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MINIREVIEWS

Ultraviolet-induced alloantigen-specific immunosuppression in transplant immunity

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Abstract

After the first observation of the immunosuppressive effects of ultraviolet (UV) irradiation was reported in 1974, therapeutic modification of immune responses by UV irradiation began to be investigated in the context immunization. UV-induced immunosuppression is *via* the action of regulatory T cells (Tregs). Antigen-specific Tregs were induced by high-dose UV-B irradiation before antigen immunization in many studies, as it was considered that functional alteration and/or modulation of antigen-presenting cells by UV irradiation was required for the induction of antigen-specific immunosuppression. However, it is also reported that UV irradiation after immunization induces antigen-specific Tregs. UV-induced Tregs are also dominantly transferable, with interleukin-10 being important for UV-induced immunosuppression. Currently, various possible mechanisms involving Treg phenotype and cytokine profile have been suggested. UV irradiation accompanied by alloantigen immunization induces alloantigen-specific transferable Tregs, which have potential therapeutic applications in the transplantation field. Here we review the current status of UV-induced antigen-specific immunosuppression on the 40th anniversary of its discovery.

Key words: Alloantigen; Ultraviolet irradiation; Donor-specific immunosuppression; Interleukin-10; Regulatory T cells

Core tip: The perception of immunological changes induced by ultraviolet (UV) exposure has changed over the past several years. Although carcinogenesis and immunosuppression due to UV irradiation are regarded as detrimental, UV irradiation is also currently considered a useful tool to induce alloantigen-specific regulatory T cells (Tregs). There is great enthusiasm for the potential to develop strategies that can use Tregs for therapeutic interventions. Alloantigen-specific immunosuppression is an ideal therapy for allotransplant recipients. Although the

full mechanism has yet to be determined, UV irradiation accompanied by alloantigen immunization produces a beneficial effect in transplant immunity *via* the induction of alloantigen-specific transferable Tregs.

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INTRODUCTION

Intermittent exposure to ultraviolet (UV) light, especially the mid-wave range (UV-B, 280-320 nm), is an important environmental factor affecting human health[1]. Although primary carcinogenesis is the most common problem[2], UV irradiation also impairs immune responses to oncogenic and infectious antigens[3,4]. Paradoxically, the immunosuppressive effects induced by UV irradiation may have therapeutic potential[5-8].

Immunosuppressants have revolutionized clinical transplantation, but have many side effects including pan-immunosuppression[9]. Infectious complications are mostly fatal for transplant recipients[10]. After organ transplantation, patients on immunosuppressants face a dilemma between infectious morbidity and graft rejection. Therefore, alloantigen-specific immunosuppression is an ideal therapy for transplant recipients[11,12]. Research has focused on the immune modulating effects of UV-B irradiation in conjunction with alloantigen immunization to induce donor alloantigen-specific immunosuppression.

Here, we review the application of UV irradiation accompanied by alloantigen immunization to induce alloantigen-specific immunosuppression and discuss the therapeutic potential of UV-induced regulatory T cells (Tregs) in the transplant immunology field.

HISTORY AND BACKGROUND

The initial observations on the immunosuppressive effects of UV irradiation were documented in 1974[13]. Thereafter, many researchers have pushed the frontiers of photopheresis and photoimmunosuppression. Two models of contact hypersensitivity and delayed-type hypersensitivity have been developed to clarify the immunological mechanisms involving UV irradiation[14-18]. The therapeutic capacity of UV irradiation to modify immune responses began to be investigated in the late 1970s[13,19,20]. By the late 1980s, many researchers had reported that antigen-specific Tregs were induced by high-dose UV-B irradiation before antigen immunization[15,21,22]. At this time it was thought that functional alteration and/or modulation of antigen-presenting cells (APCs) by UV irradiation was required for the induction of antigen-specific immunosuppression[23].

