

**Recent Progress of Research
on AHCC
Active Hexose Correlated Compound**

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1: *Introduction*

AHCC (Active Hexose Correlated Compound) which has been developed by own technology of Amino-up Chemical, is poly- or oligosaccharide mixture obtained from the extract of mycelium of several basidiomycetes cultivated for long term in a large-scale tank. AHCC is remarkable for its function as a BRM (Biological Response Modifier), of which the term originally was used in the research program of NCI cancer therapy division on biomaterials such as BCG or interferon. In Japan, it was started to research on BRM mainly for anti-cancer activities from 1960s and classified as follow:

- 1: Immuno-modulator and -stimulator
- 2: Interferon and its inducer
- 3: Zymosane
- 4: monoclonal antibody
- 5: effector cell
- 6: other differentiation inducer

Today, the definition and class of BRM are expanded widely, and many materials as BRM like substance has been attracted the attention of scientists in the field of not only medicine but food. AHCC is also one of the spotlights for the function as BRM, especially immuno-modulator, and appreciated as a supplement in clinical sites. Recently, there are many reports of worldwide scientists on the various functions of AHCC in the fields of medicine, pharmacy, and dietetics.

2: *Immunotherapy for Cancer*

It is known that there is an immunotherapy for cancer as the fourth methods in addition to surgical, chemical and radiation therapies. The anti-tumor activities were confirmed by administration of immuno-activating substance when the load of tumor to model animal was reduced by surgical treatment and/or chemotherapy. When the animal implanted model tumor cell line with large antigenicity, only administration of the immuno-activator is considerably effective. The effects for immunotherapy are much more expectable when there are following conditions.

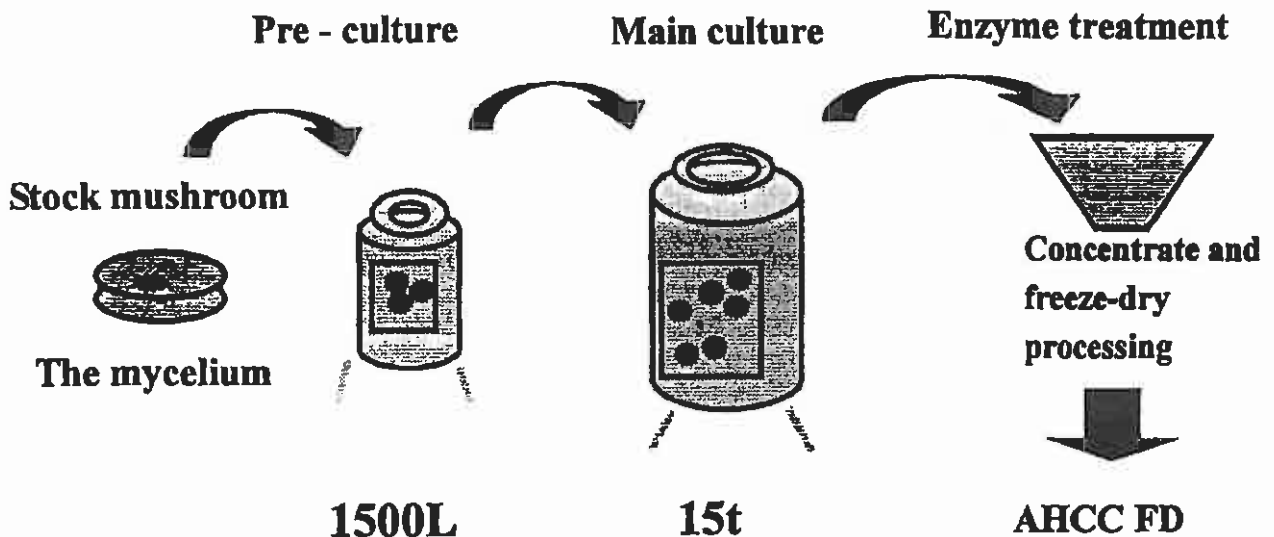
- 1: The numbers of tumor cell are lead to minimum or resulted such status.
- 2: In order to decrease tumor cell numbers, combination together with advantageous conventional cancer therapy.
- 3: When the tumor has much more antigen activity, the immuno-response of the body is stronger and easy to observe the effect of immunotherapy.

The administration route, dose, and period of the immuno-activating substance in immunotherapy are ground on the basic research information. Actually, BRMs from natural origin are expected the various clinical effects. AHCC has been attracted the notice in the basic and clinical wide applications.

