Friend or Foe? Can We Selectively Shut Off Immune Responses?

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Abstract
In lieu of an abstract, below is the first paragraph of the paper.

The immune system of the human body serves as both an enemy and an ally. It is an ally when it constantly fights off attacks from several types of microbes. However, it is an enemy when it attacks a life-saving heart transplant or mistakenly eats away the tissues of the body (Marx, 1990). It is the job of the immune system to keep the body healthy and free of harmful substances. Researchers have been aiming for ways to suppress certain parts of the immune system while not interfering with the entire defenses of the body. By analyzing how the immune system works researchers can gain a better understanding on what might help them succeed in this process (Janeway & Travers, 2006).
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The immune system of the human body serves as both an enemy and an ally. It is an ally when it constantly fights off attacks from several types of microbes. However, it is an enemy when it attacks a life-saving heart transplant or mistakenly eats away the tissues of the body (Marx, 1990). It is the job of the immune system to keep the body healthy and free of harmful substances. Researchers have been aiming for ways to suppress certain parts of the immune system while not interfering with the entire defenses of the body. By analyzing how the immune system works researchers can gain a better understanding on what might help them succeed in this process (Janeway & Travers, 2006).

The immune system serves a very significant role in the human body. The body is persistently invaded with substances that can cause harm such as toxins, fungi, bacteria, parasites and viruses. If any of these microbes entered the body and were left untouched the body would become damaged. It is the role of the immune system to act as an army and to defend against the constant stream of foreign invaders. The immune system is the key element in retaining the overall health of the body and resistance to disease (Janeway & Travers, 2006).

The immune system is organized into innate and adaptive components. The innate system serves as the first line of defense. The innate system uses nonspecific cells such as phagocytic cells to interact with the microbe and protect the host. Natural killer cells are important in the innate response because they can lyse virally infected cells. Interferons also work in the innate response by inhibiting the replication of viruses (Nairn & Helbert, 2007). If the invading microbes become too numerous and the innate system is overwhelmed, the adaptive system is triggered. This system has the capability to distinguish self from nonself. However, the adaptive system does not happen as rapidly as the innate system does. The adaptive system takes many days to mobilize. The fact that each lymphocyte expresses a unique antigen receptor is critical to understanding the adaptive system. When an antigen comes in contact with a lymphocyte containing the receptor that fits with the particular antigen, the pre-existing cells divide and produce genetically identical daughter cells. This results in an increased availability of receptors specific for a particular antigen (Nairn & Helbert, 2007). The adaptive immune system is categorized by three major features. The first feature is specificity. The immune system is described as specific because it discriminates among a variety of molecular entities. The adaptive system is diverse because it has the ability to respond to various antigens that it encounters. Lastly, the adaptive system is characterized by having a memory. The adaptive system can remember previous antigens that infected a particular area and therefore increase the strength of response when infected again. This mechanism is referred to as immunological memory. Immunological memory adds to the overall strength of immunity of the body (Kamradt & Mitchinson, 2001).

The state of having adequate biological responses to microbes is known as immunity (Kamradt & Mitchinson, 2001). Immunity has three further divisions known as active/adaptive immunity, innate and passive immunity. The individual plays a direct role in response to an antigen in active immunity. This type of immunity develops as children and adults experience different types of invaders throughout their lifetime. Also, active immunity is protective immunity that results after exposure to an infection or a vaccination. Lymphocytes play a major role in active immunity (Kamradt & Mitchinson, 2001). Lymphocytes are cells that are involved in the recognizing of previous invaders and destroying them. These cells originate in bone marrow and either remain there or further mature into B cells. They can also migrate to the thymus gland and mature into T cells. B lymphocytes serve as the military intelligence system. B cells watch for the targets and then construct a plan to capture their targets. T cells are the soldiers, using the intelligence system that the B cells have previously created to destroy the invader. In general, the structure of lymphocytes remains similar throughout the different types. Lymphocytes are usually small, and most of the DNA and protein is located inside the nucleus. Receptors are located on the surface of lymphocytes. Each receptor is specific for a particular antigen. Lymphocytes travel through the bloodstream and peripheral lymphoid organs. The three main types of peripheral lymphoid organs are the spleen, lymph nodes, and the gut-associated lymphoid tissue. The spleen serves the role of collection of the antigens from the bloodstream. The lymph nodes collect antigens from the tissues at sites of infection and the gut-associated lymphoid
tissue collects the antigens from the gut. These components of the immune system are essential to proper functioning (Janeway & Travers, 1996).