METHODOLOGY FOR SUCCESSFUL UV-INDUCED IMMUNE EFFECTS

Many researchers have used mice in their studies on the immunosuppressive effect of UV irradiation. Animal care during and after UV irradiation is critically important for successful UV irradiation experiments[24,25]. Murine skin must be carefully shaved without any injuries. To prevent unevenness of UV irradiation, mice are anesthetized during UV exposure with their feet fixed to a metal plate. Thus, the shaved abdominal wall is sufficiently extended with even exposure to the UV lamps. Therefore careful shaving of the irradiation area and adequate anesthesia and restraint are very important for stable UV irradiation with even exposure. If challenge with antigen or graft beds for transplantation is required after UV irradiation, these sites should be protected from UV irradiation. High-dose UV-B exposure is very damaging, therefore post-irradiation care is also crucial. Adequate analgesic medication is thus a serious requirement after UV irradiation. UV-irradiated mice should be placed in separate cages to avoid scratching of irradiated skin by cage mates. They are also fed with a supply of Ringer's lactate solution. As irradiated skin undergoes contraction to become scar tissue, post-irradiated stiffening severely restricts movement and activity in mice. Therefore, some ingenuity to prevent unexpected death and post-irradiation dehydration (such as a raised floor for easy access to food and water and availability of gels containing sugar, water and dietary supplements to ensure a steady supply of nutrients and water) is required.

ALTERATION AND/OR MODULATION OF APC FUNCTION BY UV IRRADIATION

UV irradiation alters APC function[23]. UV-induced DNA damage has been recognized as the major molecular trigger for photoimmunosuppression[26-28]. Interleukin (IL)-12 reduces DNA damage and prevents the generation of UV-induced Tregs[28,29]. Langerhans cells (LCs) were initially regarded as the most important APC in the epidermis[18,30,31], and it was believed that LCs were killed by UV irradiation. However, it is now accepted that the primary APC in the skin is not LC but dermal dendritic cell (DC)[32-34], and UV irradiation destroys the DC network of LC in the skin[31]. LCs appear to be involved in down-regulating immune responses[35], and inducing and activating Tregs[36,37]. Recently, the functional role of LCs was redefined, and it was shown that UV-damaged LCs in the regional lymph nodes were required for Treg induction[28]. Damaged but viable LCs will present antigen in a nonprofessional manner, which will induce Tregs rather than effector T cells[27].

ANTIGEN-SPECIFIC IMMUNOSUPPRESSION

Many researchers have reported that antigen-specific Tregs were induced by high-dose UV-B irradiation prior to antigen immunization[15,21,22]. At the time it was thought that UV-induced functional alteration and/or modulation of APC function was required for the induction of antigen-specific immunosuppression[23]. This may explain why previous researchers documented that antigen immunization must follow UV-B irradiation and not *vice versa*[15,21,22]. However, the successful use of UV irradiation after antigen immunization has also been reported[24,25,38-41]. In both models, with UV irradiation before or after antigen immunization, antigen presentation in a nonprofessional manner is the key to inducing antigen-specific Tregs[23,27].

UV-induced Tregs and their phenotypes

UV-induced antigen-specific immunosuppression is attributable to T cells with suppressive activity (formerly called, "suppressor T cells")[42,43], and currently these T cells are referred to as Tregs[17,44,45]. A number of studies have investigated the phenotype and mechanism of UV-induced Tregs. UV-induced Tregs express CD4, CD25 and CTLA4[17,46,47] and the lymph node-homing receptor CD62L and therefore migrate into the lymph nodes[46,48].

The early inflammatory phase in the skin has been well studied[49]. When we investigate UV-induced Treg subsets, the role of natural killer T (NKT) cells and mast cells should also be considered. NKT cells are a unique class of T cells. They express T-cell receptor molecules and co-express surface antigens normally found on natural killer (NK) cells. NKT cells have a critical role in UV-induced tumor immune responses[37,50], and they appear to be dependent on IL-4[37]. Researchers have also focused on the role of mast cells in UV-induced immunosuppression[51,52]. Although mast cells were formerly ignored in the field of UV-induced immunosuppression, it has been suggested that they may have immunosuppressive potential[53]. The concept that LCs, mast cells and NKT cells can act in an unconventional manner is now well accepted in the communities of photobiology and immunology[26,27]. The LCs transmit an immunosuppressive signal from the skin to lymph nodes, where they activate NKT cells to secrete regulatory cytokines[26].

