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Glucan and bone marrow

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The close connections and interactions between the immune and hematopoietic systems are well established. Therefore, it is not surprising that after numerous reports on the effects of glucans on various aspects of immune reactions, there has been a focus on the potential role of glucan in changes of the hematopoietic system.

In late 1970, the early studies were performed by using an animal model (control mice). Using an insoluble glucan (the only form available at that time), these pioneering studies showed that glucan administration resulted in an increase of granulocyte progenitor cells in bone marrow and the spleen. Later, a series of follow-up studies were performed by Patchen's group. She found that glucan not only affected cells of the granulocyte lineage, but even all the progenitors including erythrocytes [1]. However, the original findings suggested that an increase in the number of blood cells and spleen cells occurred simultaneously with a decrease in the bone marrow cellularity. This led to the hypothesis that glucan mobilizes bone marrow stem cells into the peripheral organs.

Later similar conclusions were provided by using soluble glucan. These studies were followed by using mushroom-derived glucan with similar results, demonstrating that these effects represent general effects of glucan and are not dependent on the type of glucan or the source of isolation.

From these studies, the manner in which glucan affects hematopoiesis in compromised animals (usually by irradiation or by chemotherapeutic agents) was evident. This was further confirmed by the whole series of studies using different glucans pre- and post-sublethal or lethal doses of irradiation [2]. The effects obtained were similiar irrespective of the solubility of used glucan.

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Later, the research on glucans and bone marrow also focused on the potential restoration of bone marrow after suppression by chemotherapeutic treatments. In 1993, the two different types of glucan were tested in a model of cyclophosphamide-induced suppression of bone marrow which showed modestly faster restoration of bone marrow. However, these effects were much more pronounced when glucan was used prophylactically, with significant increases in bone marrow hematopoietic progenitor cells [3]. It is important to note that these studies used different types of glucan. The potentiating effects on the cells of the granulocyte-macrophage lineage including protection of stem cells were also found using a mushroom-derived glucan Maitake in a model of doxorubicin-caused myelosuppression. Using a glucan isolated from seaweed (Phycarine), our group showed strong and fast restoration of both bone marrow and spleen cellularity after cyclophosphamide-induced suppression [4]. In addition to direct effects on bone marrow, mushroom glucan has been found to induce proliferation of hematopoietic stem cells and differentiation of progenitor cells in umbilical cord blood after experimental damage with doxorubicin.

For a long time, only injected glucan was used in bone marrow studies, while recently the researchers have switched to physiological oral administration. The reason was the uncertainity among scientists about the possible biological activity of orally administered glucan, which has been answered recently.

The use of highly purified linear seaweed-derived glucan showed that oral administration not only stimulated both humoral and cellular immunity, but also induced cell recovery in bone marrow, spleen, thymus, and peripheral blood in both the models of irradiation as well as 5-fluorouracil-induced damage of bone marrow. In addition, the type of recovery observed in this study was a preferred one, as no short-term overstimulation of myelopoiesis, often observed in other glucan studies, was found. In addition, the study demonstrated that regardless of whether the glucan was used simultaneously with experimental damage or one or two weeks earlier, there was a significant improvement in the recovery of bone marrow and other organs.

Mushroom glucan isolated from Ganodermalucidum was used orally and tested for post irradiation protection. For comparison, a clinically used radioprotective drug,

amifostine, was used. The data showed that both the components increased the survival of irradiated animals by 80%. Detailed analysis demonstrated a significant reduction in the number of aberrant cells and types of aberrations.

Lentinan, one of the few glucans approved for clinical practice was tested in preclinical studies using a model of acute myeloid leukemia in rats. Oral administration of nutritional grade lentinan resulted in weight gain, increased number of blood cells including monocytes and circulating cytotoxic T lymphocytes, but there was decrease in the production of cytokines such as IL-4, IL-6 and IL-10. A combination of glucan with standard treatment with idarubicin and/or cytarabine significantly increased the survival.

Ross's group explained the glucan effects in accelerating myeloid recovery and survival after radiation exposure by acting via CR3 receptors, using knock-out mice lacking CR3 receptor that showed no such effects. Subsequent experiments showed that ingested insoluble glucan particles traveled to spleen and bone marrow. Glucan optimized production of IL-12 and several other inflammatory cytokines including GM-CSF. IL-12 is known to stimulate production of oncostatin-M, which is a stimulator of hematopoiesis. Another role of glucan lies in co-stimulation of bone marrow with iC3b fragment of complement, as C3-deficient and CR3-deficient mice showed the same problems in recovery following radiation exposure.

The effects of glucan on damaged bone marrow, including restoration of lymphopenia and neutropenia caused by irradiation, led to suggestions that glucan might be widely used as radioprotectant that could mitigate the biological effects of radiation exposure in case of radiation accidents such as Chernobyl or Fukushima. Not surprisingly, glucan as radioprotectant was also the subject of army research in numerous countries. However, later observations reported that the same effects can be also found in bone marrow suppressed by cytotoxic drugs which diverted the attention to the clinical practice, because these effects offered significant help for patients undergoing chemotherapeutic treatment, as damage to leucopoiesis represents a major part of the development of the post-irradiation or post-chemotherapy hematopoietic syndrome. In addition, protection against ionizing radiation is of paramount importance during unavoidable or accidental exposure. Therefore, the pharmacologic protection against bone marrow damage is of considerable interest, with the development of novel and effective medical approaches to combat radiation or cytotoxic damage. Glucans seem to offer an ideal solution as they are inexpensive, free from side effects and capable of significantly protecting against radiation through restoration of the bone marrow with cell production.

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Author Contributions

Vaclav Vetvicka – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission

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Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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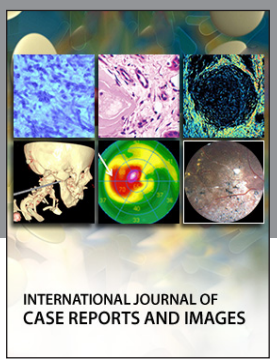

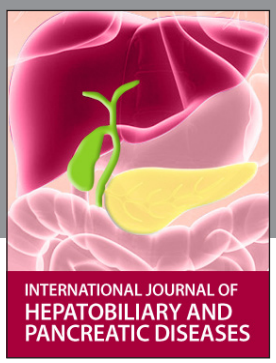

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