U-Fn is a pure natural food product from a highly concentrated extract of *Laminaria japonica*, a sea vegetable known as *kombu* in Japanese cuisine. This potent extract, dried and encapsulated in the USA, has proven to be one of the most powerful cancer-killers in the natural arsenal.

U-Fn contains U-Fucoidan, a polysaccharide found in kombu that has been found to cause cancer cells to self-destruct. This occurs through a normal biological process known as *apoptosis*, a natural means by which living organisms eliminate harmful or no longer necessary cells from their tissues.

U-Fn works best against cancers located where the U-Fucoidan can be absorbed most readily, such as the glands (breast, prostate, lymph nodes, etc.), the gastrointestinal tract (liver, pancreas, colon, etc.), and the bloodstream.

U-Fn is not just another blend of dried ground seaweed, nor is it an isolate of fucoidan whereby its bioavailability has been compromised and its cost inflated. When taken as a capsule with water, U-Fn delivers all of the naturally occurring vitamins and minerals of *Laminaria* in a soluble, bioavailable form. It is easily digested and healthful to the "good" cells, while safely destroying the "bad" ones.

**The Source of U-Fn**

This very special *Laminaria japonica* brown seaweed is now harvested from one of the clearest ocean beds in the world in the south Pacific. Skillful local divers harvest this kelp in an environmentally sustainable manner using sharp knives to hand-cut the selected fronds underwater. They bring the harvested kelp to shore and hang the huge fronds on wooden racks to dry quickly in the sun.

The dried kelp is then transported to a manufacturing plant in the United States where it is reconstituted by soaking in fresh water—which is retained so as not to lose any of the water-soluble polysaccharides. Within about eight hours the fronds return to their original size and the outer skin and fibers can be removed.

The soft inner part of the brown seaweed is then pressed out of the leaves and reduced to a dry powder. A cold-temperature vacuum extraction process is used in order to retain all of the important organic elements.
Research on U-Fucoidan

In 1996, the Biomedical Research Laboratories of Takara Shuzo and the Research Institute for Glycotechnology Advancement, a company funded by the Bio-oriented Technology Research Institute, studied this material.

They discovered that the polysaccharide known as U-fucoidan, found in kombu and other types of brown seaweed (wakame, mozuku, and hijiki), causes various types of cancer cell lines to self-destruct.

1. What is U-Fucoidan?

About 4% percent of the total dry weight of many types of brown seaweed such as kombu consists of a polysaccharide known as fucoidan. Fucoidan is a sulfated polysaccharide that possesses a complex structure. Its chief components include a sulfuric esterified L-fucose, and trace elements of galactose, xylose, and glucuronic acid.

Working together, Takara Shuzo's Biomedical Research Laboratories and Research Institute for Glycotechnology Advancement were able to confirm the presence of two different types of fucoidan molecules in brown seaweed. The first type, bearing the name F-fucoidan, consists mainly of sulfated fucose. The second type bears the name U-fucoidan and approximately 20% of it consists of glucuronic acid.

Researchers at both institutions were able to use a technique known as pyridlamination, developed by Takara Shuzo in conjunction with the University of Osaka, to shed light on the chemical structure of U-fucoidan.

2. The Biological Activity of Fucoidan

Numerous accounts have ascribed to fucoidan properties such as the ability to act as an anti-contraceptive, to reduce cholesterol levels, and to act as an anti-tumor agent. However, a definitive consensus concerning the precise nature of fucoidan has still not been reached. The Biomedical Research Laboratories of Takara Shuzo and the Research Institute for Glycotechnology Advancement have focused their attention on the anti-tumor properties of fucoidan, and have managed to confirm that this substance causes certain types of rapidly growing cancer cells to self-destruct. Examples of cancer cell strains where this self-destruct phenomenon was observed include human acute promyelocytic leukemia cells (HL-60 cell line), human stomach cancer cells (AGS cell line), human colon cancer cells (HCT-116 cell line), and cancer cells of the descending colon (SW-480 cell line/WiDr cell line). Moreover, this self-destruction was observed to take place without affecting normal cells. Currently, efforts are underway to clarify the precise mechanism by which this phenomenon occurs.
Some of the reasons which have until recently prevented the formation of a definitive scientific consensus concerning the precise nature of fucoidan include the fact that it possesses an extremely complex structure, as well as the difficulty of obtaining pure samples of fucoidan. Both Takara and Research Institute for Glycotechnology Advancement strove to overcome these difficulties, and after having managed to produce pure samples of fucoidan, carried out the studies that led to the above conclusions.
3. The Mechanism Through Which Cancer Cells Self-Destruct

