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Regulatory T Cells Induced by Ultraviolet Radiation

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Abstract
Regulatory T cells belong to a subset of T lymphocytes which suppress immune reactions in an antigen-specific fashion. They play an important role in the prevention of autoimmune diseases. Ultraviolet (UV) radiation was also found to suppress the immune system in an antigen-specific fashion mediated by UV-induced regulatory T cells. Induction of these cells by UV radiation is an active process which requires antigen presentation by UV-damaged but still viable Langerhans cells in the lymph nodes. UV-induced regulatory T cells have been recently characterized to express CD4 and CD25 and to release the immunosuppressive cytokine interleukin-10 upon activation. Once activated in an antigen-specific fashion, they suppress immune responses in a general fashion via the release of interleukin-10, a phenomenon called bystander suppression. Upon intravenous injection, UV-induced regulatory T cells primarily migrate into the lymph nodes, explaining why they preferentially suppress sensitization. Recently, the development of regulatory T cells was demonstrated in an experimental model of photopheresis, a therapeutic regimen which is used for the therapy of autoimmune diseases, transplant rejection and graft-versus-host disease. Further characterization of these cells will determine whether they can be applied therapeutically in the future with the ultimate aim to induce specific immunosuppression.

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Ultraviolet (UV) radiation, in particular the middle wavelength range (UVB, 290–320 nm), suppresses the immune system. The phenomenon of UV-induced immunosuppression was first described around 25 years ago when it was observed that UV radiation prevents the immunologically mediated rejection of transplanted tumors in a similar mode as observed for immunosuppressive drugs [1]. The same immunosuppressive effect was described in another immunologic in vivo model, the induction of allergic contact dermatitis. Allergic contact dermatitis represents a kind of delayed-type hypersensitivity response which is induced by topical application of contact allergens. The vast majority of contact allergens used in this model are chemically reactive substances of low molecular weight which have to bind to proteins of the host to exert their antigenic properties. Thus, these substances are also called haptens. Topical application of haptens onto razor-shaved skin of mice results in sensitization in almost all animals treated. In contrast, if the hapten is painted on skin which was immediately before exposed to rather low doses of UVB radiation, contact hypersensitivity (CHS) is not induced [2]. The suppression of the induction of CHS is associated with a decrease

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in the number of Langerhans cells (LC) in the UV-exposed area [3]. Since LC are the major antigen-presenting cells in the epidermis it was concluded that UV radiation inhibits antigen presentation in the skin. Since, in this setting, sensitization and UV exposure affect the same skin area, this alteration in the immune response was called local immunosuppression.

UV Radiation Induces Regulatory T Cells

Application of haptens onto UV-exposed skin, however, does not only result in the failure to induce sensitization but induces long-term hapten-specific unresponsiveness. Application of the very same hapten a few weeks later onto a non-UV-exposed skin area of the same animal again does not induce CHS [2]. However, these mice are not generally immunosuppressed since immune responses to other unrelated haptens are not affected. This indicated that the application of haptens onto UV-exposed skin results in hapten-specific immunotolerance. This observation was the first indication that UV radiation – unlike immunosuppressive drugs – does not cause a general but rather specific immunosuppression.

In 1983, Elmets et al. [4] postulated that UV-induced immunotolerance is mediated via the induction of specific suppressor T cells. Prove of this hypothesis was provided by the observation that intravenous injection of splenocytes obtained from animals which were tolerized by the application of a hapten onto UV-exposed skin rendered the recipient animals unresponsive to the same hapten. In contrast, other immune reactions were not suppressed in the recipient mice. Thus, it was convincingly shown that hapten-specific tolerance was adoptively transferred on a cellular basis. In this process, T cells appeared to be critically involved since depletion of T cells before injection resulted in a loss of transfer of suppression. Based on these findings it was concluded that application of haptens onto UV-exposed skin results in the induction of T cells which suppress CHS in an antigen-specific fashion. Logically, these cells were called suppressor T cells. [4].

Although the transfer experiments demonstrated in a rather indicative way that UV-induced immunosuppression is mediated via antigen-specific suppressor T cells, many attempts to purify, to clone or to further characterize these cells and their postulated secretory mediators ('suppressor factors') failed despairingly. Thus the term suppressor T cells and the entire concept of suppression were drawn into question in general immunology. For almost 2 decades, the term suppressor T cells was almost banned. Scientific papers were rejected or ignored simply because of the fact that they mentioned the ostracized term suppressor T cells. Unfortunately, it was not appreciated in those days that the experiments performed by Elmets et al. [4] demonstrated in principle that such cells have to exist. Scientists working in the field of photoimmunology were the only ones who persistently pursued the concept of UV-induced suppressor T cells for years.