Dominant transferability of UV-induced Tregs

As described above, UV irradiation accompanied by antigen immunization induces antigen-specific Tregs. Moreover, these Tregs are dominantly transferable[19]. This transferability confirms that UV-induced immunosuppression is mediated by Tregs. Moreover, this transferability is an advantage for alloantigen-specific immunosuppression in the transplantation field as UV-induced Tregs dominantly have the same immune effect in recipients[24,25].

Role of cytokine milieu

$CD4^+$ Th2 lymphocytes secrete pro-inflammatory cytokines (IL-4, IL-5 and IL-13)[54,55]. IL-4 is thought to promote the induction of transplantation tolerance and alloantigen-specific Tregs[56]. IL-4 also promotes both regulatory and effector T cells in the initial immune response. Moreover, IL-4 activation of effector cells can mediate rejection and will not support alloantigen-specific Tregs that could transfer specific tolerance[56]. Transforming growth factor (TGF)-β is a growth and differentiation factor that displays multiple functions[57]. It is known that the combined use of IL-10 and TGF-β effectively generates $CD4^+$ Tregs[57,58].

Immunosuppression induced by UV irradiation and immunization is dependent on $CD4^+$ Tregs[59-61] and cytokines play an important role[17,62]. The immunosuppressive effects induced by UV irradiation before immunization were explained by a shift in the activation of T cells from a Th1 to a Th2 immune response[63-67]. However, alloantigen-specific immunosuppression induced by UV irradiation after immunization depends not on IL-4, IL-5, IL-13 or TGF-β but on IL-10[24,25,38-41]. Thus, the mechanism of immunosuppression by UV irradiation after immunization cannot be simply explained only by a Th2 shift[24,25,38-41].

Role of IL-10

IL-10 is a well-known immunosuppressive cytokine[68,69], and is important for UV-induced immunosuppression[70-73]. The inhibitory capacity of UV-induced Tregs depends on IL-10 expression[46]. Antigen-specific activation of Tregs by APCs induces the release of IL-10[46,47], which mediates the inhibitory activity of UV-induced Tregs[47,74]. The source of IL-10 in UV-induced immunosuppression is therefore UV-induced Tregs themselves[17,71], although mast cell[52,75] and $CD11b^+$ macrophages[76] have also been suggested. IL-10 is crucial for both the induction[25,72,77] and effector phases[46,78] of UV-induced Tregs, though some researchers reported that IL-10 is not required for Treg induction by UV irradiation[73].

$CD4^+$ T cells with cytokine profiles displaying a large amount of IL-10, but no IL-4, are labelled regulatory T cell type 1 cells (Tr1)[79]. The presence of IL-10 gives rise to $CD4^+$ T-cell clones with a low proliferative capacity that in turn produce high levels of IL-10, low levels of IL-2 and no IL-4[69,79]. These antigen-specific T-cell clones suppress the proliferation of effector $CD4^+$ T cells in response to antigen[69,79]. Thus, IL-10 drives the generation of a $CD4^+$ T-cell subset, designated Tr1, which suppresses antigen-specific immune responses and actively down-regulates pathological immune responses *in vivo*[69,79]. As described above, UV irradiation before immunization induces $CD4^+$ Tregs, and resulted in a shift to Th2 immune response[63-67], and IL-10 plays an important role in this. However, in immunosuppression induced by UV irradiation after immunization, $CD4^+$ Tr1-like cells with high expression of IL-10 are important for alloantigen-specific immunosuppression[24,25,38-41].