In the presence of certain substances, as well as under other unusual environmental conditions, cells may self-destruct and disappear altogether. This self-destruct phenomenon is known as apoptosis, and it is to be distinguished from necrosis, which is the death of cells directly brought about by external stimuli such as poisonous substances and physical damage to the cell.

Properly speaking, apoptosis is brought about by a mechanism that is programmed into the natural make-up of cells. Organisms activate this mechanism when necessary, and once the apoptosis mechanism has been triggered, the genetic blueprint of the cell (DNA) is rendered useless through activation of the deoxyribonuclease found within the cell itself. Apoptosis thus may said to be a natural means through which living organisms manage to eliminate harmful cells from their systems.

4. The Significance of This Discovery and Future Prospects

From ancient times (dating from the Jomon era, approximately before the 2nd Century BC onwards), brown seaweed has been a mainstay of the traditional Japanese diet. It is precisely these seaweeds that contain the U-fucoidan that serve to trigger the apoptosis mechanism described above.

The prefecture of Okinawa, whose inhabitants enjoy some of the highest life expectancies in Japan, also happens to have one of the highest per capita consumption rates of kombu—1 gram per person per day. The cancer death rate in Okinawa is the lowest of all the prefectures in Japan.

The average per capita consumption rate of kombu in Japan is approximately 0.5 grams per day. Such a serving of kombu would include roughly 5 mg of U-fucoidan. In vivo experiments are currently underway to determine the effects of U-fucoidan within living organisms. If it is confirmed that U-fucoidan can help bring about apoptosis solely in cancer cells that are multiplying at uncontrolled rates, we would then have within our reach the long-dreamt-of cancer drug—one that does its job without causing adverse side effects.

Details of the above discovery were disclosed at the 18th Annual Conference of the Carbohydrate Symposium (August 19-21), the 69th Annual Proceedings of the Japanese Biochemical Society (August 26-30), and the 55th Annual Proceedings of the Japanese Cancer Society (October 10-12, 2000). Details concerning the Research Institute for Glycotechnology Advancement: With funding from the Bio-oriented Technology Research Advancement Institute (a special legal person under the joint jurisdiction of the Ministry of Agriculture, Fisheries and Forestry and the Ministry of Finance), Aomori prefecture, Hirosaki city, as well as eleven private sector companies, the Research Institute for Glycotechnology Advancement was founded in February 1991. The Institute ranks as a research organization operating under the auspices of the Intelligent Research Institute, a body that was formed as part of the overall efforts to promote the development of the Tohoku area.
Fucoidan Properties of U-Fn™

Analysis of U-Fn in dry powder form:

**Total U-Fucoidan** 35%

- **Fucoidan** 11%
- **Laminaran** 24%
- **Alginic acid** 29%
- **Dietary fiber** 31%
- **Protein** less than 2%

* Fucoidan and Laminaran are major elements among the many which comprise U-Fucoidan.

Hydrolysis test results of the U-Fucoidan fraction (Fucoidan plus Laminaran) in U-Fn:

- **L-Fucose** 52%
- **Glucose** 36%
- **Glactose** 5%
- **Mannose** 2%
- **Xylose** Below detection level

It is important to understand that U-fucoidan is a broader-spectrum, more bio-available form of fucoidan that exists in combination with Laminara and other minerals. “Straight” fucoidan cannot be absorbed by the gastrointestinal tract when it is chemically extracted and introduced for consumption.
Fucoidan Research

Blockade of Selectin-Mediated Leukocyte Adhesion Improves Postischemic Function in Lamb Hearts

Takuya Miura, MD, David P. Nelson, MD, Marc L. Schermerhorn, MD, Toshiharu Shin'oka, MD, Gregor Zund, MD, Paul R. Hickey, MD, Ellis J. Neufeld, MD, John E. Mayer, Jr, MD. Departments of Cardiovascular Surgery, Pediatrics, Cardiology, and Anesthesia, Children's Hospital and Harvard Medical School, Boston, Massachusetts

Background. Leukocyte-endothelial interactions appear to have an important role in ischemia/reperfusion injury and are mediated by specific leukocyte and endothelial adhesion molecules. The selectins are adhesion molecules found on leukocytes (L-selectin) and endothelium (P and E selectin) that bind to oligosaccharide ligands containing fucose and sialic acid to mediate leukocyte rolling on the endothelium. Fucoidin is a nontoxic sulfated fucose oligosaccharide derived from seaweed that blocks the selectins.

