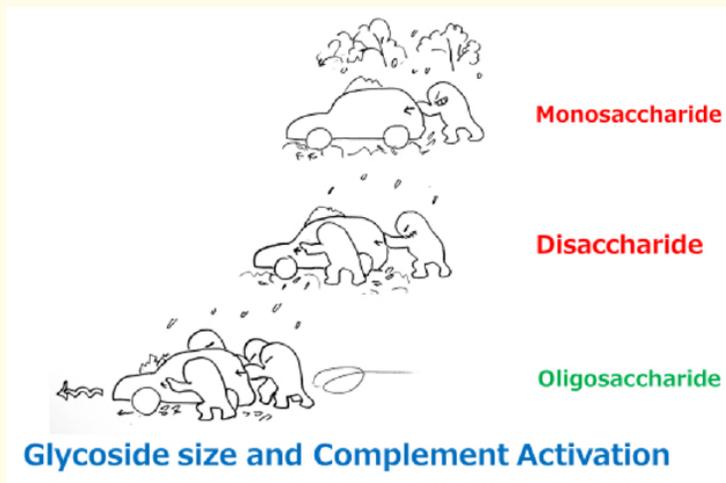


Figure 3: Glycoside size and complement activating capacity.

The fate of these low molecular saccharide was different each other where they select final organ. One is for the functional cell worked for the energy source. However, when they stay in lymph fluid, they can contact with complement component. Mono-saccharide and di-saccharide cannot activated complement pathway especially for alternative pathway of complement system.

	Digestive Enzyme in Stomach and Gut	Intestinal Passage Mode	Potential for Activate Alternative Complement Pathway (in situ)
High Molecular Poly Saccharide	Digestion ^{*1}	Mono and/or Di-Saccharide ^{*2}	Silent ^{*2}
1/2 Saccharide Oligo-Saccharide (Fermented materials)	Free from Digestion	Mono/Di and Oligo-Saccharide ^{*2}	Activated

Table 1: Glycoside size and permeability.

^{*1}: A high molecular polysaccharide is recognized by the enzyme in stomach and intestine, resulting single and/or twined glucose.

^{*2}: A single and twined glucose can pass through gut associated channel to the lymph but cannot activate alternative complement pathway.

It was possible to focus on another important factor of immunological component, complement either classical and/or alternative pathway. These protein are compose of at least 9 components. These protein are famous for its acute arrangement against infections organisms as in the defense immunity. However, we had found that the complement had worked when we introduced fragmented/fermented polysaccharide as complement activator, so called alternative pathway conjunct to Alternative Medicine.

How to activate the complement component

The complement system; another stage for focusing by fragmentation of polysaccharide

There was a linkage between fermented polysaccharide and effector phase of peripheral activity. The linkage substances were complement component system.

It was possible to focus on another important factor in the immunological component, which complements either the classical and/or the alternative pathway. The complement component proteins consist of 9 components. These proteins are known for their acute disposition to infection organisms as in immunological defense for infection. However, we had found that the complement works when we introduced fragmented/fermented polysaccharide as complement activator, the so-called alternative pathway associated with alternative medicine. In this chapter we want to show the nature of the complement and the activated mechanism that leads to the activation of all physical activities by enlarging the cells with positive structure of the complement receptor. Activation of the complement system exhibited in a cascade system of component proteins that worked in the production of complex/fragment which became a next activator of consecutive component. The standard activation mechanism is making antigen-antibody complex. Then the complex hit C1, C4, C2, C3, C5~C9 the coating of particles such as bacteria or immune complexes with certain components of the complement facilitates the uptake of the particle by micro and macrophage (opsonic function of the complement). Second, the activation event produces many cleavage products of complement proteins for which specific receptors exist on a variety of inflammatory cells such as granulocytes, lymphocytes, and other cells. The binding of these complement-derived products to such receptors leads to biological activities such as chemotaxis and hormone-like activation of cellular functions, complement inflammatory function [15,16].

