

HORMESIS AND IMMUNITY: A REVIEW

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The hormesis concept demonstrates that in contrast to the toxic effect of high doses of materials, irradiation, etc., low doses of them are beneficial and, in addition, help to eliminate (prevent) the deleterious effect of high doses given after it. By this effect, it is an important factor of (human) evolution protecting man from harmful impacts, similarly to the role of immunity. However, immunity is also continuously influenced by hormetic effects of environmental [chemical (pollutions), physical (background irradiations and heat), etc.] and medical (drugs and therapeutic irradiations) and food interactions. In contrast to earlier beliefs, the no-threshold irradiation dogma is not valid in low-dose domains and here the hormesis concept is valid. Low-dose therapeutic irradiation, as well as background irradiations (by radon spas or moderately far from the epicenter of atomic bomb or nuclear facilities), is rather beneficial than destructive and the fear from them seems to be unreasonable from immunological point of view. Practically, all immune parameters are beneficially influenced by all forms of low-dose radiations.

Keywords: background irradiation, immune functions, hormetic effects, immune cells, cancer, autoimmunity, faulty hormonal imprinting, nutrition

Introduction

The toxicological notion of hormesis is well known since centuries; however, it was not studied thoroughly from medical standpoint [1]. At the beginning of the 21st century, the works of Calabrese [2–6] brought it in the frontline of medicine and since then a mass of papers had been published approaching different aspects theoretically and practically (clinically) alike [7]. Hormesis demonstrates the beneficial effect of an environmental factor, drug, occupational pollutant, natural, artificial irradiation, etc., which is toxic (harmful) in high doses; however, it is innocuous, even beneficial if affects in small dose or doses. In addition, the pretreatment with this hormetic dose is conditioning against the deleterious effect of toxic dose given afterward [8, 9].

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In general, the phenomenon of hormesis can be found in the whole animal world in the nature, in experimental objects as well as in human beings. It was developed during the evolution, protecting the living world from deleterious effects as it is done by the immune system, but preceding this latter and also collaborating with it. It is estimated that centuries ago, the natural background radiation was about fivefold larger than in recent times and mammals could survive with the help of hormesis [10].

The hormetic effect can be activated by stressors, which activate cellular signal molecules as gases (oxygen, carbon monoxide, and nitric oxide), the neurotransmitter glutamate, calcium ion, tumor necrosis factor (TNF), etc.

The quality and quantity of immune functions are strongly influenced by hormesis, and this can be demonstrated and clearly measured by studying the effect of irradiation directly on the immune system (cells or products) or on the diseases influenced by the state of the immunity. Irradiation is a good test for studying the hormetic effect, as it is easily measurable, doses can be changed, and its deleterious, as well as therapeutic effects are well known in high doses. In addition, it is very frequently used for treating human diseases. However, its deleterious effect was recognized when its discoverers had serious signs of destructions and since then it was registered as a dangerous tool and the fear from it was characteristic to man. A long time passed up to the recognition of beneficial effects of low-dose irradiation and longer time up to the acceptance of beneficial radiation hormesis. The linear no-threshold (LNT) hypothesis was accepted for more than hundred years, believing that the irradiation is harmful in any doses and that large dose is very harmful, while small (low) dose is also a little bit harmful; however, small doses are collected and they are approaching a level, when they become deleterious. This imagination was also valid to the relation between the irradiation and immune system. However, since the LNT hypothesis had lost its dominance, the beneficial effect of low-dose irradiation won its place as stimulator (benefactor) of immunity.

Effect of Hormetic Irradiation on Immunity

When immunity is studied, there is a possibility for measuring direct immune response by counting cell numbers and proportions, amount of antibodies, etc., however, knowing the role of immunity also in the fighting against different diseases (infections, tumor development and mortality, lifespan, etc.) by the state of them. As a sum, it shows the functional condition of the immune system.