Methods. We tested the effects of fucoidin in an isolated blood-perfused neonatal (age range, 3 to 7 days; mean age, 4.3 days) lamb heart model undergoing 2 hours of cold cardioplegic ischemia. In group F (n = 8) fucoidin (30 mg/L) was added at initial reperfusion. Group C (n = 9) received only cardioplegia with no reperfusion intervention. Isovolumic maximum developed pressure and the maximum positive and negative first derivatives of pressure were measured using a catheter-tip transducer in an intraventricular balloon before ischemia and at 30 minutes of reperfusion. Coronary blood flow, myocardial oxygen consumption, and white blood cell counts in the circulating blood were also measured.

Results. Percent recoveries of baseline maximum developed pressure and maximum positive and negative first derivatives of pressure in group F (86% ± 5%, 81% ± 10%, and 74% ± 8%, respectively; mean ± standard deviation) were higher than in group C (77% ± 5%, 70% ± 9%, and 65% ± 6%; p < 0.05). Group F postischemic coronary blood flow was greater (190% ± 35%) than in group C (102% ± 10%; p < 0.05). Recovery of myocardial oxygen consumption in group F (86% ± 14%) was greater than group C (72% ± 11%; p < 0.05). Postischemic white blood cell count in group F (88% ± 4%) was greater than in group C (81% ± 5%; p < 0.05).

Conclusions. Selectin blockade with fucoidin resulted in better recovery of left ventricular function, coronary blood flow, and myocardial oxygen consumption after cold ischemia, despite a higher circulating white blood cell count. These data support the hypothesis that endothelial-leukocyte interactions play an important role in ischemia/reperfusion and suggest that selectin blockade may be a useful therapeutic strategy.


Sulfated glycosaminoglycans enhance tumor cell invasion in vitro by stimulating plasminogen activation.

Brunner G, Reimbold K, Meissauer A, Schirrmacher V, Erkell LJ. Division of Cellular Immunology, German Cancer Research Centre, Heidelberg, Germany. Georg.Brunner@man.ac.uk

Metastasizing tumor cells invade host tissues by degrading extracellular matrix constituents. We report here that the highly sulfated glycosaminoglycans, heparin and heparan sulfate, as well as the sulfated polysaccharide, fucoidan, significantly enhanced tumor cell invasion in vitro into fibrin, the basement membrane extract, Matrigel, or through a basement membrane-like extracellular matrix.
The enhancement of tumor cell invasion was due to a stimulation of the proteolytic cascade of plasminogen activation since the effect required plasminogen activation and was abolished by inhibitors of urokinase-type plasminogen activator (uPA) or plasmin. Sulfated polysaccharides enhanced five reactions of tumor-cell initiated plasminogen activation in a dose-dependent manner. They amplified plasminogen activation in culture supernatants up to 70-fold by stimulating (i) pro-uPA activation by plasmin and (ii) plasminogen activation by uPA. (iii) In addition, sulfated polysaccharides also protected plasmin from inactivation by alpha 2-antiplasmin. Sulfated polysaccharides also stimulated tumor-cell associated plasminogen activation; e.g. (iv) cell surface pro-uPA activation by plasmin and (v) plasminogen activation by cell surface uPA. These results suggest that sulfated glycosaminoglycans liberated by tumor-cell mediated extracellular matrix degradation in vivo might amplify pericellular plasminogen activation and locally enhance tumor cell invasion in a positive feedback manner.

