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Review Article

From Bench to Bedside: The Growing Use of Arabinoxylan Rice Bran (MGN-3/Biobran) in Cancer Immunotherapy

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Abstract

MGN-3/Biobran is a denatured hemicellulose obtained by reacting rice bran hemicellulose with multiple carbohydrate hydrolyzing enzymes from Shiitake mushrooms. Over the last 24 years, our fundamental research objective has been to study the biotherapeutic activity of MGN-3 as a treatment for cancer based on its ability to activate the immune system. This objective has been pursued *in vitro*, and in animal and human studies. This review is focused on the immunomodulatory effects of MGN-3 and on its potential as an anti-cancer agent. *In vitro* studies showed that culturing different human and murine cancer cell lines with MGN-3 resulted in a reduction of the survival rate of cancer cells. *In vivo* studies have also shown that MGN-3 induces tumor regression in several models of animal bearing tumor, including gastric cancer, neuroblastoma, and Ehrlich carcinoma. In addition, the anti-cancer activity of MGN-3 has been shown in human clinical trials and in several case reports on patients with Hepatocellular Carcinoma (HCC) and progressive and partially metastasized cancer. Patients that were treated with MGN-3 in addition to Conventional Therapy (CT), as compared with CT alone, showed: 1) less recurrence of cancer, 2) higher survival rate and 3) improved Quality of Life (QOL) as characterized by improvements in physical activity, appetite, sleep, and digestion, and a decrease in pain and anxiety.

This review summarizes the preclinical and clinical research on MGN-3/Biobran since it was first patented in 1992. Various animal studies and human clinical trials including different types of malignancies have demonstrated that MGN-3 is a potent Biological Response Modifier (BRM). MGN-3 enhances the cytotoxic reactivity of immune cells with anti-cancer activity such as NK and CD8+ T cells via increasing cell granularity, stimulates the production of interferons, IL-2 and IL-12, and functions as a natural adjuvant for Dendritic Cells (DC). Therefore, MGN-3 may be used in DC-based vaccine strategies against infections and cancer. Importantly, MGN-3 is a unique BRM because it is a safe non-toxic agent and does not exhibit hyporesponsiveness. MGN-3 has the potential to be a novel and promising immune modulatory adjuvant that could complement the existing immunotherapeutic modalities for cancer patients.

Keywords: Biobran; Arabinoxylan; Natural Killer cells; Dendritic cell; BRM

Introduction

Despite the last decade of advances in treatment options, cancer remains the second leading cause of death in the United States [1]. Unfortunately the outcome of standard cancer treatments is often poor due to the emergence of Multidrug Resistance (MDR) during the course of treatment. MDR cells are a significant factor in the failure of chemotherapeutics as evidenced by high relapse rates for the majority of patients [2,3]. Therefore, to increase cancer survival and improve symptom control, there is a strong need for new and better approaches to cancer treatment. Today, the National Cancer Institute (NCI) has acknowledged the importance of immune therapy for the treatment of cancer. NCI, other health organizations, and professionals in the field of oncology are currently working to harness the immune system to fight cancer and to expand immunotherapy in combination with other types of cancer treatment, such as targeted therapy, chemotherapy, and radiation therapy.

The field of cancer immunotherapy has recently received increasing interest as a promising approach to tackle cancer. This approach involves fighting off cancer cells by using the patient's own immune system. The theory of immune surveillance postulates that immune effectors can recognize and destroy spontaneously arising malignant tumor cells. Tumors may develop when transformed cells escape the immunologic host defense mechanism [4-6]. With respect to immunotherapy, Biological Response Modifiers (BRM) are designed to activate the host immune response to destroy cancer cells. Several BRMs of fungal and bacterial origin have been developed, but most of these BRMs have been associated with severe side effects and exhibit hyporesponsiveness. MGN-3/Biobran, an arabinoxylan

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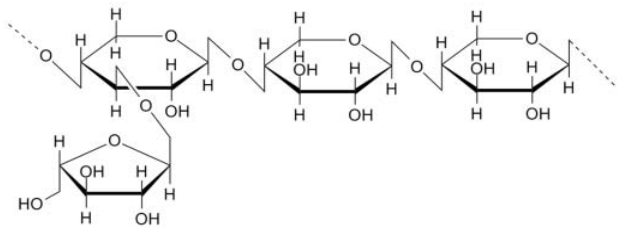

Figure 1: Chemical structure of MGN-3/Biobran.