The second type of immunity, passive immunity, involves the transferring of responses from one individual to another. The immune cells from an immunized individual get passed to an unimmunized individual. The anti-rabies shot is an example of passive immunity. After a dog bite, the victim is treated with anti-bodies to the rabies virus; however they have been produced by individuals other than the victim. Another example of passive immunity is the antibodies in the breast milk of mothers, which provide temporary protection for the infant. The final type of immunity, innate immunity, includes the external barriers of the body. The external barriers of the body are technically the first line of defense in preventing disease (Nairn & Helbert, 2007). The degree of immunity regulates the types of immune responses needed to keep the body healthy.

The immune system is the driver behind immune responses. Immune responses are integrated bodily reactions to antigens. The immune system uses a series of steps to trigger immune responses which will attack the organisms and substances that invade the human body and aim to cause disease. Immune responses are the way in which the body recognizes and defends itself against the bacteria, viruses, and other material that may appear harmful to the body (Nairn & Helbert, 2007).

Foreign substances that invade the body are known as antigens. When the body detects that an antigen has entered, many cells work together in the recognition of the antigen and a response to defeat the antigen. These cells immediately trigger the B cells which start to produce antibodies. Antibodies are specialized proteins that lock onto specific antigen receptors. These antibodies remain in the body even after the invader is destroyed. This is an advantage because if the invader returns into the body, the antibodies will already be present and immediately destroy the foreign substance. Antibodies can not work single-handedly on this task. Once they have bound to the receptor on the antigen the T cells destroy the antigen that has been tagged with antibodies (Marx, 1990). These antigens are the substances that trigger an active immune response.

An active immune response involves a series of steps initiated by the immune system. The first phase is the cognitive phase in which the particular antigen is recognized. When the antigen reaches a cell containing the particular receptor the cell becomes activated and proliferation occurs. As more clones of the same cells are produced the next phase, activation, is triggered. During this phase the cells differentiate and enable a response. In turn, the antibodies try to eliminate the antigen in the effector phase. Once the antigen is fully eliminated a series of steps occur to regulate the response and more importantly inhibit the response from occurring once the antigen is neutralized (Nairn & Helbert, 2007). An active immune response is an involuntary action but does there lie a way to make an immune response voluntary?

The regulation of immune responses is the major medical goal of research in the field of immunology. Researchers want to be able manipulate immune responses in way that would enable suppressing the response when it is unwanted and stimulating a response in such cases of prevention of infectious disease. Suppression of the immune system includes the topic of organ transplant. If there was a way to induce the immune system to tolerate a transplant the patient would no longer have to take immunosuppressants for the rest of his/her life. The implications of discovering a way to suppress the immune system could help with treatment of autoimmune diseases. The reason why this has not yet been discovered is because the immune system is very particular and sensitive. Manipulating with one part of the response can cause the whole immune system to react. Also specifically with organ transplants, there is no way to judge if tolerance has occurred unless the patient is taken off of the immunosuppressant drugs which provides an increased risk of rejection. Immunologists have discovered many techniques for inducing, measuring, and characterizing immune responses. (Janeway & Travers, 1996). Allergic reactions and organ rejections are two major areas of research dealing with suppression of the immune system.

In the case of organ failure, transplantation has become the most common and efficient procedure to replace the organ. The main risk of organ transplantation is the rejection of the allograft by the host of the immune system. To avoid rejection of the transplant a variety of immunosuppressant drugs are used to target the adaptive T-cell response. Many of these same drugs are used to treat allergic reactions. It is therefore predicted that those patients using the immunosuppressant drugs should at no point while under therapy develop an allergic reaction to any
substance. The objective of this study was to evaluate in a cross-sectional design, the prevalence of immunoglobulin E-mediated sensitizations and type 1 allergy in solid-organ transplanted children and adolescents and to identify the risk factors (Dehlink, 2006).

The participants came from the Medical University of Vienna between the years of 2004 and 2005. In total there were seventy eight patients with kidney, lung or liver transplants used. The patients were treated with different combinations of steroids, proliferation inhibitors, kinases and phosphatases inhibitors based on the individual patient. The medical charts of the patients were marked with the date of transplantation as well as the starting date of immunosuppressive therapy. To determine if there was a history of allergies in the patient or in the family, the patient was given an interview based on the International Study of Asthma and Allergies in Childhood criteria. The allergic sensitizations of each patient were examined by serum-IgE measurements and a skin prick test. The serum – IgE measurements were conducted by using a solid-phase immunoassay. The patients were tested for dust mite, cat and dog dander, cod fish, wheat flour, soy bean, peanuts, hazelnut, almond, coconut, rye, birch and other common allergens. Other sensitizations were tested if there was some other allergen present in the family determined in the survey. The total serum-IgE levels were converted into z units to account for the various differences in ages. The skin prick test was used to test a panel of allergens. To avoid interference with the skin prick test the patients were advised to stop using antihistamines for two weeks prior to the test. If there was further indication of specific allergens in the patient’s history those were also done in the skin prick test. Each patient was classified as sensitized if they presented a positive skin prick test and had a reaction to at least one of the allergens or as allergic if they had additionally history of allergic diseases in the family (Dehlink, 2006).