PMID: 9521847, UI: 98189141

_Anticancer Res_ 1996 May-Jun;16(3A):1213-8

**Antitumor and antiproliferative effects of a fucan extracted from ascophyllum nodosum against a non-small-cell bronchopulmonary carcinoma line.**


Fucans, sulfated polysaccharides extracted from brown seaweeds, have been shown to be endowed with inhibitory effects on cell growth in various experimental models. We studied both the antiproliferative and antitumor properties of a fucoidan extract (HF) obtained from the brown seaweed Ascophyllum nodosum on a cell line derived from a non-small-cell human bronchopulmonary carcinoma (NSCLC-N6); this type of carcinoma is particularly chemo-resistant. HF exerts in vitro a reversible antiproliferative activity with a block observed in the G1 phase of the cell cycle. Studies performed with the NSCLC-bearing nude mice show antitumor activity at subtoxic doses. These preliminary results indicate that HF exhibits inhibitory effect both in vitro and in vivo and is very potent antitumor agent in cancer therapy.

PMID: 8702239, UI: 96273150


**Changes in adhesion molecule expression and function in B-cell chronic lymphocytic leukaemia after in vitro interferon-alpha stimulation.**

Csanaky G, Vass JA, Ocsovszki I, Milosevits J, Szomor A, Schmelczer M. Department of Pathology, University Medical School of Pecs, Hungary.

Peripheral blood mononuclear cells (PBMCs) from 10 B-CLL patients were investigated after 24 hours of in vitro interferon-alpha (IFN-alpha) stimulation. The constitutional expression of the L-selectins (LECAM-1), LFA-1/CD11a, VLA alpha-4/CDw49d and ICAM-1/CD54 adhesion molecules was detected, and changes in their density after IFN-alpha stimulation were compared to results obtained by the high endothelial venule (HEV)-binding assay and a carbohydrate (phosphonomannan core polysaccharide: PPME and fucoidin) immobilization test. The LECAM-1 and ICAM-1 molecules were expressed on the great majority of CLL cells, while the LFA-1 and
VLA-4 alpha-chains were expressed by only a small number of cells. Statistically significant changes (p < 0.001) were observed in LECAM-1 antigen density (changes in mean cell fluorescence), as well as in functional tests (HEV-, PPME- and fucoidin-binding; p < 0.01) after in vitro IFN-alpha stimulation. Based on a prior study (Jewell et al., Leukemia 1992: 6: 400-404) and on the present findings, not only an increased expression but also an enhanced function of the L-selectins seem to be well substantiated after IFN-alpha stimulation, which may explain the therapeutic effect of IFN-alpha in reducing the accumulation of leukaemic B cells in the blood. The remarkably high expression of ICAM-1 in this series necessitates further studies to clarify the exact expression rate and role of this molecule. PMID: 7532138, UI: 95163724

Inhibitory effect of oversulfated fucoidan on invasion through reconstituted basement membrane by murine Lewis lung carcinoma.

Soeda S, Ishida S, Shimeno H, Nagamatsu A. Department of Biochemistry, Faculty of Pharmaceutical Sciences, Fukuoka University.

We investigated the effects of native, oversulfated, and desulfated fucoidans and heparin on the invasion of 3 LL cells through Matrigel. Of the four polysaccharides tested, oversulfated fucoidan was the most potent inhibitor of tumor cell invasion and inhibited most potently and specifically the tumor cell adhesion to laminin. Sodium dodecyl sulfate-polyacrylamide gel electrophoretic analysis of the binding of elastase-cleaved laminin to fucoidan- and heparin-Sepharoses showed that both polysaccharides bound to the 62 and 56 kDa fragments. Pretreatment of 3 LL cells with native or oversulfated fucoidan reduced their adhesive potency to laminin. The two fucoidans inhibited further the laminin binding of 3 LL cells which had been pretreated with a laminin-based pentapeptide, YIGSR. These results suggest that fucoidan specifically binds to not only the heparin binding domain(s) of laminin but also site(s) other than the cell surface laminin receptor. 3 LL cells secreted a 50 kDa form of urokinase-type plasminogen activator (u-PA). The extracellular level of u-PA activity was increased 1.7 times by addition of laminin but not type IV collagen. Oversulfated fucoidan most potently reduced the increased u-PA levels. Therefore, the reduction in in vitro invasiveness of 3 LL cells in response to either fucoidan or its oversulfated derivative may result from an inhibition of physical interaction between the tumor cells and the Matrigel (laminin), followed by a suppression of the laminin-induced increase in extracellular u-PA. PMID: 7829400, UI: 95130424

Cancer Lett 1994 Sep 30;85(1):133-8
Aminated fucoidan promotes the invasion of 3 LL cells through reconstituted basement membrane: its possible mechanism of action.