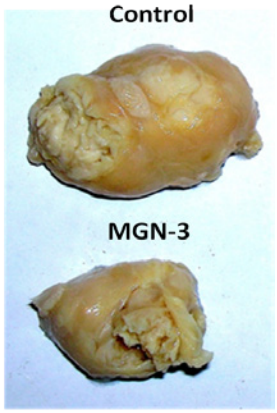

Figure 2: Mice tumors show a significant decrease in volume and weight after treatment with MGN-3/Biobran.

from rice bran, is a notable BRM that possesses the two important characteristics of a successful BRM: 1) safe, non/minimal toxicity [7-12] and 2) does not exhibit hyporesponsiveness [13,14].

Bran and fiber can provide health benefits of cancer risk reduction [15], including reduction on the growth of colorectal cancer cells [16] and the number of intestinal adenomas in mice [17]. Further studies have been focused on the anti-cancer activity of rice bran extracts and products derived from them [18,19], such as IP6 [20], and several phytosterols and triterpenoids [21]. The current review describes rigorous bench research on MGN-3/Biobran over the last 24 years. The research shows its translational potential as a novel adjuvant for the treatment of cancer by demonstrating its anti-cancer activity and the mechanisms underlying its effect. The treatment potential of MGN-3 is exemplified through animal studies and human clinical trials on patients with different types of malignancies, including a 3-year randomized clinical trial of the anti-cancer activity of MGN-3 against Hepatocellular Carcinoma (HCC) [22].

The mechanisms by which MGN-3 exerts its anti-cancer activity involve chemotherapy sensitization and immune modulation. The chemosensitizing effect of MGN-3 has previously been reviewed in [18]. Therefore, in this review we focus on the immune modulatory effect of MGN-3 as manifested by its ability to activate different arms of the immune system such as NK cells [9,13,23-26] and DCs [27-29], and modulation of the production of cytokines such as interferons [9,23,28,29], IL-2 and IL-12 [25,28]. This research review shows that MGN-3 has translational potential as a novel immune modulatory adjuvant for the treatment of cancer. Further studies are needed in multiple clinical trials.

Preclinical research

Preclinical research on the anti-cancer effects by MGN-3 has been examined. MGN-3 is a denatured hemicellulose obtained by reacting rice bran hemicellulose with multiple carbohydrate hydrolyzing enzymes from Shiitake mushrooms [30]. The main chemical structure of MGN-3 is an arabinoxylan with a xylose in its main chain and an arabinose polymer in its side chain (Figure 1). Earlier studies have shown reduction in the survival of different human and murine cancer cell lines post cultures with MGN-3. In a dose- and time-dependent manner, MGN-3 reduced the survival rate of human Breast Cancer Cells (BCC) MCF-7 and ZR-75-1, murine metastatic BCC 4T1 [31-33], and human multiple myeloma cell line U266 [34].

MGN-3 has also been shown to induce cancer regression in several models of animals bearing tumors. These include: 1) Swiss albino mice inoculated with Ehrlich carcinoma cells. Daily supplementation of MGN-3 (25 mg/kg body weight) for 25 days resulted in significant decrease in tumor volume and tumor weight (Figure 2) [35]. 2) Wistar rats induced with gastric cancer by carcinogen Methylnitronitrosoguanidine (MNNG). Daily supplementation of MGN-3 (40 mg/kg body weight) for 8 months resulted in a significant decrease in the percentage of animals bearing dysplasia and adenocarcinoma as well as suppression of the expression of tumor marker Ki-67 [36]. 3) NOD-scidIL-2Rγ null mice bearing neuroblastoma. Significant neuroblastoma growth inhibition was observed in mice that received MGN-3 stimulated NK cells [26]. 4) Mice bearing liver cancer. MGN-3 treatment caused a significant decrease in the incidence of liver cancer in animal bearing tumor (article in prep).