The data depict the prevalence of sensitization as well as the allergies among the patients. The sensitization refers to a positive result from the skin prick test or a specific IgE level greater than 0.35. 75.6% of the total number of patients had a negative result to the skin prick test while 24.4% had a positive sensitization. The majority of the positive skin prick results came from the kidney patients, but what also must be taken into account is that the greatest numbers of patients were kidney recipients. The next highest percentage were of sensitization followed by the lung recipients. The same order from greatest to least, kidney, liver, lung was displayed for the negative skin prick results. The data display the prevalence of allergy in the patients. 89.7% of all patients had no allergy, defined in this study as a sensitization and additional history of allergic disease. 10.3% were defined as having the prevalence of allergies (Dehlink, 2006).

The results of this study were surprising. The population of patients consisted of 50 kidney transplant patients, 19 liver transplant patients, and 9 lung transplant patients. All of the patients did take part in the interview and serum IgE-measurements. However, there were 20 allograft recipients that refused to take a skin prick test. Out of the total population of 78 patients, 19 were discovered to be sensitized to allergens and 16 patients of those 19 patients displayed particular serum IgE. Also 13 of the 19 had a positive skin prick test to at least 1 allergen. Only 8 participants of the total population were designated as “allergic” because they reported a clinical history to type 1 atopic diseases. The prevalence of sensitization and allergy was similar among all three types of transplant patients although between the subgroups the spectrum of sensitizations was different. Both kidney and liver recipients were sensitive to nutritive and inhalant allergies while the lung recipients were solely sensitive to inhalant allergies. The sensitized patients did not differ too much of an extent from the nonsensitized patients in regards to gender, age, date of transplant, history of allergies, or time of immunosuppressive medicine. No major differences were found when analyzing the various types of immunosuppressants or duration of the treatment (Dehlink, 2006).

These results show that regardless of the immunosuppressive treatment, the organ transplant patients still can acquire certain sensitizations to inhalant or food allergies. The immunosuppressive treatment does not prevent allergic reactions. The most common symptoms of the allergies were seasonal rhinitis and rhinoconjunctivitis. No immunosuppressive drug was proven to be associated with the occurrence of allergies. There was no correlation between the transplanted organ and the prevalence of allergy because sensitization and allergy were equally distributed. It was demonstrated that the long-term immunosuppressive therapy does not have an effect on allergies in transplant patients. One suggestion for these results could be that the allergy had already existed before the organ allograft took place.
In this case the immunosuppressive drugs would not be able to control the allergen. The allergy may also develop within the time period of therapy and the immunosuppressive drugs do not recognize it as a foreign substance. In many cases of developing an allergy during post transplantation drug treatment the calcineurin inhibitor tacrolimus seemed to be the cause. This suggests that the immunologic mechanism behind this could be a suppression of the T-helper cells (Dehlink, 2006). The presence of the allergen before the therapy was started is a possibility but there must be a underlying cause. Perhaps the allergen was present but not active inside the body, the immunosuppressant drugs triggered the allergen and therefore the symptoms of an allergic reaction appeared. An allergic reaction is a response from the immune system.

The immune system releases a response to antigens that trigger certain allergic reactions. An allergy or atopy is an immediate hypersensitivity to reaction to environmental antigens, mediated by immunoglobulin E (IgE). Allergies are very rapid reactions and the symptoms of a reaction occur within minutes of exposure to the particular antigen. The specific antigens that trigger the allergic reactions are called allergens. Allergens find a way into the body either by inhalation, becoming ingested, or injecting directly into the skin. Treatment of allergies is simply identification of the particular antigen that is causing the allergy and avoidance of those harmful allergens (Nairn & Helbert, 2007).

Mast cells and eosinophils are the cells involved in allergies. Mast cells are resident in a wide number of tissues, whereas eosinophils migrate into tissues where type I hypersensitivity is taking place (Nairn & Helbert, 2007). These eosinophils release the mediators that cause the reaction to the allergen. After the specific allergen and IgE have come in contact with each other the mast cells initiate the symptoms of an allergic reaction. The production of IgE is essential for hypersensitivity reactions. Once the B cells are stimulated by interleukin-4 and T-helper 2 cells, the production of IgE begins. IgE then binds to FceRI which is located on the mast cells in tissue and eosinophils that have been activated. This is why when investigating the cause of the allergic reaction the IgE levels can be tested and used to help find the answer (Ling, 2004).