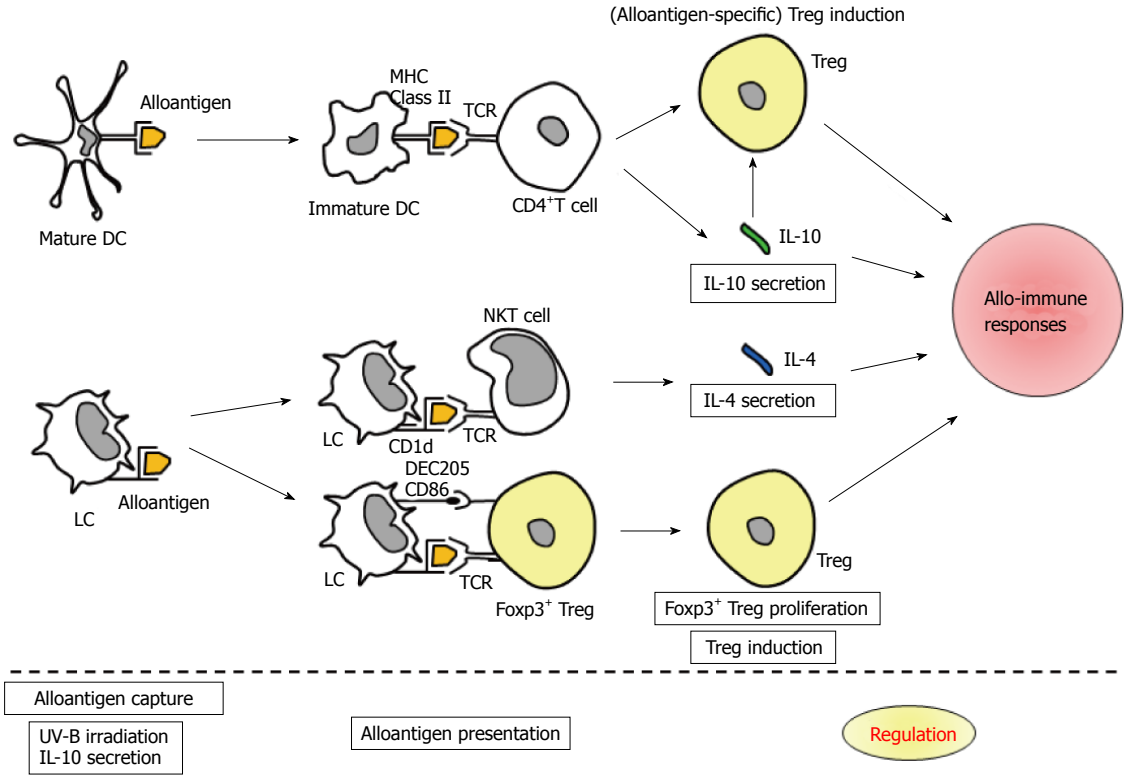

Figure 1 Schema illustrating the postulated reactions in achieving alloantigen-specific immunosuppression by ultraviolet-B irradiation accompanied with alloantigen immunization. APCs, such as mature DC and LC, capture alloantigen. UV-B irradiation and subsequent IL-10 secretion will cause antigen presentation in a nonprofessional manner to induce antigen-specific immunosuppression. Immature DC presents alloantigen to $CD4^+$ T cell, and then, Treg induction and IL-10 secretion arise. LC presents alloantigen to NKT cell, and IL-4 secretion subsequently occurs. Also, LC presents alloantigen to $Foxp3^+$ Treg, and thereafter, $Foxp3^+$ Treg proliferation and Treg induction are triggered. Hence, alloantigen-specific Treg, $Foxp3^+$ Treg, IL-10 and IL-4 will regulate allo-immune responses. MHC: Major histocompatibility complex; TCR: T cell receptor; CD: Cluster of differentiation; DEC: Dendritic and epithelial cells; APCs: Antigen-presenting cells; UV: Ultraviolet; DC: Dendritic cell; LC: Langerhans cell; IL: Interleukin; NKT: Natural killer T.

Panoptic finding in alloantigen-specific immunosuppressiton induced by UV-B irradiation

As described above, UV-B irradiation accompanied with alloantigen immunization is a useful tool to induce alloantigen-specific immunosuppression. Here, we reviewed previous documents which have described the possible mechanisms in achieving alloantigen-specific immunosuppression induced by UV-B irradiation[17,26,27,38,39,44,50,72], and summarized the postulated reactions in Figure 1.

In brief, APCs, such as mature DC and LC, capture alloantigen. UV-B irradiation and subsequent IL-10 secretion will cause antigen presentation in a nonprofessional manner to induce antigen-specific immunosuppression[23,27]. Immature DC presents alloantigen to $CD4^+$T cell, and then, Treg induction and IL-10 secretion arise. LC presents alloantigen to NKT cell, and IL-4 secretion subsequently occurs. Also, LC presents alloantigen to $Foxp3^+$Treg, and thereafter, $Foxp3^+$Treg proliferation and Treg induction are triggered. Hence, alloantigen-specific Treg, $Foxp3^+$Treg, IL-10 and IL-4 will regulate allo-immune responses.