Clinical research

Further studies were carried out to examine the anti-cancer activity of MGN-3 in clinical trials and case reports. A 3-year randomized clinical trial of the anti-cancer activity of MGN-3 against Hepatocellular Carcinoma (HCC) was conducted [22]. Sixty-eight patients with HCC (stages I and II) were divided into two groups: group 1 was treated with Conventional Therapy (CT) alone, and group 2 was treated with CT plus MGN-3 (1g/day). CT included transarterial oily chemoembolization, pericutaneous

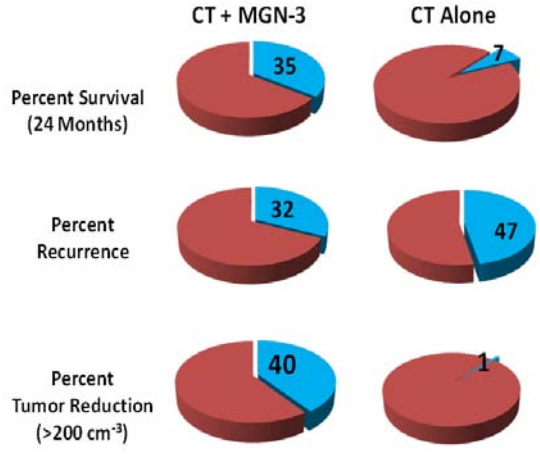

Figure 3: Patient survival, recurrence, and tumor reduction after treatment with CT alone *vs.* CT+MGN-3.

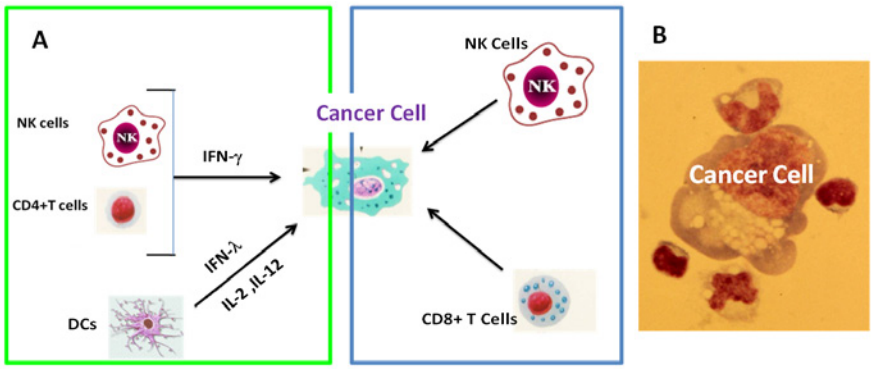

Figure 4A & 4B: MGN-3/Biobran enhances the activity of different immune cells to attack cancer cells. (A) Schematic of MGN-3 enhancement of cytotoxic reactivity of immune cells with anti-cancer effect and of production of different cytokines. (B) MGN-3 enhances the binding of different immune cells to cancer cells. Notice the blebbing of this cancer cell membrane and the presence of vacuoles (Giemsa stain).

ethanol injection therapy, or a combination of both. Patients that were treated with CT plus MGN-3, as compared with CT alone, showed: 1) reduced tumor size, 2) less recurrence of cancer, 3) higher survival rate, 4) lower alpha fetoprotein level, and 5) lower alanine transaminase (Figure 3). In contrast, other BRMs, including PSK, lentinan, and OK-432, showed no effect when combined with 5-FU for the treatment of HCC [37]. Another major clinical study in Japan involved 205 progressive and partially metastasized cancer patients treated with chemotherapy and MGN-3 (3g/day) [38]. The patients with MGN-3 demonstrated prolonged life expectancy and an increase in appetite. In another study, 16 cancer patients (Stage IV) treated with chemotherapy followed by MGN-3 (3g/day) for 6 months showed no changes in body weight and enhanced NK cell activity [39]. An additional study involving 5 cancer patients showed improvements in tumor markers post treatment with MGN-3 [40]. A recent study by Golombick, et al. in Australia examined the effect of the combination of MGN-3 with curcumin for the treatment of patients with early stage B-cell lymphoid malignancies (monoclonal gammopathy of undetermined significance, smoldering multiple myeloma, or stage 0/1 chronic lymphocytic leukemia). Patients who had been on oral curcumin therapy for 6 months or more were then administered the combination therapy of MGN-3 (2 g/day) and curcumin for an additional 6 months. They reported the combined treatment resulted in increased neutrophil counts of patients who were neutropenic and reduction of raised Erythrocyte Sedimentation Rates (ESR) [41].