The entire subject was revived by the description of T cells in a colitis model, which upon antigen-specific activation actively suppressed immune reactions [5]. Upon antigen-specific stimulation, the cells released high amounts of the immunosuppressive cytokine interleukin (IL)-10. These cells were called type I regulatory T cells (Tr1). Tr1 cells proliferated only weakly, which could explain why cloning of these cells might be so difficult or even impossible. Subsequently, the groups led by Sakaguchi and Shevach demonstrated that the depletion of CD4+CD25+ T cells induces the development of autoimmune diseases [6, 7]. In turn, reinjection of these cells prevented the development of these autoimmune phenomena, indicating that these CD4+CD25+ cells prevent autoimmunity and thus can act in a suppressive mode. Finally, a third population of cells with suppressive capabilities was described in a model of oral tolerance [8]. These cells, which exert the inhibitory activity primarily via the release of transforming growth factor-β, were designated Th3 cells.

Probably for tactic reasons, these newly detected cell populations were given the name regulatory T cells. Avoiding the term suppressor T cells, it was made easier for those immunologists who had prosecuted the concept of suppressor T cells in an obsessed way for years to accept now this concept of suppression and active down-regulation, respectively. Thus, priority is given to the term regulatory T cells. However, quite often the terms regulatory and suppressor T cells are used interchangeably. Because of the recognition that regulatory T cells may be the gateway to the understanding of autoimmunity, the biology of regulatory T cells is currently one of the most intensively studied fields in immunology [9].

Phenotypic and Functional Characterization of UV-Induced Regulatory T Cells

Various studies attempted to describe the phenotype of regulatory T cells which are responsible for mediating antigen-specific suppression of CHS by UV radiation. Ex-

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pression of a specific marker was mostly proven by using antibody depletion. Upon depletion of a specific surface molecule with an antibody, the loss of transfer of suppression indicated that this molecule might be expressed on the surface of regulatory T cells. Utilizing this technique, it was demonstrated that UV-induced regulatory T cells express CD4 und CD25 [10] and the negative regulatory molecule CTLA-4 (CD152) [11]. In addition, UV-induced regulatory T cells bind the lectin dectin-2 [12]. In vitro, activation of these cells by antigen-presenting cells coupled with the specific hapten induces the release of IL-10 [11]. IL-10 appears to be relevant for the suppressive activity since suppression is prevented by the injection of antibodies neutralizing IL-10 [11]. Thus, IL-10 seems to play a crucial role in mediating UV-induced immunosuppression. Meanwhile, other molecules expressed on CD4+CD25+ regulatory T cells were described, including GITR [13], neuropilin [14] and CD103 [15]. In addition, a subtype of regulatory T cells expresses the transcription factor *FoxP3* [16]. Whether UV-induced regulatory T cells also express these molecules is currently under investigation.

Induction of Regulatory T Cells by UV Radiation Is an Active Process

UV radiation depletes LC from the epidermis [3]. Since LC are the essential antigen-presenting cells in the epidermis, it was concluded that the failure to induce sensitization following UV exposure is due to the depletion of LC according to the motto 'where no antigen-presenting cells, no sensitization'. However, it was also concluded that the induction of regulatory T cells is a direct consequence of the depletion of LC, too. It was surmised that the free antigen which was no longer trapped by the LC diffuses into the dermis where it is taken up by non-specific antigen-presenting cells, including macrophages, and presented in the lymph nodes to T cells in a non-specific way, thereby avoiding sensitization and inducing tolerance. Furthermore, it was assumed that the vast majority of LC are simply killed by UV radiation and undergo apoptotic cell death. Recent studies indicate that this does not appear to be the case.

A major molecular trigger for UV-induced immunosuppression is UV-induced DNA damage. UV radiation induces preferentially two types of DNA lesions, cyclobutane pyrimidinedimers and (6-4) photoproducts. A reduction in the UV-induced DNA damage of the skin by topical application of exogenous DNA repair enzymes prevents UV-induced immunosuppression [17]. Likewise, the release of the immunosuppressive cytokine IL-10 by UV radiation is inhibited by these repair enzymes [18]. Thus, these studies convincingly showed that DNA damage is a major molecular trigger in UV-induced immunosuppression. UV-induced immunosuppression can also be prevented by the immunostimulatory cytokine IL-12. After injection of IL-12 either before or after UV exposure, CHS can be induced even when the hapten is applied onto UV-exposed skin [19–21]. Accordingly, no regulatory T cells are induced upon injection of IL-12. Until recently, it was quite unclear how IL-12 prevents and inhibits UV-induced immunosuppression. Recently, it was observed that IL-12 exhibits the capacity to reduce UV-induced DNA damage [22]. Although the mechanism underlying this surprising phenomenon is quite unclear it is assumed that IL-12 affects nucleotide excision repair (NER), the endogenous DNA repair system, since the effect of IL-12 cannot be observed in NER-deficient mice [22, 23].