So-called "bystander immunosuppression" or "linked suppression"

UV-induced Tregs will demonstrate unique behavior referred to as "bystander suppression". Antigen specificity appears to be restricted to the activation of UV-induced Tregs and not to the suppressive activity itself, as once activated by their cognate antigen, they release IL-10 and thereby suppress other immune reactions nonspecifically[46,80]. Previous researchers also demonstrated a rigor rule for activation of UV-induced Tregs[46,71,80]. Migratory behavior of UV-induced Tregs can be reprogrammed by APCs[81], and UV-induced Tregs switch APCs from a stimulatory to a regulatory phenotype[81]. This alteration of APC function may help to explain bystander suppression. In summary, once IL-10 is released upon antigen-specific activation by UV-induced Tregs, IL-10 suppresses other immune responses in a nonspecific fashion through bystander suppression[74]. The therapeutic potential for Tregs generated in response to antigens that are not necessarily the same antigen driving the pathogenic process has been reported in the literature[74,80].

Possibilities for clinical use, and some future perspectives in human

The view of photoimmunology has changed over the past several years[26,27]. The mechanisms involved are much more complex than those many researchers initially thought. The skin is an organ close to immunity,

and many autoimmune diseases affect the skin. One of the best routes to immunize is *via* the skin. The majority of these reactions are T cell-driven[82]. Therefore, many researchers focused on the tentative theory that UV-induced T cells may not always be beneficial, but more often harmful[26,27]. Nowadays, many researchers assume that a fine-tuned balance is optimal[26,27]. Hence, suppression may be as relevant as induction, and replacing the negatively perceived term "suppression" with "regulation" is preferable[17].

Clinical physicians recognized that UV-induced immunosuppression has a therapeutic potential in human, and therefore, UV-irradiation itself have been already applied for actual clinical use[5-8]. Experimental studies demonstrated that UV-induced immunosuppression supports the exacerbation of skin infections and the suppression of T-cell reactions against microbial antigens[83]. However, the clinical experience differs. The risk for infections, in particular bacterial infections, after UV-B exposure is low[27]. Atopic dermatitis is frequently superinfected with Staphylococcus aureus, but can be improved by UV-B irradiation even without antiseptic or antibiotic measures.

A strong association of UV-susceptible and UV-resistant phenotypes in humans with single-nucleotide polymorphisms in the tumor necrosis factor region was found, suggesting this region to contain genes that determine the outcome of an UV response[84]. Human volunteers developed tolerance when the hapten was initially painted onto UV-treated skin[85]. UV-B irradiation not only depleted LCs but also induced $CD11b^+$ macrophages, which released IL-10[76].

Experimental studies demonstrated that high-dose UV-B irradiation accompanied with antigen immunization is required for antigen-specific Tregs. From the viewpoint of transplant immunity, a simple question arises. How do we establish an actual regimen without severe rejection and intractable infection? Moreover, the development of tolerance versus suppressed contact hypersensitivity appears to correlate with the timing of antigen application after UV-B exposure[27]. How do we consolidate the timing of alloantigen immunization, in an emergent case of available allograft from a deceased-donor. Hence, in current status, translational researched and clinical trials are seriously required, and we should carefully attempt those studies for the further developments.

CONCLUSION

Paradoxically, although high-dose UV exposure is toxic, it is suggested that photopheresis and photoimmunosuppression may have therapeutic potential. The perception of UV-induced immunological changes has thus changed over the past several years[26,27]. Carcinogenesis and immunosuppression due to UV irradiation were regarded as detrimental; however, a finely-tuned therapeutic dose may be possible[26,27]. To induce alloantigen-specific transferable $CD4^+$ Tregs, UV irradiation is a very useful tool[15,19,21,22,24,25,39-41]. Clinically, there is great enthusiasm for the potential to develop strategies that can use Tregs for therapeutic interventions[71]. Alloantigen-specific immunosuppression is an ideal therapy for transplant recipients[86-88]. Although the full mechanism has not yet been determined, UV irradiation accompanied by alloantigen immunization to induce alloantigen-specific Tregs may have great benefits in the transplant immunology field.

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