Pathways of complement activation and complement proteins

The complement components can be activated in two ways: the classical and the alternative way. Both processes lead to a common terminal channel corresponding to the pathway of the membrane attack complex. It is known that plasma proteins are part of these pathways. These proteins can be subdivided into functional proteins that are the elements of the different pathways, and regulatory proteins that have every function. The blood level of proteins in normal humans varies over a wide range in each individuals. They are produced in the liver but also by cells of the lympho-reticular system, such as lymphocytes and monocytes. An amplification phase occurred involving the action of proteases and the recruitment of additional molecules. This is followed by a terminal phase of membrane attack complex in which the target cell dies. The classic C1 recognition pathway consists of three separate proteins, C1q, C1r and C1s. The starting of this complement pathway fundamentally involves the reaction of an antigen-antibody complex that may be soluble or located on the surface of a target cell membrane. It has been demonstrated by electron microscopy that C1q's ultra-structure consists of six subunits close to a pedals of six flowers. The central stems of C1q resemble collagen in the primary and secondary complex. Upon binding of a C1q molecule to the Fc regions of two or more antigen-bound antibody complex, C1r proenzymes are activated for start. The chemical basis of this activation is the cleavage of a peptide bond by an autocatalytic mechanism leading to the formation of activated C1r, a protease that subsequently cleaves the proenzyme C1s. Thus, combining of C1q to an immunoglobulin in complex with the antigen-antibody is the recognition event of the classical pathway, resulting in the activation of C1r and C1s. The end construction is the generation of an enzymatically active component, C1s, which cleaves and thereby activates the next proteins in such a cascade system, resulting in an augmentation of the recognition event. The other activation step, the polysaccharide molecule, also affects the complement component, so called alternative complement pathway. Therefore, a polysaccharide molecule alternatively encounters the complement component. Thus, molted rice derivatives activated the human complement component and demonstrated this by immunoelectrophoretic methods.

The enzymatic protein C1s has two physiological substances, C4 and C2. C4 is cleaved by C1s in C4a, one of the three anaphylatoxins (molecules that enhance increased vascular permeability and smooth muscle contraction), and C4b, which binds to the surface of the target cell. C1s also cleaves C2 if C2 is complex with C4b. The cleavage of C2 generates C2b that is released and C2a that remains bound to C4b. The bimolecular complex C4b, 2a is a protease that cleaves C3 and is therefore called C3 convertase. The degradation of C3 by the C3 convertase makes two important biologically active peptides, C3a (another anaphylatoxin) and C3b, which attach to the surfaces of target cells and bind to C5. C5 can be cleaved in complex with C3b from the C3 convertase (then called C5 convertase). The C5 convertase hydrolyzes C5 to give C5a-anaphylatoxin and C5b. C5b is the nucleus for the formation of the membrane attack complex. Immediately upon generation, C3b and C4b show a special transient ability to covalently bond to labeled cells ("intern binding site"). This might have been indicated to be due to an intramolecular thioester fixing between the sulfhydryl group of a cysteine residue and the γ -carbonyl group of a

glutamine residue at C3 and C4. With activation of C3 or C4, this thioester turn to highly reactive and can react with a hydroxyl or amino group on the target cell. This makes to covalent bonding of C3b or C4b to the target cell surface. An integrative activity of the thioester binding is the hydrolysis by water that makes during the augmentation of the alternative pathway, as shown following.

The alternative pathway show to be activated when a molecule of C3b is bound to a target cell surface membrane. This C3b molecule makes to the plasma protein factor B, which is a zymogen and which, when turn to C3b, can be integrated by cleavage into two pieces, Ba and Bb, by the plasma protein factor D. The Bb fragment containing the active enzymatic site remains bound to C3b as C3b, Bb. In this article, we tried to show Fb fragment as an fact of materials by immune-electrophoresis. This complex, like C4b, 2a in the classical pathway, is a C3 convertase (C3b, Bb); it is rigid by the binding of another plasma protein, properdin. So that, the alternative pathway was naturally named the properdin way. The evidence of a single molecule of C3b generates many molecules of C3b, Bb, resulting in maxim enhancement. The C3 convertase (C3b, Bb) cleaves C3, thereby produced more molecules of C3b that can bind to other B-molecules to yield more molecules of cab, Bb, which in turn can divide more molecules from C3. Therefore, the central evidence of the alternative path is a positive feedback network that enhances the original recognition site. As shown in the classical pathway, the conjugating of many C3b molecules to the target cell surface will allow the integrating of C5 and its cleavage in C5a and C5b by the enzyme C3b, Bb, which is regard to as C5 convertase.