MGN-3 has also been studied in several case reports. In one instance, a group of medical doctors at the Mayo Clinic in Jacksonville, Florida, described the effects of MGN-3 treatment on their patient as follows: "the lung masses steadily decreased in size and at 34 months after the initiation of therapy, the tumor was undetectable by computed tomography" [42]. In another instance, a 64-year-old female with terminal cancer and an extremely poor prognosis (umbilical metastasis of recurrent colorectal cancer) was treated with a combination of chemotherapy and MGN-3, which led to a prolongation of lifespan (2 years) and maintenance of Quality of Life (QOL) [43]. Recently, Hajto, et al. in Hungary and Switzerland reported complete remission in two case reports post-treatment with chemotherapy followed by immunotherapy including MGN-3. The first patient had uterus and ovary sarcoma [44] and the second patient had lung adenocarcinoma [45]. Hajto, et al. also reported on QOL observations in 35 patients with various cancer types whose treatment included MGN-3 [46]. These observations included significant improvements in physical activity and appetite (66-71%), in sleep and digestion (40-43%), as well as decreases in pain, anxiety, and in side effects during oncotherapy.

Immune modulation

The mechanistic basis of the anti-cancer effects by MGN-3/Biobran that were mentioned in the preclinical and clinical research studies are founded on the ability of this agent to act as a potent biological response modifier (BRM). (Figure 4A & B) illustrates a schematic of MGN-3 enhancement of activities of different arms of the immune system to attack cancer cells. These include the cytotoxic reactivity of immune cells with anti-cancer activity, such as NK cells and CD8+ T cells, and modulation of the production of cytokines such as interferon-gamma (IFN-γ), -lambda (IFN-λ), IL-2 and IL-12.

In both *in vitro* and *in vivo* studies, immune cell activity was examined in splenic cells or human Peripheral Blood Lymphocytes (PBLs). We have established the success of MGN-3 as a BRM by studying its: 1) safety, 2) dose response, 3) duration of effectiveness, 4) hyporesponsivness, and 5) effectiveness in modulation of immune cells and the mechanisms underlying its immune-modulatory effect. Below is a review of studies on each of these cells and cytokines.

Natural Killer (NK) cells: NK cells mediate spontaneous cell-mediated cytotoxicity against a variety of malignant tumors and virally infected cells, and thus play a crucial role in the first line of defense against cancer and viral infections [4,47,48]. NK cells initially attach to cancer cells and then release their granules, which form holes that ultimately cause target-cell death. Several studies demonstrated that MGN-3 is a potent BRM that enhances NK cell activity *in vitro*. For example, MGN-3 treatment of splenic lymphocytes from aged C57BL/6 mice caused an increase in NK activity ($p<0.01$) [24]. In addition, MGN-3 cultured PBLs, as well as purified NK cells from healthy individuals, showed a significant increase in the cytotoxic function of NK cells [9,23]. Furthermore, human NK cells cultured with MGN-3 recently demonstrated an increase in their cytotoxic activity when tested in a panel of human cancer cell lines: K562,