Effects on the immune cells

In general, high-dose irradiation causes the suppression of immunity and low-dose irradiation stimulates immunity [11, 12]. This is a typical case of hormesis and it can be used clinically in the radiation treatment of numerous diseases [11]. The low-dose irradiation enhances the proliferation of immune cells as well as the interactions of innate and adaptive immune systems [13, 14]. The low-dose irradiation positively influences numerous cell types of the immune system, such as natural killer (NK) cells [15], dendritic cells [16], T lymphocytes [11], especially helper T lymphocytes [17], B lymphocytes, and macrophages [18–21]. Cytokine production by macrophages and splenocytes is stimulated by low doses of X-rays [22].

NK cell proliferation and activity were enhanced and also their cytotoxic functions by synergizing them [23–25]. The secretion of cytokines, such as IL-2, IL-10, IL-12, interferon gamma, and TNF- α , had also been stimulated [22, 26]. IL-12 production of dendritic cells was also activated [27]. Apoptosis was decreased in NK cell and dendritic cell populations [28]. Chronic low-dose irradiation activated the immune system of the whole body [27]. At the same time, this could modulate the capacity of bone marrow cells to differentiate into dendritic cells. The immunomodulatory alterations stimulate the immune system to kill neoplastic cells in experimental animals and man [29]. In the bone marrow, hematopoietic cells are proliferating under the effect of low-dose whole-body irradiation [30]. This is also supported by observations demonstrating that people living near nuclear power plants have higher than normal blood cell count [31].

Annual doses of irradiation not higher than twice the natural radiation exert positive effect on DNA damage repair in white blood cells, thereby increasing cellular resistance (and decreasing oxidative stress) [32–34]. In mice, continuous low-dose whole-body irradiation stimulated the immune functions.

It seems to be possible that the hormetic effect on the immune system is taking place via glutathionylation [35, 36].

Effects on cancer

Low-dose ionizing radiation can cause reduction in tumor development [37], and in animal (rat) experiments, metastasis formation was suppressed by it [38, 39]. Such low dose of single irradiation (0.1 Gy) suppresses the development of experimental (mice) tumor metastases, likely by the stimulation of NK cell functions [40]. Human observations show that low-dose radiation exposure decreases human cancer incidence and mortality, by enhancing anticancer

immunity [40, 41]. What seems to be the most important is that the low-dose radiation causes cell proliferation in human embryonic lung fibroblasts, while it does not affect lung cancer cells [42].

Background Irradiation

Background irradiation is a low-dose irradiation, which has a natural (in spas and in high-altitude spaces), or artificial (i.e., human made, such as nuclear facilities, isotope laboratories, X-ray treatments, and diagnostics), or mixed (as in man-made buildings, where the irradiation is coming from the clay of bricks) source [43].

Radon is a gas, which is radioactive and comes from the natural breakdown of uranium, thorium, and radium in the soil and groundwater. People are breathing or drinking radon and its soluble form is used as a curative substance in certain spas. It can be found in the air of many buildings causing lower or higher irradiation of the owners' homes. It was believed earlier that radon concentrations of homes are dangerous, causing lung cancer; however, at present, the opinion is the opposite, i.e., radon helps to avoid lung cancer that would be caused by smoking [44, 45] and to stimulate DNA-repair and apoptosis. Dose-response data from studies of nuclear workers suggest that about 0.4 cGy/month is beneficial and responsible for enhanced immune competence [46]. Low-dose radon-spa therapy provoked a long-lasting increase in T cells, monocytes, and neutrophils and eosinophils as well as dendritic cells were temporarily modulated after therapy [47].

It is known that radon of mines and spas as well as thorium-bearing monazite sands and enhanced radioactive uranium obtained from a natural geological reactor are suitable for treating inflammations and carcinous alterations [48]. In animal models, water-dissolved radon suppressed atopic dermatitis and tumor metastasis in mice [49]. In high-level radon-rich areas of Iran, the inhabitants have higher level of IL-4 and more responsive immune system [50]. Similar observations were done in radon-exposed mice [51].