With this potential of this positive feedback loop to quick use up Factor B and C3, the positive feedback must be occasionally regulated. There are two major proteins in plasma. The initiate protein, Factor H (formerly referred to as PIH), struggling with Factor B for binding to C3b and also dissociates C3b, Bb into C3b and Bb. The second array protein, Factor I (formerly referred to as C3b inactivator), cleaves C3b that is bound to Factor H or to a same protein made on the surface of the host target cell. The fate of cleaved C3b, termed iC3b, can no more for C3 convertase. The function of these two control proteins interfere the use-up of Factor B and C3 in plasma; in addition, these two proteins inactivate C3b, Bb on host target cell. In contrast, surfaces of many target host cells, such as bacteria and other microorganisms, protect C3b, Bb from inactivation by Factors H and I. This protection makes the positive feedback loop to activate on the surface of the target cell, leading to the activation of the pathway and subsequent target cell death. In other words, the alternative pathway is activated by those substances that prevent the inactivation of the positive feedback loop enzyme C3b, Bb. A substance is therefore regarded as “foreign” if it limits the action of Factors H and I and turns the positive feedback loop to succeed.

The chemical structures on surfaces of target particles and cells responsible for the activation or non-activation of the alternative signaling pathway have been reported [16]. The evidence is that carbohydrates are involved, especially sialic acid. The alternative pathway proteins responsible for the recognition of these structures have been identified. As already reported, activation of the alternative pathway requires a C3b molecule bound to the surface of a target cell surface. A reasonable question is: “Where makes the critical molecule of the first cabin stuff come from?” Although it may be provided by the classical pathway C3 convertase or by cleavage of C3 by plasmin and certain bacterial cell and other cellular proteases, the alternative complement route may produce this first C3b molecule instead of these proteases. The intramolecular thioester, which is highly active in the resulting C3b and responsible for covalent binding to target cells, is also accessible to native molecules in water molecules. Thus, in the plasma, spontaneous hydrolysis of the thioester bond occurs constantly at a slow rate within the body. The C3 molecules in which the thioester bond was hydrolyzed behave like C3b, although the C3a domain was not excluded. C3 with a hydrolyzed thioester is called C3 or C3b-like C3. It can conjugate factor B and allow factor D on activated factor B, resulting in the formation of a liquid phase C3 convertase C3, Bb. This enzyme is constantly formed and produces c3b molecules that can be randomly attached to cells surface. Although these C3b molecules are rapidly inactivated by host factors H and I, they makes the positive feedback loop on foreign surfaces as previously described. In other words, the alternative pathway is constantly activated at a slow rate, but amplification followed by cell death occurs only on foreign particles, some molecular saccharide without mono and di-saccharides [17].

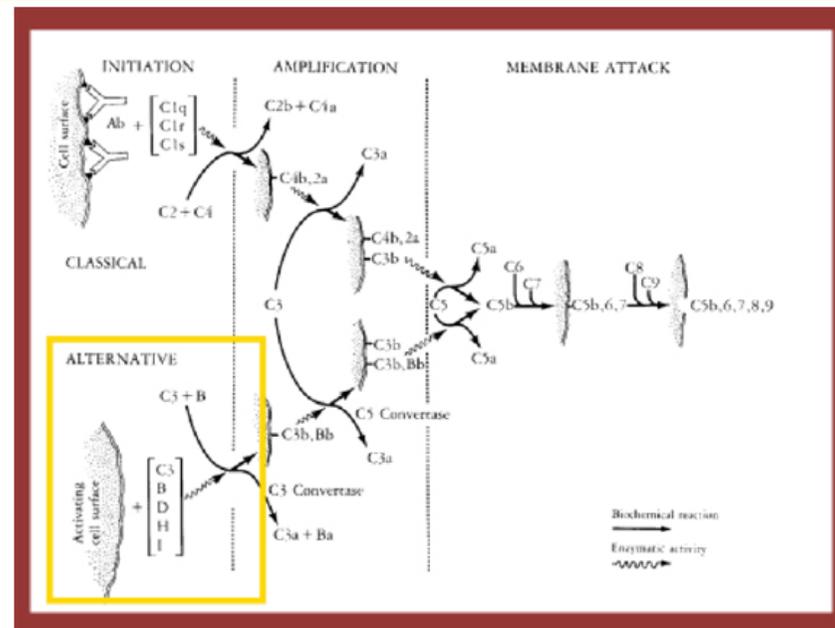


Figure 4: Complement component in human, indicating classical and alternative pathway.