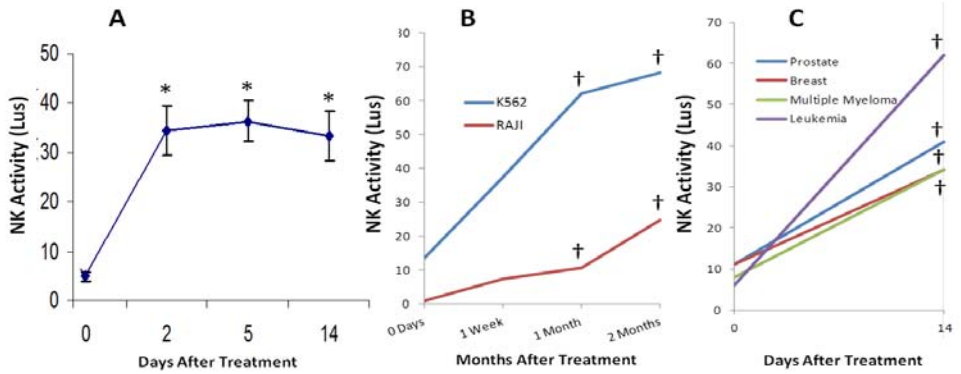

Figure 5A-C: MGN-3 enhances NK cell activity *in vivo*. (A) Aged mice (B) human immune compromised individuals and (C) patients with different malignancies. Significance at *p<0.01, †p<0.001.

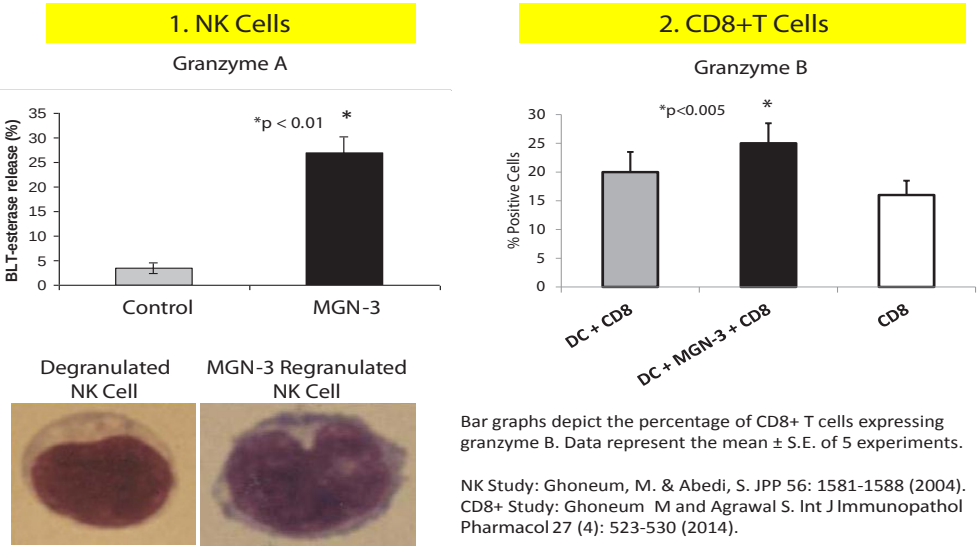

Figure 6: MGN-3 increases the granular content of NK and CD8+ T cells, which subsequently enhances their cytotoxic reactivity.

Jurkat, A673, NB1691, A-204, RD, and RH-30. The increase in NK activity was accompanied by an induction of a higher expression of the activation-associated receptors CD25 and CD69 on NK cells, as compared with control untreated cells [26].

MGN-3 also enhances murine NK cell cytotoxic reactivity *in vivo*. One study examined the effect of MGN-3 on NK activity in aged mice, which is associated with the decline of immune function [24]. Two strains of mice (C57BL/6 and C3H), at age 18 months, showed significantly low NK cell activity. However, treatment with MGN-3 via oral administration and intrapetitoneal injection resulted in enhanced splenic NK and peritoneal NK activity, respectively. The increase in activity was noticed as early as 2 days post treatment (Figure 5A), and was associated with an increase in the percentage of conjugates between NK cells and YAC-1 tumor cell targets, and an increase in the granular content of NK cells. The immune modulatory effects of MGN-3 were also observed in animal bearing tumor. These included an elevation in NK cell activity in Erlich-carcinoma bearing mice [35], an increase in the percent of lymphocytes in Wistar rats bearing gastric cancer [36], and stimulation of NK cell cytotoxicity against neuroblastoma and selective augmentation of the expansion of NK cells [26].