Since UV-induced DNA damage was regarded as the major molecular trigger for UV-mediated immunosuppression and since IL-12 was both able to prevent UV-induced immunosuppression as well as to reduce DNA damage, the question of whether the immunoreconstitutive effect of IL-12 is related to its effect on DNA damage had to be answered. To address this issue, DNA-repair-deficient mice (*Xpa*–/–) were studied. Because of a mutation in the *Xpa*–/– gene, an essential component of NER, *Xpa*--/– mice do not have a functional NER and thus are not able to repair UV-induced DNA damage [23]. If the immunoreconstitutive effect of IL-12 is mediated via its effect on NER, IL-12 should not prevent UV-induced immunosuppression in *Xpa*–/– mice. This was exactly the case proving that IL-12 prevents UV-induced immunosuppression via reducing UV-mediated DNA damage [24].

UV-induced DNA damage appears to be also responsible for the depletion of LC from the epidermis following UV exposure. Injection of IL-12 after UV exposure prevents the depletion of LC. This is not observed in *Xpa*–/– mice, implying that DNA damage may be directly responsible for the depletion of LC [24]. Accordingly, double-color FACS analysis using an antibody against the LC-specific marker Langerin [25] and an antibody against UV-induced DNA damage detected an increased number of LC carrying DNA damage in their nuclei in the regional lymph nodes. Injection of IL-12 did not reduce the number of LC significantly but the amount of DNA damage. In *Xpa*–/– mice, IL-12 did not reduce DNA damage,

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indicating that upon UV exposure LC triggered by DNA damage leave the epidermis and migrate into the regional lymph nodes [24], where they obviously still exhibit the capacity to present the antigen to T cells (fig. 1). Nevertheless, due to the UV stress, LC are so damaged that they are no longer able to present the antigen in a professional way which does not result in sensitization but tolerance. In contrast to previous studies, this indicates that the induction of regulatory T cells is not a null event but an active process which requires damaged but still viable LC in the lymph nodes.

Migratory Behavior of Regulatory T Cells Is Essential

Intravenous injection of hapten-specific regulatory T cells into naïve mice inhibits sensitization in an antigen-specific mode since immune reactions against other antigens are not suppressed [2]. Since regulatory T cells suppress immune reactions in an antigen-specific manner, these cells carry quite a therapeutic potential, since their administration may avoid general immunosuppression. In comparison to conventional immunosuppressive drugs, this would have great benefits for the patients since the side effects of general immunosuppression, including secondary infections and the increased risk to develop malignancies, could be avoided or prevented. Therapeutic administration, however, only makes sense if these cells are not only able to prevent sensitization but also to inhibit the elicitation in sensitized hosts. In general, the aim of immunosuppression is not to prevent but to treat and cure diseases. To determine the therapeutic potential of UV-induced regulatory T cells, Glass et al. [26] injected these cells in already sensitized mice and not in naive mice, which is in contrast to previous studies . However, in this setting, challenge performed 24 h after injection was not suppressed. From these studies, the authors concluded that regulatory T cells are only suppressed in naive but not in sensitized hosts. They further postulated that regulatory T cells are no longer suppressed in the presence of T effector cells and thus are inferior to T effector cells. These conclusions gave a devastating testimony of the therapeutic potential of regulatory T cells, since based on these observations regulatory T cells would only act in a preventive but not a curative mode.

