SPECIAL LECTURE SESSION

Possible Application of the Laser in Immunobiology

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Abstract. The human immune system acts a defence mechanism against exogenous or indigenous potentially harmful bodies, such as bacteria and viruses. The major histocompatibility complex (MHC class I and class II antigens) form key elements of legitimate body components, and the organization of MHC molecules allows T-lymphocytes to distinguish between legitimate and foreign bodies. On detection of a foreign component, T-cells activate the necessary pathways for destruction of the foreign body. Occasionally however the system breaks down and the result is a disease of an autoimmune nature. Both visible light and infrared low reactive-level laser therapy (LLLT) has been shown to act on immune system cells in a number of ways, activating the irradiated cells to a higher level of activity. Infrared LLLT has been shown to increase both the phagocytic and chemotactic activity of human leukocytes *in vitro*, for example. This is an example of photobiological activation. Photobiological cell-specific destruction is also possible using doses of low incident laser energy on cells which have been photosensitized for the specific wavelength of the laser, such as in photodynamic therapy (PDT) for superficial cancers. LLLT has also been shown to act directly and selectively on the autoimmune system, restoring immunocompetency to immunoincompetent cells. Although much more research needs to be done, there are enough experimental and clinical data to show that the laser, and LLLT in particular, has a possibly exciting role both in immunobiological therapy for diseases of the immune system, and to activate and boost the normal reaction of the immune system components against harmful foreign bodies. (Keio J Med 42 (4): 180–182, December 1993)

Key words: lasers, immune system

Introduction

The immune system of an individual can be defined as the defence mechanism to maintain the integrity of the individual (self) by the recognition and subsequent exclusion of unfamiliar exogenous and indigenous foreign substances (nonself) which originate or appear outside or inside the individual's body. To discriminate between self and nonself components, major histocompatibility complex (MHC) products, (class I and class II antigens), are employed as the key elements of self components, and T-lymphocytes can recognize self or nonself by observing how the self MHC molecules are organized. The MHC is a group of at least four linked loci, (A, B, C and D) on the sixth human chromosome collectively termed the human lymphocyte antigen (HLA) complex in man, which codes cells to produce histocompatibility antigens on the surface of cells.

Foreign substances or antigens are captured by antigen-presenting cells, processed, and presented on the cell surface together with class II antigens.

The role of the helped T-cell

When a specific type of thymocyte-derived lymphocyte, the helper T cell, recognizes the antigen and clas II complex as nonself, the helper T cells are activated to produce a variety of cytokines, nonantibody proteins such as lymphokines, which act as intercellular mediators for example in the generation of immune response. In addition to their function as effector cells in the production of delayed hypersensitivity, helper T cells exert their helper effects by the following two pathways. First, helper T cells facilitate the differentiation of B cells, which are already activated as antibody-production cells by the recognition of antigens as intact forms. Secondly, helper T cells are involved in the generation of cellular immunity, and the maturation of killer T precursor cells into killer T cells. Which pathway is preferentially induced depends on the nature of the antigens, but the

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effector cells thus produced are responsible for the removal of undesirable foreign substances from the body.

It should be pointed out however that the ability to distinguish self from nonself is not absolute. Occasionally the system breaks down and turns against the body, causing diseases of an autoimmune nature.

Laser Thepapy and The Immune System

Laser treatment can participate in the process of these immunological phenomena in two ways: Photobiological activation, and photobiological destruction. Photobiological activation can be defined as the mechanism whereby cellular function is normalized by means of light energy of very low intensity, and can be used to activate immunological responses nonspecifically. In contrast, photobiological destruction can be used to destroy cells at the molecular level, including the application of photodynamic therapy (PDT) employing a photosensitizer. Therfore, we should consider carfully the wavelength of the laser and its absorption rate in the target cells: and trials should be focused on those cells particularly disadvantageous to the body. In this case, it is recommended to heighten the photoselectivity of the target cells by using a cell-specific phtosensitizer at the molecular level. These types of photobiological reaction are applicable in the immunological field in both *in vitro* or *in vivo* treatment, for *in vivo* application, however, an appropriate irradiation methodology must be devised due to the high rate of absorption by the superficial tissues in the body. *In vivo* modulation of immunological responses has been achieved so far by; (1) irradiation of the superficial tissue (skin, mucosa, etcetera); (2) extracorporeal irradiation od circulating blood cells; and (3) interstitial fibreoptic irradiation of deeply located tissue.