Soeda S, Ishida S, Honda O, Shimeno H, Nagamatsu A. Department of Biochemistry, Faculty of Pharmaceutical Sciences, Fukuoka University, Japan.

Fucoidan is reported to have an antimetastatic activity. In the present study, we prepared an amino group-introduced derivative of fucoidan and examined its effect on the invasion of 3 LL cells through a reconstituted basement membrane (Matrigel™). Unlike native fucoidan, the aminated derivative promoted the tumor cell invasion: maximal promotion (240% of control invasion) was obtained with 5 micrograms/ml. However, with higher concentrations (10-30
of the fucoidan derivative, the promotion was gradually reduced to 130% of control. Both native and aminated fucoidans inhibited specifically the attachment of 3 LL cells to laminin. Interestingly, aminated fucoidan, unlike the native one, promoted the tumor cell adhesion to immobilized synthetic laminin B 1 chain peptide, YIGSR, over a concentration range of 0.5-5 micrograms/ml. Higher concentrations (7-20 micrograms/ml) of the aminated derivative suppressed the adhesive ability of 3 LL cells to YIGSR. 3 LL cells secreted a 50-kDa form of urokinase-type plasminogen activator (u-PA) in the culture medium. Addition of aminated fucoidan (5 micrograms/ml) or YIGSR (10 micrograms/ml) resulted in a 1.7-fold increase in u-PA activity. This effect was enhanced up to 3.5-fold when both substances were simultaneously added. The addition of native fucoidan had no effect. The present results suggest that the 67-kDa receptor-mediated binding of 3 LL cells to laminin activates their invasiveness, especially by enhancing the extracellular u-PA levels. Aminated, but not native, fucoidan may act to enhance the laminin-receptor interaction at the limited concentration range.

Anticancer Res 1993 Nov-Dec;13(6A):2045-52

Antitumor activity and immunological properties of marine algal polysaccharides, especially fucoidan, prepared from Sargassum thunbergii of Phaeophyceae.

Itoh H, Noda H, Amano H, Zhuauag C, Mizuno T, Ito H. Laboratory of Marine Biochemistry, Faculty of Bioresources, Mie University, Japan.

Marine algal polysaccharide, GIV-A from Sargassum thunbergii markedly inhibited the growth of Ehrlich ascites carcinoma at the dose of 20 mg/kg per day X10 with no sign of toxicity in mice. GIV-A is suggested to be a hexuronic acid containing L-fucan sulfate, fucoidan by the analyses of physicochemical properties and IR- and NMR-spectra. The results of carbon clearance activity with fucoidan demonstrated that it is acting as a so-called activator of the reticuloendothelial system. Fucoidan enhanced the phagocytosis and chemiluminescence of macrophages. By the immunofluorescent method, binding of the third component of complement (C3) cleavage product to macrophages and the proportion of C3 positive cells were increased. In crossed immunoelectrophoresis, human serum C3 was converted by fucoidan and appeared as the 3rd peak (converted C3). The height of the 3rd peak was directly proportional to the doses of fucoidan. The residual CH50 units of human serum decreased dose-dependently. These results suggest that the antitumor activity of fucoidan is related to the enhancement of immune responses. The present results indicate that fucoidan may open new perspectives in cancer chemotherapy. PMID: 7923097, UI: 95007484

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**Laryngorhinootologie** 1991 May;70(5):243-9

**Histochemical identification of endogenous lectins using labelled neoglycoproteins in human head-and-neck squamous cell carcinoma. [Article in German]**