Further studies showed that human ingestion of MGN-3 caused enhancement of NK cell activity. Oral administration of MGN-3 at 15, 30, and 45 mg/kg/day significantly increased NK activity in 24 human individuals in a dose-dependent manner. (Figure 5B) [9]. MGN-3 treatment also resulted in a marked increase in NK cell activity of cancer patients at 2 weeks (Figure 5C) [13]. Another study demonstrated increased NK activity in 48 multiple myeloma patients at 1 and 2 months post treatment with MGN-3, as compared with baseline and placebo groups [25]. In addition, Hajto et al. reported an increase in the levels of circulating NK cells of healthy subjects as early as 24 hours post treatment with MGN-3 (15mg/kg/day) in combination with a mistletoe plant extract [44]. On the other hand, an earlier study on MGN-3 treatment did not significantly alter the total NK cell population or NK cell subsets (CD56+, CD16+) [9]. The combination of treatments in Hajto, et al. study could be the source of the difference between the two studies with respect to the levels of circulating NK cells.

NK cells and CD8+ T cells recognize and kill virally infected

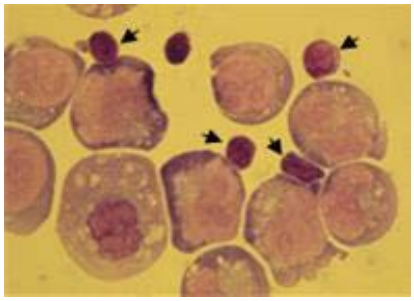

Figure 7: MGN-3 stimulated NK cells (arrows) bind to cancer cells.

or transformed cells through the granular exocytosis pathway; that is, they operate through the delivery of cytotoxic granules to target cells, causing their rapid death [49]. Cancer patients are frequently characterized as having low NK activity, attributed to a decrease or absence of perforin and granzyme containing granules [50-52]. Several MGN-3 studies have shown that its treatment causes an increase in the granular content (perforin and Granzyme-B) of NK cells, as has been demonstrated morphologically and biochemically (Figure 6) [13,24]. Furthermore, MGN-3 treatment resulted in an increase in the binding capacity of NK cells to cancer cells (Figure 7).

Dendritic Cells (DCs): Our work and that of others showed that MGN-3 also has the ability to activate human monocyte-derived DCs *in vitro* [27-29]. DCs are considered the most influential of the Antigen-Presenting Cells (APCs): they bridge innate and adaptive immunity, and they are one of the major cells involved in generating anti-tumor immune response. Mature DCs are able to migrate to lymphoid organs to present antigens to naive T cells and to efficiently mount adaptive immune responses [53,54].

A- MGN-3 activates human DCs. MGN-3 has been shown to be a potent activator of DC maturation and function. MGN-3 upregulates the expression of co-stimulatory molecules CD80 and CD86, which are expressed on mature DCs. These stimulated DCs cause increased production of pro-inflammatory and immuno-regulatory cytokines, including IL-1β, IL-6, IL-10, TNF-α, IL-12p40, and low levels of IL-12p70 and IL-2 [28], and type III IFN (-IFN lambda, IL29) [29]. Though the mechanism underlying the stimulatory effects of MGN-3 on DCs is not fully understood, it is possible that MGN-3 triggers signaling pathways involved in cell activation and cytokine production by binding to the cell surface receptors (TLRs and /or C type lectins) or to intracellular receptors (NLRP3 inflammasome) [27-29].

B- MGN-3 enhances generation of cytotoxic CD8+ T cells via upregulation of DEC-205 expression on DCs. Several reports indicate the critical roles of DEC-205 and CD8+ T cell responses against cancer and viruses [55]. Data of our recent study demonstrated that stimulation of DCs through MGN-3 alone induces high cytolytic CD8+ T cells. DCs stimulated with MGN-3 induced significant levels of granzyme B-positive CD8+ T cells. These findings were associated with an increased expression of DEC-205 and type III IFN production [29].

C- MGN-3 stimulated DC induced CD4+T cell proliferation and their production of cytokines. Treatment with MGN-3 has been shown to stimulate DCs to induce CD4+T cell proliferation and their production of cytokines IFN-γ, IL-10, and IL-17 [28]. MGN-3 thus functions as a natural adjuvant for DC activation and may be used in DC-based vaccine strategies against infections and cancer.