When 290 male subjects who were exposed to only 50–149 cGy in Nagasaki (Japan) showed a lower mortality compared with unexposed males, it is a peculiar indirect proof that the beneficial effect of low-dose irradiation to the immune system is the effect of peripheral A-bomb radiation [52]. In the United States, there are such areas (counties) that are settled in planes or in elevations. In the higher settled areas, the cancer mortality was about 54/100,000, whereas in counties at the plain, it was about 74 and the significance between the two values was strongly significant [53]. By the comparison of counties where nuclear testing occurred with other counties without nuclear testing and the analysis of lung cancer

incidence, it was found that the more background radiation exposure was associated with less lung cancer [54]. A similar case was found in Taiwan, where recycled steel contaminated with cobalt 60 was used in groups of apartment buildings. Cobalt 60 is radioactive with a half life of 5.3 years. People who were living in these apartments received 40 mSv/year. When the cancer death rate was reviewed, it was clear that during the time period it was studied, deaths from cancer averaged 3.5/100,000 person-years for the cobalt-60 irradiated population, as compared with 116 per 100,000 person-years for the general population of Taiwan, which means a 33-fold reduction in cancer deaths, instead of the earlier (LNT) expected increase [55].

Considering human observations, e.g., in India, it was found that where the background radiation was higher, the cancer risk was invariably less [56]. In a spa area in Japan, with a high radon background, the stomach and lung cancer rates were less compared to that in the whole Japanese population [57] and inside the nuclear facilities (workers) or around them (inhabitants), higher cancer morbidity or mortality was not found [58, 59], and also reduction of certain cancer incidence was observed [60].

There could be a background radiation for an organ caused by the therapeutic high-dose irradiation of another organ. In the case of the irradiation of breast cancer or rectosigmoid cancer, ovary gets low-dose background irradiation. This could reduce the risk of ovarian cancer by 44% [61].

Autoimmunity and Allergy

Low-dose irradiation ameliorates arthritis and other autoimmune diseases [62]. Repeated low-dose (0.5 Gy) treatment attenuated experimental autoimmune encephalitis through suppression of inflammatory cytokines, reduction of cytotoxic T cells, and stimulation of Treg cells [63] and suppressed the proliferation of CD3⁺CD4⁻CD8⁻B220⁺T cells as well as the synthesis of IL-6 and autoantibodies [64]. Similar effects were observed in the case of collagen-induced arthritis, where suppression of proinflammatory cytokines and autoantibody production as well as induction of Treg cells were observed [65]. In a model of systemic lupus erythematosus, the suppression of development of the disease was observed [14]. Ultraviolet (UV) light could help to prevent certain autoimmune disorders [66].

Effects on Infections

According to Calabrese [67], at least 90 immune-system-related hormetic-like responses were studied and 100 drugs as well as 70 endogenous

agonists, which demonstrate the hormetic effect and these decrease the extent of infection-associated tissue damage without directly targeting pathogenic microorganisms [68–70].

Effects of Nutrition

Dietary restriction and fasting prevent or lessen the severity of cancer, and autoimmune diseases [71] caused changes in the development of B and T cells in primary and secondary lymphoid organs [72]. The protecting hormetic effect of mild air pollution against DNA damage does not interact with diet factors in lymphocytes of pregnant women [73]. Observations on honeybees showed that after eating insecticide (thiacloprid)-polluted foods, the bees had significantly longer lifespan [74].

Conclusions

The hormetic effect seems to be surprising; however, it is absolutely normal, if we start from another end of the story. If we are studying a substance which is beneficial using in a low dose and toxic or has altered properties using high doses, this seems to be a natural thing. However, in the present case of hormesis, substances (or irradiation) were studied, registered earlier as toxic in higher doses and the quality of the effect was different (opposite) in lower dose.

According to Luckey [46, 75], the background radiation is gradually diminished during millions of years and during the presence of man in the earth and the modern humans are now living in a radiation-deficient world. However, some background radiation is needed for repair and detoxification and the deficiency is substituted by natural or artificial low-dose irradiation. It is also supposed that supplementation with about 0.4 cGy/month is beneficial, not destructive and it is not only tolerable, but also necessary for the normal life [46]. This “chemo-defense system” could have been developed before the establishment of the immune system in the first living organisms of the earth [76, 77].