According to the “Population-based cancer register” of the Federal Republic of Germany, only malignant neoplasms of the buccal cavity, the pharynx, and larynx as well as cancers of the respiratory tract show an increasing rate of incidence and mortality. The molecular mechanisms and etiological factors causing this phenomenon are still little understood despite intensive research work. Recognition between receptors on a cellular level may be mediated by specific amino acid sequences on the level of protein-protein recognition. Additionally, the interactions between cell sugars and the corresponding protein receptor may play a decisive role in development, regeneration, and organisation of cells and tissue. The high specificity of the binding of biotinylated neoglycoproteins in tissue sections enables to detect glycohistochemically binding sites for the carbohydrate ligands of the glycosylated carrier protein. The evidence of lectins in squamous cell cancer of the oral cavity, oropharynx, larynx, and hypopharynx has not been established so far. Squamous cell cancer tissue samples of twelve patients with different tumour locations were investigated by incubation of sections of paraffin-embedded samples and application of an avidin-biotin-peroxidase complex for visualisation with synthetic biotinylated neoglycoproteins. Altogether, 168 stained sections were evaluated including controls. Pronounced cytoplasmatic staining was seen with the following neoglycoproteins: sialic acid-bovine serum albumin (BSA), glucuronic acid-BSA, N-acetylglucosamine (glcNAc)-BSA, N-acetylgalactosamine (beta-galNAc)-BSA, lactose-BSA, maltose-BSA, mannose-BSA, mannose-6-phosphate-BSA. No corresponding lectins seems to exist for the following investigated sugars: fucoidan, heparin, and the alpha-anomeric form of N-acetylgalactosamine, because no specific staining was seen. PMID: 2064700, UI: 91291219

**Experientia** 1989 Jun 15;45(6):584-8

**Blocking of lectin-like adhesion molecules on pulmonary cells inhibits lung sarcoma L-1 colonization in BALB/c-mice.**


Adhesion and inhibition experiments with pulmonary cells of BALB/c-mouse origin and syngeneic sarcoma L-1 cells indicated that L-fucose specific lectin-like adhesion molecules, presumably situated on pulmonary cell surfaces are (at least partly) responsible for the specificity of this cell-cell interaction. Addition of specific sugars and glycoconjugates (L-fucose and fucoidan, respectively) to the incubation medium evidently inhibited the adhesion process as quantified using radiolabelled tumor cells. Unspecific carbohydrates (e.g. D-galactose) did not affect the cellular interaction. In vivo, repeated administration of fucoidan (but not of unspecific glycoconjugates) significantly inhibited the settling of metastatic sarcoma L-1 cells in the lungs of BALB/c-mice. Therefore, when lectin-like adhesion molecules on pulmonary cells were blocked with competitive glycoconjugates, tumor cell colonization of the lung could be significantly inhibited. PMID: 2737266, UI: 89289934
Histopathologic evaluation of application of labeled neoglycoproteins in primary bronchus carcinoma.

Kayser K, Gabius HJ, Ciesiolka T, Ebert W, Bach S. Department of Pathology, Thoraxklinik Heidelberg-Rohrbach, Germany.

Neoglycoproteins are readily available conjugates of a histochemically inert carrier protein and histochemically crucial carbohydrate moieties which are covalently attached to the carrier protein by chemical synthesis. Biotinylation renders these conjugates detectable in formalin-fixed, paraffin-embedded tissue sections of human lung cancer by standard staining protocols, thereby localizing endogenous receptors for carbohydrate moieties. Examination of 30 cases of main types of human lung cancer revealed the presence of alpha-fucosyl-, alpha-mannosyl-, and alpha-glucosyl-specific receptors in adenocarcinomas or epidermoid carcinomas with high positivity rates. The extent of the expression of receptors for alpha- and beta-galactosides appeared to be comparatively lower. Within the standard protocol, using a concentration of the biotinylated probes of 10 micrograms/mL, this panel of probes consistently failed to detect endogenous sugar receptors in ten cases of small cell anaplastic carcinoma of the lung. Whereas none of the sections from the tumor cases bound the sulfated fucan fucoidan, the accompanying inflammatory cells, especially the granulocytes, expressed receptors for the sulfated fucan. Pronounced labeling for macrophages was observed for the alpha-galactoside-specific probe, whereas no binding to inflammatory cells and pneumocytes was detectable for the beta-galactoside-specific probe. The results indicate that expression of endogenous receptors for neoglycoproteins may be useful in discriminating between small cell and non-small cell lung carcinoma and carcinomatous cells from accompanying inflammatory cells.

PMID: 2467870, UI: 89197199

Laminin-dependent and laminin-independent adhesion of human melanoma cells to sulfatides.