3: Development of AHCC

AHCC was developed at first as the preventive supplement against adult diseases from its activity on anti-glycemia and anti-hypertension. As the study of AHCC progressed, it has been found that AHCC possesses remarkable immuno-activation effects. AHCC is now studied and sold in the USA, Mexico, Korea, China, Taiwan, and European country as well as Japan. The process of AHCC production is illustrated. The long-term cultivation of mycelium of basidiomycetes and the following enzymatic degradation of the mycelium gave successfully extract of the components of the fungi. The final products of freeze dried AHCC are developed as hard capsule coated by phyto-hardend oil, soft capsule coated by gelatin. There is also liquid product contained concentrated AHCC solution. The dose is generally one gram a day, while the dose for therapy as the supplemental material under the control of doctor is 3 and 6 grams a day.

Process of AHCC Production



4: Physiological effects of AHCC

AHCC has been known to have validity against allergy, diabetes, hypertension and various malignant tumors. However, the effects against these diseases were sometime poor in pharmacological and statistical evidence, so the mechanisms of the action were not clarified. Although neutrophil accumulation effect, TNF production, and activation of NK cell have been reported in the field of basic study, further data to support the clinical results are required. As the remarkable effects in clinical studies have been recognized recently, the basic data with attention of many researchers have been grown abundant. This report describes the summary for some examples such recent studies on AHCC activities.

4-1) Liver protective effect of AHCC

It is confirmed that AHCC effects for liver injury, hepatitis, and cirrhosis. Among the cases, patients of virus hepatitis took AHCC 3 and 6 grams a day, then about 1 month later, the serum GOT, GPT, and g-GTP were significantly reduced. In some cases, these indexes became lower into the normal level of liver function. The mechanism of this effect, however, is not clear pharmacologically. So, we try to manifest the mechanism using an acute hepatitis rat prepared by administration of CCl₄. After forced oral feeding of AHCC (1g/kg/day) to ICR mice for 3 days, then 0.4mL/kg of CCl₄ was administered intraperitoneally for 5 days. As a result, AHCC feed group compared with non-feed group was reduced the restraint of spontaneous movement, color change of hair to yellow, and loss of body weight. This group perhaps induced metabolic enzyme in liver such as P-450 and GST. Pathological tissue observation indicated that the wide necrosis of hepatocyte was occurred around intravenous of the tissue in the control group, whereas AHCC group was evidently prevented the destruction and necrosis of liver cell.

These facts mentioned above exhibit that AHCC has the protective effects for internal organs like liver.

4-2) Prevention effect on recurrence of liver cancer after surgical treatment

Prof. Kamiyama of Kansai medical university and his co-workers studied the protection effect of AHCC for recurrence after the operation of liver cell cancer. All the patients were received the excisional operation for the hepatocellular carcinoma. Among these patients, 27 cases were AHCC orally administered group and 83 cases non-administered group as control. As the result, the survival rates after one year were

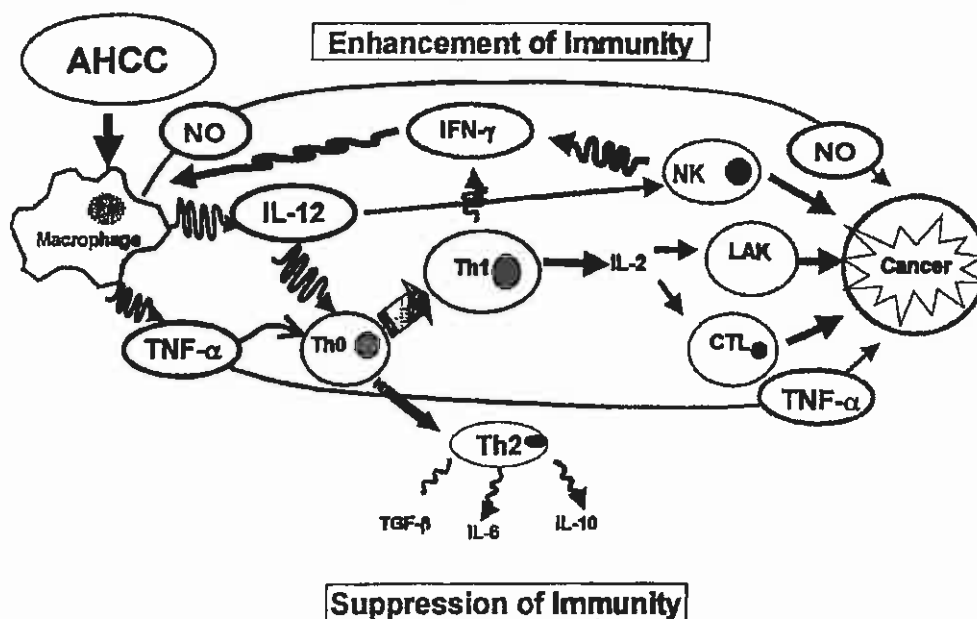
100% of AHCC group and 83.8% of control group, while after 2 years, 100% of AHCC group and 73.8% of the control. On the recurrence rate of the cancer, AHCC group showed 6.2% to the control 38.5% for one year while after 2 years 6.2% to 53%, respectively. The tumor markers in the serum of AHCC group such as α -fetoprotein or PIVKA II were significantly lower than those of the control group. Now the observations are progressed under more cases. AHCC as the BRM activated the immune cells and has contributed to prevention and cure against various diseases through the enhancement of defensive reaction of the body.