It was possible to focus on another important factor of immunological component, complement either classical and/or alternative pathway. These protein are compose of at least 9 components. These protein are famous for its acute arrangement against infections organisms as in the defense immunity. However, we had found that the complement had worked when we introduced fragmented / fermented polysaccharide as complement activator, so called alternative pathway conjunct to Alternative Medicine.

It was found that the alternative signal path is not activated by mono- and di-saccharides [16]. There is evidence that carbohydrates such as oligo-saccharide except mono and di-saccharides are involved, especially including sialic acid. The alternative pathway proteins responsible for the recognition of these saccharide structures have determined. As already shown, activation of the alternative pathway requires a C3b molecule bound to the surface of a target cell surface. A fascinating question is: "Where does the critical molecule of the first cabin come from?" Although it may be provided by the classical pathway C3 convertase or by cleavage of C3 by plasmin and certain bacterial and other cellular proteases, the alternative route may produce this first C3b molecule without these proteases. The intramolecular thioester, which is highly reactive in the resulting C3b and responsible for covalent attachment to targets, is also accessible to native molecules in water molecules. Thus, in the plasma, spontaneous hydrolysis of the thioester bond occurs constantly at a slow rate. C3 with a hydrolyzed thioester is called C3 or C3b-like C3. It can bind factor B and allow factor D on activated factor B, resulting in the formation of a liquid phase C3 convertase C3, Bb. This enzyme is continuously formed and produces c3b molecules that can be randomly attached to cells. Although these C3b molecules are rapidly inactivated by host factors H and I, they trigger the positive feedback loop on foreign surfaces as previously described. In other words, the alternative pathway is constantly activated at a slow rate, but amplification followed by cell death occurs only on foreign particles [17].

These facts could be proved by immune-chemical technic integrated the charge of protein surface. The human serum was prepared after administration of molted specimen. Immunoelectrophoresis was performed for 90 minutes, and then incubated with anti-human

serum specific for the C3 and Bf components protein. These special prepared anti-serum had resented personally Dr Syunnosuke SAKAI, Cancer Research Institute of Kanazawa University, Japan (Figure 5).

Direct evidence of complement products activation by fermented materials and translation of biological activity

Activation of either the alternative or classical pathway results in the generation of many key peptides involved in an inflammatory disease. Anaphylaxis increasing vascular permeability Degranulation of mast cells and basophils with release of histamine degranulation of eosinophils. Aggregation of platelets, opsonization of particles and solubilization of immune complexes with consequent facilitation of phagocytosis. Release of neutrophils from the bone marrow, resulting in vascular leukocytosis Smooth muscle contraction permeability. Smooth muscle contraction increasing the vascular permeability modification of mast cells and basophils with release of histamine degranulation of eosinophils aggregation of platelets chemotaxis of basophils, eosinophils, neutrophils and monocytes release of hydrolytic enzymes from neutrophils chemotaxis of neutrophils release of hydrolytic enzymes from neutrophils of migration and the spread of monocytes and anaphylatoxins C3a, C4a and C5a are derived from the enzymatic cleavage of C3, C4 and C5, respectively. In the past, C3a and C5a were defined as factors derived from activated serum with spasmogenic activity. Anaphylatoxins are now considered to have many additional biological functions complement alternative pathway. It is known that both C3a and C5a induce the release of histamine from mast cells and basophils. As shown in the figure, anaphylatoxins cause smooth muscle contraction and induce the release of vasoactive amines that cause an increase in vascular permeability. The effect of C5a-anaphylatoxin on neutrophils is of considerable importance for the inflammatory response. Not only can C5a induce neutrophil aggregation, but this anaphylatoxin appears to be the most important chemotactic peptide generated by activation of either complement pathway. *In vitro* nanomolar concentrations of C5a induce the unidirectional movement of neutrophils. It has also been shown that other inflammatory cells, such as monocytes, eosinophils, basophils and macrophages, show a chemotactic response to C5a. The removal of carboxyl-terminal arginine from C5a by serum carboxyl peptidase N, producing C5a, inactivates the spasmogen. Cancellation of complete chemotactic activity of C5a des can, however, be in the presence of serum. Therefore, C5a may also be responsible for neutrophil chemotactic activity *in vivo*. As previously described, cleavage of C3 by either the alternative or classical C3 convertase results in the production of two major cleavage products, the C3a anaphylatoxin and the C3a-Cab. The larger C3b fragment can serve as opsonin (enhancer of phagocytosis by phagocyte) by binding to a target via the thioester mechanism. This makes the particle or cell immediately susceptible to uptake by a variety of phagocytic cells carrying specific receptors for C3b. A lot of studies indicated additional roles for complement fragments in regulating the activity of dynamics of the immune competent system. These observations include the presence of lymphocyte receptors for various complement proteins, including C3 cleavage products and Factor H, which affect B and T cell function. This is an important area for future investigation [18] (Figure 5).