Roberts DD, Wewer UM, Liotta LA, Ginsburg V. Laboratory of Structural Biology, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Maryland 20892.

Sulfatides (galactosylceramide-I3-sulfate) but not neutral glycolipids or gangliosides adsorbed on plastic promote adhesion of the human melanoma cell line G361. Direct adhesion of G361 cells requires densities of sulfatide greater than 1 pmol/mm2. In the presence of laminin, however, specific adhesion of G361 cells to sulfatide or seminolipid (galactosylalkylacyl-glycerol-I3-sulfate) but not to other lipids is strongly stimulated and requires only 25 fmol/mm2 of adsorbed lipid. The effects of laminin and sulfatide on adhesion are synergistic, suggesting that laminin is mediating adhesion by cross-linking receptors on the melanoma cell surface to sulfatide adsorbed on the plastic. Although thrombospondin binds to sulfatides and G361 cells, it does not enhance, but rather inhibits direct and laminin-dependent G361 cell adhesion to sulfatide. In contrast, C32 melanoma cells also adhere specifically to sulfatide, but adhesion of these cells is not enhanced by laminin or inhibited by antibodies to laminin that block laminin-dependent adhesion of G361 cells. Thrombospondin is a potent inhibitor of C32 cell adhesion to sulfatide. Fucoidan, which inhibits laminin binding to sulfatide, inhibits laminin-dependent adhesion of G361 cells by 50% at 0.2 micrograms/ml. Several other tumor cell lines also attach directly on sulfatide-coated...
surfaces. Laminin stimulates adhesion to sulfatide of three of the six cell lines tested. The ability of laminin to promote adhesion of tumor cells to sulfatide suggests that binding to sulfatide could participate in laminin-mediated cell-cell adhesion. Thus, many tumor cell lines can attach on sulfatide substrates using endogenous sulfatide binding proteins, and in some cells laminin but not thrombospondin can promote tumor cell adhesion to sulfatide.

PMID: 2967105, UI: 88223173


**Sulfated homopolysaccharides with immunomodulating activities are more potent anti-HTLV-III agents than sulfated heteropolysaccharides.**

Mizumoto K, Sugawara I, Ito W, Kodama T, Hayami M, Mori S. Division of Biochemical Genetics, Meiji Institute of Health Science, Kanagawa, Japan.

We reported previously that homopolysaccharides with sulfate groups revealed immunomodulating activities--lymphocyte mitogens. We further investigated the role of homopolysaccharides in a different system--cultivation of Molt-4 clone no.8 with supernatant from human T cell lymphotropic virus type III (HTLV-III)-infected TALL-1, utilizing cytopathic effects (CPE), fluorescence antibody technique (FAT), reverse transcriptase (RT) assay and cell proliferation assay. Sulfated homopolysaccharides such as fucoidan, dextran sulfate with three different molecular weights, cellulose sulfate and k-carrageenan showed most potent anti-HTLV-III activities at mitogenic doses. However, neutral homopolysaccharides had no effects on anti-HTLV-III activities. Sulfated heteropolysaccharides such as heparin and heparan sulfate had a little effect on anti-HTLV-III activities. It is suggested that sulfate group is most important in inhibiting growth of HTLV-III, but the structure of the polysaccharides is also important, because homopolysaccharides are more potent anti-HTLV-III agents than heteropolysaccharides.

PMID: 2903262, UI: 89037751

**Cancer Immunol Immunother** 1987;24(1):1-7

**In vitro and in vivo release of cytostatic factors from Lactobacillus casei-elicited peritoneal macrophages after stimulation with tumor cells and immunostimulants.**

Hashimoto S, Nomoto K, Nagaoka M, Yokokura T.