4-3) Interleukin-12 production by AHCC

Prof. Yagita of Kinki University demonstrated that AHCC induces IL-12 by oral administration. IL-12 is produced mainly in macrophage and accelerates the function of various types of immune cells as follow.

- 1: Activation of T- and NK-cell through production of the other cytokine such as IFN- γ and TNF- α from macrophage.
- 2: Increase of cytotoxicity of NK-cell or CD8+T-cell.
- 3: Acceleration of the differentiation from Th-0 to Th-1 cell.
- 4: Acceleration of the proliferation of activated NK and T cell.
- 5: Inhibition of angiogenesis.
- 6: Suppression of TGF- β .

These facts mean that IL-12 regulates immune defense system through induction and enhancement of specific or non-specific immune reaction. In spite of such the convenient effects, artificial recombinant IL-12 has severe side effect to limit the clinical application. According to Yagita's reports, out of 630 cases of progressive end-stage cancer, 40 of CR and 52 of PR were obtained. Among them, 5 of 6 cases of testicle cancer were better than PR, and it is effective for the breast cancer in which 2 cases of Paget's disease disappeared completely as CR. There are many high efficacy cases for liver, tongue, uterine cervix, and gastric cancer. Furthermore, IL-12 had positive correlation with TNF- α and IFN- γ and negative with TGF- β .



4-4) Reduction of the side effects of anticancer drugs

One of the main cancer treatments is chemotherapy, which contains the drugs such as alkylating agents, metabolic antagonists, antibiotics, plant alkaloids, and hormonal drugs. Those, however, usually have severe side effects depending on the use of dosage. These side effects are baldness, nausea, diarrhea, fever (pyrexia), anorexia, bone marrow suppression, liver injury, renal injury, and other immuno suppression. Practically, AHCC showed the reduction of those side effects caused by the drugs and improvement of QOL of patients in the clinical treatment. Prof. Hosokawa of Hokkaido University reported that elongation of survival time and suppression of metastasis of tumor bearing animal models by treatment with UFT combination with AHCC. We also confirmed the prevention effect of AHCC for bone marrow suppression caused by cancer chemotherapy drugs. Administration of fluorouracil (5-FU: 50mg/kg) or cyclophosphamide (CY: 100mg) to male ddY mice for 14 days with and without free nutrition of 5% solution of AHCC in water simultaneously resulted decrease in relief of the side effects such as body weight loss, alopecia, decline of peripheral RBC and WBC etc. as compared with control.

5: AHCC and QOL

Various changes usually occur during the cancer therapy. For example, after surgical excision of digestive organs or high dosage chemotherapy, it causes the decline of digestive function, waste of energy, and suppression of immune response. Therefore, long term decline of the QOL caused the delay of the social return and the deterioration of social ability. Application of BRM for such situation has been emphasized its usefulness for decline of strength and/or immune response after operation. When the cancer patient who received surgical therapy was treated by combination chemotherapy with AHCC after the surgery, it was confirmed the patient got suppression of alopecia and nausea, the increase of appetite and body weight, the elongation of survival time, and so on.

For the assessment of treatment for malignant tumor, objective evaluations such as tumor size reduction, survival time and cure rates have been used conventionally. From the reflect, however, that only the objective evaluation is insufficient, so subjective assessment by patient himself for the therapy is required all over the cure process, actually, preparing questionnaire. We request to patient who accepts AHCC treatment to answer their QOL by the questionnaire under the limit of usual treatment.

6: Conclusion

It has been reported that AHCC possesses various functions, especially, activation of defense system through stimulation of immune cells. However, a living body is not controlled by artificially classified function but maintained by network of all the organs. The functions were roughly divided into three main functions; endocrine, nervous, and immune systems, which work for maintenance of the living body in connection with each other. Although AHCC has been studied with respect to the immune, henceforth, the studies on the fields for endocrine and nervous systems will be required. Then it will play important role in the field concerning [Food and Health]. Furthermore, the role will be grown largely toward aged society in the future.