Our own results had shown that upon activation regulatory T cells release high amounts of IL-10, which is ultimately responsible for mediating the suppression [11]. A couple of years ago, we and other groups demonstrated that IL-10 exhibits the capacity to inhibit the induction and the elicitation of CHS [27, 28]. If IL-10 plays a crucial role, regulatory T cells in principle should also be able to suppress the elicitation via the release of IL-10. Inhibition of sensitization has to take place in the lymph nodes, while suppression of elicitation occurs in the periphery, the site of the inflammatory response (e.g. skin, joints and intestines). Thus, we surmised that upon intravenous injection regulatory T cells do not suppress the effector phase because they do not get into the periphery. To prove this theory, dinitrofluorobenzene (DNFB)-specific regulatory T cells were injected intracutaneously into the ears of DNFB-sensitized mice [10]. In this setting, the CHS response was significantly suppressed (fig. 1). Inhibition was antigen-specific since DNFB-specific regulatory T cells had no suppressive effect in mice sensitized and challenged with the unrelated hapten oxazolone. In contrast, when DNFB-specific regulatory T cells were injected into oxazolone-sensitized mice and ears were treated with a low dose of DNFB before application of oxazolone in order to activate the DNFB-specific cells, the CHS response to oxazolone was also significantly suppressed. This phenomenon is called 'bystander suppression' and has been reported for regulatory T cells [29]. This indicates that the activation of regulatory T cells is antigen specific which results in the release of IL-10. However, once activated, regulatory T cells suppress immune reactions in a non-specific way via the release of IL-10 [10].

The inability of regulatory T cells to migrate into the periphery is determined by their unique expression pattern of homing receptors. FACS analysis revealed that UV-induced regulatory T cells express the lymph node homing receptor CD62L (L-selectin) [10], but not the ligands for the skin homing receptors E- and P-selectin [30, 31]. This explains why regulatory T cells upon intravenous injection migrate into the lymph nodes and are stuck there. Therefore, these cells are able to inhibit sensitization which takes place in the lymph nodes (fig. 1). To suppress the elicitation phase, they have to reach the periphery because this is the only place where they can interfere in the interaction of LC and effector T cells. Because of the capacity of the bystander suppression, speculations exist about the therapeutic potential of regulatory T cells which could be generated in response to antigens known to be present in the target organ, which are not necessarily the antigen that drives the pathogenic response [29]. However, these findings indicate that this strategy will only be successful if the regulatory T cells home to the target organs. Thus it will be of crucial importance whether it will be possible to manipulate the expression pattern

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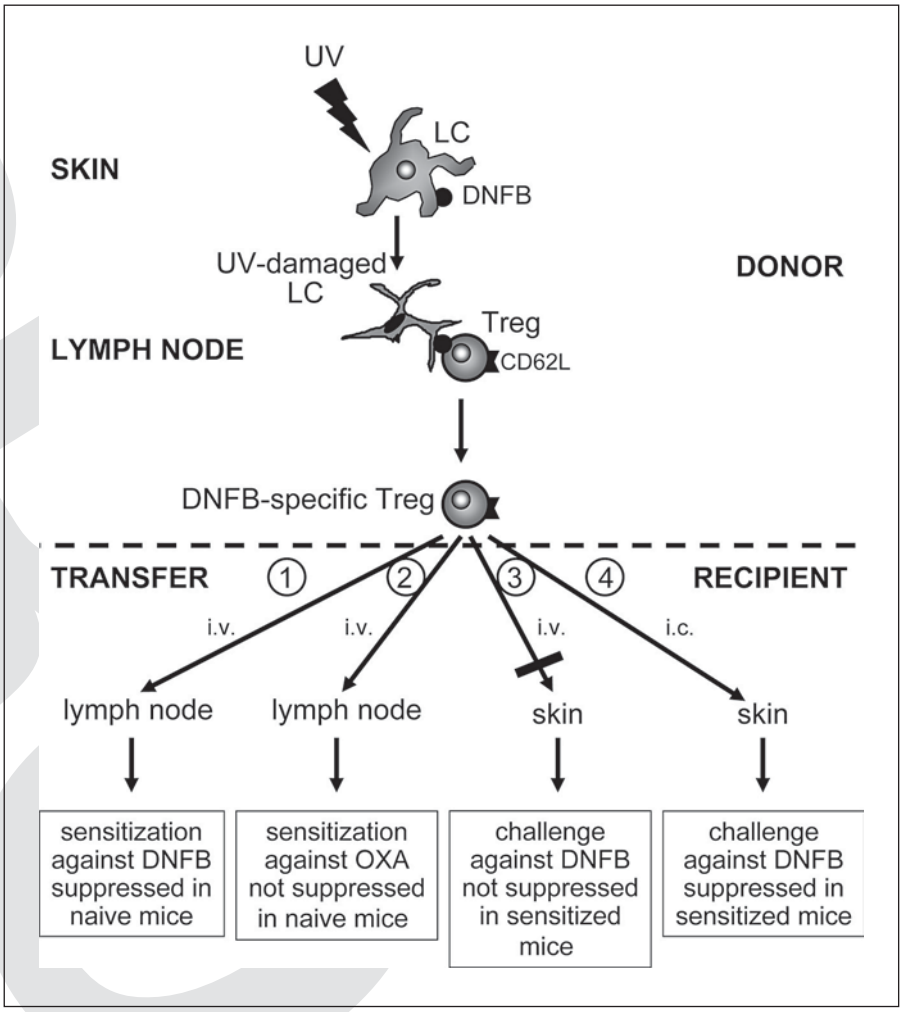