A further study of MGN-3 on DCs of multiple myeloma patients was carried out. Results showed oral administration of MGN-3 resulted in a significant increase in the levels of circulating myeloid DCs, as well as a remarkable increase in mDC/pDC ratio at 3 months ($p=0.030$) [25].

T and B lymphocyte proliferation: The effect of MGN-3 on T and B lymphocyte proliferation was examined *in vivo*. Healthy subjects were given MGN-3 orally (15 mg/kg/day) for 2 months and their Mononuclear Cells (MNC) before and after MGN-3 treatment were cultured in the presence or absence of Phytohaemagglutinin (PHA), Concanavalin A (Con A), and Poke Weed Mitogen (PWM). MGN-3 treatment significantly enhanced MNC proliferation in the presence of PHA, Con A, and PWM (137% - 146%) [30]. Similarly, an increase in T and B cell proliferation in response to PHA, Con A, and PWM was also observed in 5 cancer patients with different types of malignancies post ingestion of MGN-3 (3g/day) for 1 month ($p<0.001$) [13].

T regulatory lymphocyte (T reg): T reg cells, or CD4+CD25+ lymphocytes, play a crucial role in the suppression of the antitumor cytotoxic immune response [56]; including their suppressive effect on NK cell activity [57]. Therefore, it has been suggested that any BRM capable of counteracting T reg activity could positively influence the progress of neoplastic disease. Lissoni, et al. [58] in Italy examined the effect of MGN-3 on the absolute number of T reg cells and their ratio with the total CD4+ T cells (TH) in 22 patients with solid tumor, 16 of whom had an untreatable metastatic solid tumor. MGN-3 therapy for two months resulted in an increased number of TH cells and a decrease in the T reg cell numbers. The individual increase and decrease were statistically insignificant as compared with the baseline values, but the increase in the TH/T reg mean ratio was statistically significant ($p<0.025$).

Macrophages: MGN-3 has also been shown to activate murine peritoneal macrophages and macrophage cell lines [59] and to enhance the phagocytic activity of human phagocytes (neutrophils and monocytes). This can increase the phagocytosis of Escherichia coli (E. coli) and trigger an oxidative burst. It was also shown to be associated with a significant induction of cytokines, including TNF-α, IL-6, IL-8, and IL-10 [60]. This suggests that MGN-3 modulates phagocytic cellular function and may be a useful agent for immune-compromised patients.

Interferons (IFN): IFN-γ and IFN-λ have been found to exert antitumor activity [61-64]. MGN-3 treatment of human PBL was observed to increase IFN-γ production [9,23] and to stimulate human DC-induced CD4+T cell IFN-γ production [28]. MGN-3 also induces the production of IFN-λ by human DCs (Figure 4) [29]. In addition, *in vivo* studies examined MGN-3 supplemented diets on cytokine production [65]. Chickens fed an 100 ppm MGN-3 supplemented diet showed significantly higher levels of splenic IFN-γ mRNA than control chickens. Other studies demonstrated increased levels of IFN-γ production ($p<0.01$) in Erlich carcinoma-bearing mice post treatment with MGN-3 [35]. Similarly, increased levels of IFN-γ were observed in multiple myeloma patients at 2 months post treatment