Discussion

There are many famous ancient cultural area known to five major civilization. Each area succeeded an original letter, cultural ceremony combined by religious activity. A fermented food include wine was a common incidences in their capitals. These custom also succeed in each civilization up to recent period. The typical food was wine, made of fermentation. They have been recognized and succeeded these product were good for storage as well as good for health. But the emotion had been required to analyze scientific approach. We have been investigated the mechanism of action by these products why these are good for many physiological functions by evidence based manner by digital technique. The interest of the products seem to attract as nutritional point of view such as taste and flavor, but few was for biomedical point of view for human physiology. A recent excessive report was found for as biochemical mechanism such as complement pathway.

One of the important activity brought by fermentation was anti-oxidative activities. Almost of the report that concern anti-oxidative activity were performed by *in vitro* system. On the other hand, our system was employing *ex vivo* system employing phagocyte of rodent. The fermented materials, for example, molted rice, was increased anti-oxidative activity [21,22].

Native & Activated Bf by Immuno-Electrophoresis

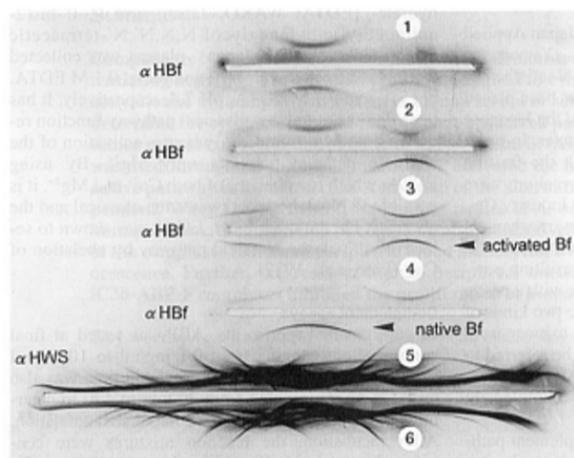


Figure 5: Native and activated Bf exhibiting by immune-electrophoresis.
immuno-electrophoretic demonstration of activated human complement.

The human serum was prepared after administrating fermented materials together with the sample with before fermentation. Immuno-electrophoresis was setting up for 90 min, followed by incubating with anti-human whole serum and specific for C3 and Bf component. These specific anti complement component serum were kindly supplied by Dr Syunnosuke SAKAI, Cancer Research Institute of Kanazawa University, Japan.

Conclusion

For summarize above contents, we could conclude as following:

1. A multi-molecular saccharide are attacked by digestive enzyme in digestive tract.
2. However, middle molecular saccharide, such as oligo-saccharide made by fermentation escape from digestive enzyme, when that introduced in digestive tract.
3. The molecular size less than oligo-saccharide could pass through intestinal barrier to the lymph.
4. A multi-chained saccharide can activate alternative complement pass way.
5. The activated complement fragments can augment many physiological function including craniological system.
6. The activated fragment of alternative pathway Bf was proved by the immuno-precipitin method after electrophoresis of human serum.

Conflict of Interest

We declare none.

Bibliography

1. Kojima Y, *et al.* "Quantitative Aspect of Constitutive Regulation Intestinal Condition by Fermented Herbal Decoction through Permeability". *EC Paediatrics* 8.8 (2019): 674-682.