Fig. 1. UV radiation hits LC in the epidermis which take up the hapten DNFB (●). UV-induced DNA damage induces the emigration of LC into the regional lymph nodes where damaged but still viable LC can present DNFB to regulatory T cells (Treg). Upon intravenous transfer into naïve recipients, Treg expressing the lymph node homing receptor CD62L migrate into the lymph nodes and suppress sensitization against DNFB (1), but antigen-specific sensitization against oxazolone (OXA) is not suppressed (2). Due to the CD62L expression, intravenously injected Treg do not enter the skin and thus do not suppress the response to DNFB in sensitized mice (3). In contrast, upon intracutaneous injection into the ears of sensitized mice, the challenge against DNFB is suppressed by Treg.

of homing receptors in such a way that they can migrate into the periphery. If this is not be possible the therapeutic potential of regulatory T cells will be limited. Since fucosyltransferase VII is responsible for the expression of the ligands of the skin homing receptors [32], we are currently trying to induce the expression of these ligands via retrorviral transfer of fucosyltransferase VII into UV-induced regulatory T cells.

Experimental Photopheresis Induces Regulatory T Cells

Extracorporeal photopheresis is a therapeutic regimen which has been developed in the early 1980s primarily for the treatment of cutaneous T-cell lymphomas [33]. Current photopheresis treatments involve a closed-loop, sterile, patient-connected, point-of-care device withdrawing approximately 5 billion peripheral blood leukocytes from the patient by apheresis followed by incubation of the cells with the photosensitizer 8-methoxypsoralen followed by UVA (320–400 nm) exposure in an extracorporeal setting. After extracorporeal treatment, cells are reinfused into the patient.

After having utilized photopheresis almost exclusively in the treatment of lymphoma patients in the beginning, in the course of time it was recognized that photopheresis is highly efficacious in autoimmune diseases, transplant rejection and graft-versus-host disease [34]. These quite heterogeneous diseases have in common that they all favorably respond to immunosuppressive therapy. Hence, it was surmised that photopheresis might exert immunosuppressive effects. In the past 25 years, photopheresis treatment has been demonstrated to be absolutely free of

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any side effects. Signs of general immunosuppression were never observed. This made us suspect that photopheresis might cause specific immunosuppression probably via induction of regulatory T cells. This question was addressed in an experimental animal model of photopheresis. Injection of leukocytes obtained from DNFB-sensitized mice which were exposed in vitro to 8-methoxypsoralen and UVA rendered recipient mice unresponsive to DNFB. Immune reactions to other allergens were not affected [35]. Injection of T cells obtained from the recipient mice into a second generation of mice again rendered the recipient mice unresponsive to DNFB. This indicates that the infusion of psoralen plus UVA-treated cells induces antigen-specific regulatory T cells in the recipients. Regulatory T cells generated by this method express CD4 and CD25, as demonstrated by depletion transfer studies. Future investigations have to show whether these types of regulatory T cells are also induced in humans undergoing photopheresis.

Conclusion

Regulatory T cells can be induced by various stimuli. UVB radiation has turned out to be a very efficient trigger for the development of regulatory T cells. Currently, regulatory T cells are the center of numerous investigations since they have been recognized as the gateway for understanding autoimmunity but also for specific immunosuppression. The possibility to suppress the immune system in a rather specific than general fashion, thereby avoiding side effects, is one of the great challenges for clinical immunologists in the future. We still do not have the capability to expand regulatory T cells in vitro, despite indications that this may take place in vivo. In addition, the identification of new and if possible more specific markers of regulatory T cells is required, enabling a better characterization of these cells. The vast majority of studies on regulatory T cells was performed in murine models. It remains to be determined whether all these findings can be transferred to humans. Irrespective of the yet unsolved problems, regulatory T cells represent currently one of the most exciting and most rapidly developing fields in immunology. In the study of the biology of UV-induced regulatory T cells, photoimmunology has greatly contributed to this success.

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