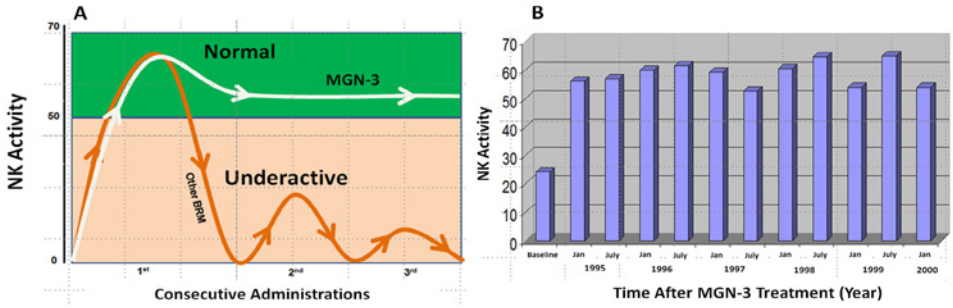

Figure 8A & B: Effect of long-term treatment of MGN-3 on human NK cell activity. (A) Schematic representation of NK cell activity in MGN-3 treatment for a longer period of time as compared with other BRMs. (B) Eight patients with breast cancer were treated with MGN-3 at a concentration of 45 mg/kg/day for 5 years. Activity was examined at effector: target ratio l00:l. NK activity was examined bi-annually and was measured by standard 5lCr-release assay using K562 as targets. Notice the maintenance of NK activity at high levels post-treatment with MGN-3 as compared with the baseline value.

with MGN-3 [25].

Interleukins: IL-2 and IL-12 cytokines may represent the main anti-cancer cytokines in humans. MGN-3 has been shown to stimulate DCs *in vitro*, resulting in the increased production of IL-2 [28]. In addition, MGN-3 has been shown to enhance the production of IL-12 in 30 multiple myeloma patients. The patients demonstrated a significant increase in IL-12 at one month post-ingestion of MGN-3 and a further increase at two months ($p \leq 0.001$) [25].

The uniqueness of MGN-3

MGN-3 is a unique BRM because it does not exhibit hyporesponsiveness. Hyporesponsiveness of NK activity has been a serious long-term problem for doctors working in the field of immunotherapy and is associated with many BRMs. Several studies showed that a single administration of a BRM significantly enhanced NK cell activity; however, repeated administration of the same BRM ultimately resulted in depression of NK cell activity [66-69]. In other words, response to the BRM was consistently reduced over time. Exceptionally, MGN-3 does not exhibit hyporesponsiveness. Oral administration of MGN-3 to cancer patients for five years resulted in enhancement of NK activity, which was maintained at a high level over the five-year period (Figures 8A & B) [13,14]. The lack of hyporesponsiveness of MGN-3 represents a unique characteristic for this agent over other BRMs.

The biosafety of MGN-3

MGN-3 has been shown to be a safe and nontoxic agent as manifested by the following: 1) the LD50 (lethal dose, 50%) of MGN-3 is greater than 36g/kg; 2) the Ames test for mutagenicity was negative; 3) the subchronic toxicity study (28-day dietary study in beagle dogs), the guinea pig antigenicity study, and genotoxic testing all demonstrate that MGN-3 is nontoxic [7,8]. Furthermore, MGN-3 was examined for toxicity in humans using blood chemistry analysis utilizing Panel 20, which includes liver enzymes (SGOT and SGPT). After 1 month of treatment, no abnormalities were detected for these parameters, as compared to baseline [9]. Earlier studies have also shown the potential for MGN-3 in reducing chemo-toxic effects in murine and cancer patients, including protection against severe weight loss induced by cisplatin in mice [10], or cisplatin and adriamycin in rats [11]. In addition, results of QOL among cancer patients treated with chemotherapy and MGN-3 have shown that patients demonstrated a marked improvement in appetite and other QOL parameters [12,46].

Recently, the Food and Drug Administration (FDA) approved ipilimumab for the treatment of advanced melanoma. Ipilimumab is a fully humanized anti-CTLA-4 monoclonal antibody Immunoglobulin (Ig) G1 isotype that has been shown to improve survival in patients with metastatic melanoma [70,71]. Several studies have shown, however, that a significant number of patients suffered immune-related adverse events [72,73]. MGN-3's action as a BRM, on the other hand, has not shown any adverse side effects after long periods of treatment in animals for 8 months [36] and in humans for 5 years [13,14]. Additionally, MGN-3 has been on the market since it was patented in 1992 and is being sold in approximately 49 countries, and there have not been any major complaints about adverse side effects nor immune-related adverse events.

Conclusion

The studies in this review strongly suggest that MGN-3/Biobran, a nutritional supplement from rice bran, exerts anti-cancer activity by a mechanism that involves an immune modulatory effect. Overall, the data suggests that MGN-3 can be used as an adjuvant to the existing immunotherapeutic modalities for cancer patients.

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