Clinical Data

Preliminary clinical data from Skobelkin based on external infrared LLLT irradiation of specific sites in cancer patients, such as tumour projections and lymph nodes show a strong immunological system response.[1] Skobelkin's group performed preoperative LLLT on selected cancer patients undergoing palliative surgery. The levels of T-lymphocytes, T-helpers and T-suppressors were assayed for the 7 days following the operation, as were immunoglobulin levels, specifically IgA, IgM and IgG. The levels of blood-borne leukocytes, lymphocytes and monocytes all rose after laser therapy. Significantly increased levels of activated T-lymphocytes and helper T-cells were seen, with a significantly lower number of T-suppressors especially by the fifth post-therapy day. Increased levels of IgA and IgG were seen by the second post-therapy day, with a sharp reduction to almost normal levels by the fifth day. IgM levels rose slowly over the first four days, then rose sharply on the fifth day and maintained a high level on the subsequent levels during the period of the study. Skobelkin proposed that these were all indications of a strong photoactivated immunological response, with boosting of the competency of the somewhat immunoincompetent systems of these long-term cancer patients. The high levels of IgG, especially cytotoxic for tumoural cells, has also been associated with a corresponding rise in killer T-cells.[1] The antigen which would normally trigger these reactions was shown to be absent in all patients, thus the reaction was entirely photoactivated. Skobelkin did not report any activation of tumoural remnants following LLLT, which has been of major concern to many researchers.

These clinical data have been confirmed in a number of *in vivo* and *in vivo* studies using animal models by Dima,[2] Karu (Laser Therapy, in press) and Abe (Laser Therapy, accepted for publication). The studies all involve implanted virile carcinomas in rat and mice models, and they all have the result in common that the life span of the LLLT-irradiated animals was increased from 50% to 95% compared with unirradiated control animals. Some animals in Abe's study actually survived. All studies report increased levels of activated T-lymphocytes, T-helper and T-killer cells, in addition to increased immunoglobulin concentrations. Karu further showed that irradiating immune system cells with a normal level of competency had no effect, whereas the levels of competency of immunoincompetent cells were restored at least partially and at best completely. There are thus two LLLT-mediated mechanisms involved, according to these data: Photoactivation of the immune system processes which increase the level of immune response, and a specific cell-selective response in immunoincompetent cells.

Data from Osanai *et al*[3] showed in an *in vitro* study that specific doses of infrared LLLT increased the phagocytic activity of pooled human neutrophils as assayed by the luminol-dependent chemiluminescence method. Chemotaxis, the chemically-motivated tendency of the neutrophil to move towards an attractant foreign body prior to phagocytosis, was also increased in the LLLT-irradiated cells compared with unirradiated controls.

Conclusions

Although much more detailed research is necessary, especially for *in vivo* studies, the early data on LLLT action on the immune system specifically in cancer-infected systems is very promising. It is clear from all the reports that *in vivo* LLLT dose not activate the tumour cells to reproduce faster, but in fact inhibits growth and increases cell-specific destruction. This is one case where *in vitro* studies might well be misleading, as *in vitro*

cancer cells are removed from their immune system mediated environment, and might well show signs of enhanced reproduction. Other immune system-related diseases, such as atopic dermatitis, some forms of eczema, asthma and asthma-related ulceration, have responded well to LLLT.[4] In the case of atopic dermatitis, irradiation of only one affected site effected a systemic cure, lending credence to the systemic effect of LLLT on the immune system components. The future of LLLT applications in many immune system diseases and conditions, given the necessary research, is certainly promising and exciting.

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