2. Yamaguchi N., *et al.* "Aspect of QOL Assessment and Proposed New Scale for Evaluation". *Open Journal of Immunology* 5 (2015): 147-182.
3. Yamaguchi N., *et al.* "A Constitution Dependent Digital QOL Assessment". *EC Gynecology* 8.5 (2019): 344-352.
4. Kitada Y. "Regulation of peripheral white blood cells in numbers and functions through hot-spring bathing during a short term - studies in control experiments". *Journal of Japanese Society Balneology Climatological Physiology* 63.3 (2000): 151-164.
5. Kishida K., *et al.* "Cranial Irradiation and Lymphocyte Subpopulation in Acute Lymphatic Leukemia". *Journal of Pediatrics* 92.5 (1978): 785-786.
6. Yamaguchi N., *et al.* "Maternal Bias of Immunity to Her Offspring: Possibility of an Autoimmunity Twist out from Maternal Immunity to Her Young". *Open Journal of Rheumatology and Autoimmune Diseases* 3 (2013): 40-55.
7. Murgita RA and Tomasi Jr TB. "Suppression of the Immune Response by Alpha-Fetoprotein". *The Journal of Experimental Medicine* 141.2 (1975): 269-286.
8. Auerback R and Clark S. "Immunological Tolerance: Transmission from Mother to Offspring". *Science* 189.4205 (1975): 811-813.
9. Koshimo H., *et al.* "Maternal Antigenic Stimulation Actively Produces Suppressor Activity in Offspring". *Developmental and Comparative Immunology* 13.1 (1989): 79-85.
10. Zoeller M. "Tolerization during Pregnancy: Impact on the Development of Antigen-Specific Help and Suppression". *European Journal of Immunology* 18.12 (1988): 1937-1943.
11. Shinka S., *et al.* "Immunological Unresponsiveness in Mice. I. Immunological Unresponsiveness Induced in Embryonic Mice by Materno-fetal Transfer of Human-Globulin". *Biken Journal* 17.2 (1974): 59-72.
12. Wacharaporn N. *et al.* "Contribution of Gamma amino butyric acid (GABA) to salt stress responses of *Nicotiana sylvestris* CMSII mutant and wild type plants". *Journal of Plant Physiology* 169 (2012): 452-458.
13. Thomas B., *et al.* "Gamma-aminobutyric acid and glutamic acid level in the auditory pathway of rats with chronic tinnitus: a direct determination using high resolution point-resolved proton magnetic resonance spectroscopy (1H-MRS)". *Frontier Systems Neuroscience* 6 (2012): 1-12.
14. Stoika RS., *et al.* "In Vitro Studies of Activation of Phagocytic Cells by Bioactive Peptides". *Journal of Physiology and Pharmacology* 53.4 (2002): 675-688.
15. Sim RB., *et al.* "Complement Research with 18th-21st Centuries: Progress come with new technology". *Immunobiology* 22.1 (2016): 1037-1045.
16. Elbim C., *et al.* "The Role of Phagocytes in HIV-Related Oxidative Stress". *Journal of Clinical Virology* 20.3 (2001): 99-109.
17. Aase J M., *et al.* "Mumps-Virus Infection in Pregnant Women and the Immunologic Response of Their Offspring". *The New England Journal of Medicine* 286.26 (1972): 1379-1382.
18. Cramer DV., *et al.* "Immunologic Sensitization Prior to Birth". *American Journal of Obstetrics and Gynecology* 120.3 (1974): 431-439.
19. Abo T., *et al.* "Studies on the Bioperiodicity of the Immune Response. 1. Circadian Rhythms of Human T, B and K Cell Traffic in the Peripheral Blood". *Journal of Immunology* 126 (1981): 1360-1363.

20. Abo T and Kumagai K. "Studies of Surface Immunoglobulins on Human B Lymphocytes. physiological Variations of Sig+ Cells in Peripheral Blood". *Clinical and Experimental Immunology* 33 (1978): 4414-4452.
21. Yamaguchi N., *et al.* "Overall Estimation of Anti-Oxidant Activity by Mammal Macrophage". *Open Journal of Rheumatology and Autoimmune Diseases* 4.1 (2014): 13-21.
22. Yamaguchi N. "Rodent Macrophage Select Vin Blank Together with Vin Rouge According to SO Level in Situ". *Open Journal of Rheumatology and Autoimmune Diseases* 4.4 (2014): 240-247.

Volume 7 Issue 1 January 2020

©All rights reserved by Nobuo Yamaguchi., *et al.*