To determine whether the amount of inhibition of allergic responses by CD4 + CD25 + T cells was related to allergic disease CD4 was used. CD4 is a marker of the helper T cell subset that interacts with B lymphocytes in induce immunoglobulin production or activate other immune cells via cytokines (Ling, 2004). Cytokines are small proteins produced by T cells that act as signals to other cells of the immune system or structural cells. CD25 is the chain of the receptor for interleukin 2. T cells are cells that control immune responses by recognition of specific sequences from foreign molecules presented by MHCs on antigen presenting cells. The correlation between activity of regulatory T cells and disease in humans was investigated. Analysis of the mechanism involved in suppression of allergen-induced T cells was also conducted (Ling, 2004).

The participants in this study were volunteers. Patients with seasonal allergies to grass pollen were from an allergy clinic. Atopic donors had positive IgE skin test and a history of allergic symptoms. The non-atopic donors had negative skin prick tests and no history of allergic symptoms in the past. The seasonal allergy donors had positive skin test to grass pollen but to no other allergens. The first part of the procedure involved cell separation. Blood samples were obtained and basic cell culture with the allergen extract was performed. The PBMC of the allergen was separated using density centrifugation. The CD4 + T cells were isolated by negative selection and the CD5 + T cells were isolated using positive selection. The CD4 + cells were enriched to a median of 96% while the CD25 + cells were enriched to a median of 82%. The cells were cultured in well plates with allergen extracts. Autologous irradiated mononuclear cells were added as antigen presenting cells to all cultures. The cultures contained the following: PBMC’s, CD4 + CD25+ cells alone, CD4+ CD25- cells alone, CD4+ CD25- and CD4+ CD25+ T cells at a ratio of two to one to control for the amplified cell density of the CD25 + CD25- cultures. Supernatant was added for cytokine analysis with the Luminex bead system. H-thymidine was also added to the culture. After the cells were harvested, counting of incorporated radioactivity as index of proliferation occurred (Ling, 2004).

CD4+ CD25, CD4+ CD25- T cells, or mixed CD4+ CD25 + and CD4 + CD25- cells in a were cultured in order to compare the regulation of non-allergen driven cultures between atopic and non-atopic donors. A cat allergen reactive Th-2 clone was generated from an atopic donor by using limiting dilution. This clone produced interleukin 5 and interleukin 13. A cat allergen peptide reactive
Th0 clone was generated from a non-atopic donor. This clone produced interleukin 2, interleukin 5, and interleukin 13. The clones were combined in a mixing experiment with CD4+CD25+ T cells. The cells were cultured. Blocking antibodies were added. Flow cytometry was conducted on CD4+ CD25- T cells. RNA was extracted from CD4+CD25+ and CD4+CD25- cell pellets with a kit. RNA was quantified and then underwent reverse transcription. PCR procedures in triplicate sequence detection system were performed. (Ling, 2004).

The data represent the mechanisms of suppression. The data display the proliferation of a Th2 cell clone by CD4+CD25+ T cells from an atopic donor. The proliferation is recorded in units of cpm for three separate experiments. The first, CD4+25+, shows a proliferation value of 0 cpm. The second experiment shows the T cell clone which had a proliferation value of approximately 67,000 cpm. The third experiment is the T cell clone with CD4+25+. The proliferation value for this experiment was approximately 10,000 cpm. The data show the allergen-induced T cell proliferation and cytokine production by CD4+CD25+ T cells with and without the presence of the antibody to glucocorticoid-induced tumor necrosis factor receptor. The data reveal the information from one donor which represents three different experiments. This data came from a non-atopic donor. The data display the control antibody and the antibody glucocorticoid-induced tumor necrosis factor receptor for CD4+25+, CD4+25-, and CD4+25-CD4+25+. The proliferation in order from least to greatest is as follows: CD4+25+, CD4+25-CD4+25+ and CD4+25. (Ling, 2004).