The general opinion – the fear – on the effect of low irradiation must be changed, as this was overestimated [78, 79]. A series of observations show that the fear of cancer caused by low-dose radiation effects is baseless, although people were moved away and buildings were demolished because of believing the danger of radiating building materials. Microdoses of substances (insecticides, pesticides, etc.) in or on the food hindered people from eating healthy fruits or vegetables. Considering the microdoses of herbicides and pesticides on the surface of the washed fruits, it can be imagined (although there are not

enough investigations) that they have hormetic effects and contribute to our longer lifespan, by stimulating immunity [80].

A special problem is the hormesis that is executed during the prenatal age or perinatally. In this period, the cells and the organs containing them are more sensitive to stress-like influences and hormetic effects can cause lifelong alterations. This can be expressed by the faulty hormonal imprinting [81], in which the extremely sensitive hormone receptors [82] are touched or the late hormone production, both strongly influenced people's innate and adaptive immunity, as well as the hormone synthesis by immune cells [83]. As hormesis and hormonal imprinting are epigenetic processes alike [84, 85], the alterations are inherited to the progenies of cells and progenies of the individual. A faulty perinatal hormonal imprinting can be deteriorating; however, it can also be beneficial, considering hormesis [86]. It is supposed that lower cancer incidence in developing nations is caused by "mimotope" hormesis, the hormetic effect of infections in the early periods, which develops a fortification of the immune system [87]. Although this theory is not exactly supported, it is not rejectable. As in our modern age, there are a mass of environmental and medicinal pollutants and chemicals stressing the organisms during early development, these effects are causing permanent traces in the victims and their progenies [88–93]. However, the basic problem is the extremely increasing amount and quality of endocrine disruptors, which acting in the pre- and perinatal periods could transform the immune system for life, causing immunodeficiency, allergy, and autoimmune diseases as well as the lost of defense against malignant diseases [94–96].

The state of immunity has a very important role in the defense against tumor formation and growth. However, its effect is characterized as a two-edged sword, as the direction of effect is dependent on many factors [97–101]. Tumor-directed immune reactants in low doses stimulate tumor growth, while it blocks tumor growth in higher doses [102–104]. In contrast to this, low-dose radiation increases immunity against cancer, by elevating anticancer parameters and retards metastasis formation, whereas high doses of it stimulates cancer growth. In addition, it inhibits carcinogenicity caused by high doses of radiation [102]. In general, cancer surveillance is increasing under the effect of low-dose irradiation [103–105]. All of the new data conclude that the earlier LNT hypothesis, which registered any radiation as harmful, is scientifically not proven and must be substantiated with the consideration of hormesis [106, 107]. This means that cancer chemotherapy and radiation therapy hormesis request the finding of doses, which are immunogenic, instead of deleterious [108–110]. However, not only irradiation or chemotherapy requires transformation of employment, but also other stressors could be employed, e.g., cold stress is recommended for cancer therapy through immune stimulation [111].

It is very interesting that hormesis shows some gender specificity. As it was mentioned, atomic bomb survivors who had low-dose irradiation are less sensitive to non-cancerous diseases than the irradiation-free population. However, this is valid only to males and NK cell activity was also higher in males than in females [112]. Similarly, in *Drosophila*, there is a gender-specific impact of thermal hormesis [113, 114] and infection hormesis [115]. Therefore, the manifestation in males is always dominant as it is happened in the case of atomic bomb survivors.

It is believed that there are certain specific places for background irradiation. However, some low-dose background irradiation is always present in more sites, in the form of, e.g., UV irradiation, from the beach to the long spaceflights [116]. This can also influence (prevent) some pathological processes [66, 117, 118], while in high doses it is deleterious.

Conflict of Interest

The authors declare no conflict of interest.

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