The effect of tumor cells and immunostimulants on the release of cytostatic factors (CF) from Lactobacillus casei YIT 9018 (LC)-, Corynebacterium parvum (CP)- or peptone-elicited peritoneal macrophages (PM) was investigated in vitro and in vivo. Significant release of CF into the culture medium from PM elicited with LC was induced by seven of eight mitomycin C-pretreated tumor cell lines and not by normal spleen cells, while no CF was released extracellularly from peptone-elicited PM given the same stimulus. CF were released from LC-elicited PM (LCEPM) after stimulation with LC, bacille Calmette-Guerin, streptococcal preparation OK-432, fucoidan or lipopolysaccharide, and LC but not CP induced CF production in the peritoneal cavities of LC- or CP-primed mice. The release of CF from LCEPM after stimulation with mitomycin C-pretreated 3T12-3 cells was inhibited by D-mannose and not by L-fucose. L-Rhamnose and mannose 6-phosphate, but not D-mannose or L-fucose, caused the release of CF from the PM. It was suggested that the release of CF from activated PM is caused by stimulation by some tumor cells, sugars, or bacterial immunostimulants, D-Mannose and L-rhamnose on the surface of tumor cells.
or bacteria, respectively, may plan an important role in the release of CF from activated macrophages. PMID: 3102062, UI: 87130857


**Antitumor effect of seaweeds. IV. Enhancement of antitumor activity by sulfation of a crude fucoidan fraction from Sargassum kjellmanianum.**

Yamamoto I, Takahashi M, Suzuki T, Seino H, Mori H.

We have reported an antitumor aqueous extract from a brown marine alga Sargassum kjellmanianum ("Hahakimoku" in Japanese). Although the extract was effective in the in vivo growth inhibition of the implanted Sarcoma-180 cells, it was not effective against L-1210-bearing mice. In the present study, we attempted to obtain a polysaccharide fraction with antitumor activity against L-1210 leukemia from this alga, on the assumption that the main active substance may be sulfated polysaccharide, especially fucoidan which is mainly composed of L-fucose and ester sulfate. Two kinds of polysaccharide fractions (SKCF and SKCF-F), which contained L-fucose and ester sulfate in the amount of 12.6% and 15.4%, 23.5% and 17.2% respectively, were first prepared starting with extraction with cold-hydrochloric acid, and their antitumor activity was examined. It was found however that they are not effective. Sulfation of SKCF was then carried out. The resulting sulfate (Sulfated SKCF) was observed to contain nearly 50% more ester sulfate than in SKCF and to be effective against L-1210 leukemia showing an ILS value of 26%. Mechanisms of antitumor action of this sulfate were also discussed from the viewpoints of negativity of ester sulfate and of activation of host-mediated immune response as known in antitumor polysaccharide preparations from other sources.

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**Fucoidan blocks macrophage activation in an inductive phase but promotes macrophage activation in an effector phase.**

Sugawara I, Lee KC.

It has been suggested that some polysaccharides play important roles in immune responses. Therefore, we used various types of polysaccharides for analysis of macrophage-mediated tumor cell killing. We report here that fucoidan blocked macrophage activation occurs in an inductive phase but enhanced macrophage activation appears in an effector phase.

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**Fucoidan-Dependent Conformational Changes in Annexin II Tetramer.**

Fitzpatrick SL, Kassam G, Manro A, Braat CE, Louie P, Waisman DM. Cancer Biology Research Group, Department of Medical Biochemistry, University of Calgary, Calgary, Alberta, Canada T2N 4N1.

Fucoidan, a sulfated fucopolysaccharide, mimics the fucosylated glycans of glycoproteins and has therefore been used as a probe for investigating the role of membrane polysaccharides in cell-cell
adhesion. In the present report, we have characterized the interaction of fucoidan with the Ca(2+)- and phospholipid-binding protein annexin II tetramer (Allt). Allt bound to fucoidan with an apparent K(d) of 1.24 +/- 0.69 nM (mean +/- SD, n = 3) with a stoichiometry of 0.010 +/- 0.001 mol of fucoidan/mol of Allt (mean +/- SD, n = 3). The binding of fucoidan to Allt was Ca(2+)- independent. Furthermore, in the presence but not the absence of Ca(2+), the binding of fucoidan to Allt caused a decrease in the alpha-helical content from 32% to 7%. A peptide corresponding to a region of the p36 subunit of Allt, F(306)-S(313), which contains a Cardin-Weintraub consensus sequence for heparin binding, was shown to undergo a conformational change upon fucoidan binding. This suggests that heparin and fucoidan bound to this region of Allt. The binding of fucoidan but not heparin by Allt also inhibited the ability of Allt to bind to and aggregate phospholipid liposomes. These results suggest that the binding of Allt to the carbohydrate conjugates of certain membrane glycoproteins may have profound effects on the structure and biological activity of Allt. PMID: 10694379