The CD4+CD25+ T cells from non-atopic donors showed little or no proliferation at all when stimulated by allergens. The culture of CD4+CD25-T cells with allergens showed a substantial amount of proliferation as well as production of interleukin 5. The non-atopic individuals with asymptomatic and symptomatic atopic allergic patients were compared. The percentage suppression of allergen-driven proliferation of CD25- T cells by CD25+ T cells was substantially reduced when the cells of the atopic donor was compared with cells from the non-atopic patients. The suppression of interleukin 5 by CD4+CD25+ T cells in cultures of asymptomatic donors did not differ significantly from the non-atopic volunteers. In the patients with seasonal allergies CD4+CD25+ T cell inhibition of grass pollen and allergen stimulated proliferation and production of interleukin 5 was lower than the non-atopic and atopic patients. Suppression of proliferation was of course greater when the individuals were studied out of season. No difference was discovered in the proportion of CD4+ cells positive for CD25+ between groups or in expression of CD69 or intracellular CTLA 4 on regulatory T cells than the activated T cells. To test capability of suppression of the T cells, allergen specific T cell clones were obtained. It was displayed that CD4+CD25+ T cells suppressed proliferation of the Th clone from the atopic donor. The CD4+CD25+ T cells inhibited proliferation of a peptide-specific Th clone from the same nonatopic donor. The antibody to glucocorticoid-induced tumor necrosis factor receptor reversed cell suppression but the antibodies against this receptor did not reverse inhibition of interleukin 5, 13, or y production (Ling, 2004).

The suppression of CD4+CD25+ T cells relates to the existence of clinical allergies has been demonstrated. This is due to the fact that the inhibition of the allergen-driven responses by cells from atopic donors was less than the non-atopic donors and the least by those cells isolated from the patients with seasonal allergies. Both the atopic-and nonatopic donors showed growth of PBMC's to allergens in the culture. However, they showed differing results in the production of Th2 cytokines. This study demonstrated that T cells can suppress allergen-driven proliferation as well as cytokine production (Ling, 2004).

The major result of this study is that as T cell activation is reduced in atopic versus nonatopic individuals and reduced even greater when exposure to an allergen is observed suggests many possibilities. The data suggest that there may be a deficiency in the regulation of CD25+ T cells in the atopic donors. Another possibility is the dilution of regulatory CD25+ T cells during allergen exposure. Another suggestion is that when exposed to an allergen the effector T cells are activated in a way that they do not respond to signals from the CD4+CD25+ T cells. Those patients with hay fever had a reduced ability of the T cells to suppress allergen responses. This suggests that perhaps their CD25-cells had been activated by certain mechanisms and therefore was not responsive to regulation. The data collected in this study suggests several reasons why some children develop allergies while others do not. The first reason could be an absence of Th1 responses which deal with infection. A deficiency in the maturation of the T cells could exist and this would therefore lead to unchecked Th2 responses. In atopic sensitization, there is a defect in the regulation of Th2 responses to T cells. The study
suggests that CD4+ CD25+ T cells can prevent the activation of certain Th2 responses in non-atopic donors. Failure of such suppression could result in allergic disease. This implies that certain T-cell mediated diseases are results of an imbalance between inhibition and activation of T cells (Ling, 2004). The data suggest that by dissecting a particular pathway of the immune system the possibility of therapy on the pathway exists.

The future in immunology looks impressive, specific suppression of immune responses is in sight. Scientists have recently discovered how to grow cells that suppress immune responses. Scientists have found a way to grow T-regulatory cells type 1. These cells are predicted to be the key to turning off unwanted immune reactions. These cells could even inhibit the action of certain immune cells that if not blocked would attack the body. This discovery could help with the developments of new treatments and therapies for many autoimmune diseases. It could also provide scientists with a better understanding of infectious diseases and could help in organ rejection after transplantation. Using this technique, scientists can now take a blood sample from a patient's arm and culture the cells. A few days later the cultured cells will be T-regulatory cells. The hope of researchers is to continue studying the factors involved in the differentiation and function of the T regulatory cells type 1. Once these factors are identified, manipulating the activity of the Tr1 cells for therapeutic use will be possible. Other colleagues found that the stimulation of CD46 and the T-cell receptors caused the growth of T lymphocytes which produced interleukin 10. This is also groundbreaking because interleukin 10 is the substance that suppresses the action and proliferation of immune cells (Kemper, 2003).

The immune system is essential to the overall health of the body. If it was manipulated in a certain way to suppress unwanted responses but at the same time not lower the degree at which it protects the body, some diseases would no longer be existent. Allergies to a common environmental substance, rejection of a life saving organ, and maternal antibody that causes the fetus to become affected by erythroblastosis would all be gone (Rowley, 1973). The possibilities if suppression was discovered would be endless. In the future it may be beneficial to suppress the antibody response to a tumor. Perhaps an antibody to the tumor prevented immunologic injury to the tumor. Small manipulations and inhibition of immune responses has already occurred. The race was started more than 60 years ago and the finish line is in sight.

References