New insight into immunosuppression and treatment of autoimmune diseases

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ABSTRACT

The achievements in photoimmunology over the last years have not only broadened our knowledge how ultraviolet (UV) light compromises the immune system but have also yielded important insights into general immunology and photobiology. Therefore, studies will not only increase our understanding how UV acts as a pathogen but will also support the development of new therapeutic strategies, e.g. suppressing (auto)immune reactions via administration of antigen-specific regulatory T cells. Major advances in biotechnology have already resulted in the development of several novel agents for the treatment of inflammatory and autoimmune diseases. Some of these new immunomodulating drugs, such as mycophenolate mofetile and rituximab, are actually evaluated in controlled clinical trials to confirm the efficacy and safety profile in patients with autoimmune diseases. However, there is urgent need for specific immunointervention and further therapeutic options, especially for patients with autoimmune diseases in life-threatening situations and for non-responders to standard immunosuppression.

Molecular mechanisms of photoimmunosuppression

Photoimmunology started with the observation that ultraviolet (UV) radiation (UVB, 290-320 nm) inhibits the rejection of transplanted tumors. UV-induced skin tumors in mice are highly immunogenic and thus rejected upon transplantation into naïve syngeneic hosts. However, if the recipient animal was immunosuppressed, e.g. by immunosuppressive drugs, the inoculated immunogenic UV-tumors were able to grow progressively, clearly indicating that the rejection is immunologic. The same was observed when the hosts were exposed to low doses of UV instead of immunosuppressive drugs, implying that UV can exert immunosuppressive features (1).

Similar observations were made in another immunologic *in vivo* model, the induction of contact hypersensitivity (CHS). Painting of contact allergens (haptens) on skin areas which had been exposed to low dose UVB did not induce CHS, whereas application of the hapten at an unirradiated site caused a normal CHS response (2). Inhibition of CHS induction correlated with a reduction in the number of Langerhans cells at the site of exposure. *In vitro* studies showed that UV-mediated alterations of Langerhans cells, the crucial antigen-presenting cells in the epidermis, are associated with a loss of the antigen-presenting function of these cells. Since the areas of UV exposure and of hapten application are identical, this type of immunosuppression was called local.

However, UV does not only inhibit the induction of CHS, but even induces tolerance, since these animals cannot be resensitized with the same hapten at a later time point (2). This long term suppression is hapten specific since the very same mice can be sensitized against another unrelated hapten, which excludes general immunosuppression by UV. UV-induced tolerance is mediated via the generation of regulatory T cells (see below). Higher UVB doses can even affect immune reactions initiated at distant, non-UV-exposed sites. For a long time it remained unclear how UV can affect immune responses in skin areas not directly affected by UV. A major breakthrough was the observation that keratinocytes upon UV-exposure release mediators with immunosuppressive properties. Although several mediators may be responsible for this effect the major player appears to be interleukin (IL)-10 (3).

UV-induced tolerance is mediated via

the generation of T cells with inhibitory/suppressive activity. Injection of splenocytes from mice which had been tolerized by the application of a hapten onto UV-exposed skin into naïve mice rendered the recipients unresponsiveness to this particular antigen (4). Although the transfer of UV-mediated suppression was subsequently shown in a convincing fashion in a variety of different immunological *in vivo* models, the phenotypic characterization of the postulated UV-induced suppressor T cells was stuck for many years which contributed to the rejection of the concept of suppressor T cells in general immunology. Nowadays the concept of active suppression is accepted in general immunology, but the term regulatory T cells (Treg) is preferred to the term suppressor T cells.

Because of the existence of different UV-mediated tolerance models (local, systemic, high dose, low dose) different Treg with unique phenotypes appear to be involved. Currently best characterized are Treg involved in the low dose suppression of CHS. Cells transferring suppression in this model appear to belong to the $CD4^+CD25^+$ subtype, they express CTLA-4, bind the lectin dectin-2 and in contrast to the classical $CD4^+CD25^+$ T cells release high amounts of IL-10 upon antigen-specific activation (5). These cells may represent a separate subtype of Treg since they exhibit characteristics of naturally occurring Treg, e.g. expression of CD4 and CD25, but also of type 1 regulatory T cells, e.g. release of IL-10. While intravenous injection of T cells from UV-tolerized mice into naïve animals renders the recipients unresponsive to the respective hapten, intravenous injection of the same cells into sensitized mice does not inhibit the CHS response in these recipients (6). This gave rise to the speculation that Treg inhibit the induction but not the elicitation of CHS and thus are inferior to T effector cells. However, when Treg were injected into the area of challenge of sensitized mice, the elicitation of CHS was suppressed in a hapten-specific fashion (6). UV-induced Treg express lymph node homing but not skin homing receptors. Thus, UV-induced Treg though principally being able to inhibit T effector cells do not suppress the elicitation of CHS upon intravenous injection since they obviously do not migrate into the skin. Since Treg do not cause general immunosuppression, speculations exist about the therapeutic potential of Treg. However, this strategy will only be successful if the Treg home to the target organ where the inflammation takes place. The unique migratory behavior of Treg might explain why in the vast majority of *in vivo* studies upon intravenous injection Treg have the capacity only to prevent but not to cure various diseases.

IL-12 has been described to prevent the suppression of CHS by UV, to prevent the development of Treg and even to break UV-induced tolerance. Since reduction of UV-induced DNA damage is associated with mitigation or loss of UV-induced immunosuppression, DNA damage is regarded as the major molecular trigger of UV-mediated immunosuppression (7). The prevention of UV-induced immunosuppression by IL-12 may be due to its recently described capacity to reduce DNA damage via induction of DNA repair (8) since the preventive effect of IL-12 is not observed in DNA repair deficient mice (9). UV-induced DNA damage appears to be also an important trigger for the induction of UV-induced Treg. This assumption is based on the observation that reduction of DNA damage containing Langerhans cells in the regional lymph nodes by IL-12 prevents the development of Treg. Again, in DNA repair deficient mice, IL-12 failed to prevent the development of UV-induced Treg.

UV-induced Treg also appear to play an important role in photocarcinogenesis. Although their crucial role in supporting the development of UV-induced skin tumors has been already described in the eighties, these cells have been characterized only recently. They appear to belong to the natural killer T cell (NKT) lineage since they express the T cell marker CD3 but also the NK marker DX5 (10). After UV exposure these $CD3^+DX5^+$ cells suppressed upon transfer antigen-specifically delayed-type hypersensitivity responses and antitumoral immunity against highly immunogenic UV-induced skin tumors in recipient mice.

The achievements in photoimmunology over the last years have not only broadened our knowledge how UV compromises the immune system but have also yielded important insights into general immunology and photobiology. Further studies will not only increase our understanding how UV acts as a pathogen but also support the development of new therapeutic strategies, e.g. suppressing (auto)immune reactions via administration of Treg.

New trends in immunosuppressive treatment

Immunosuppressive agents are the mainstay of treatment in patients with autoimmune diseases and have helped to improve the survival and prognosis of e.g. systemic lupus erythematosus (SLE) in the past decades. In most cases, a combination of different therapy regimens is needed either to increase clinical effectiveness or to reduce side effects of the individual drug. However, optimal therapy regimens have still to be defined. Numerous uncontrolled, retrospective trials are available based on empirical knowledge or case reports, but there is urgent need for specific immunointervention and further therapeutic options, especially for patients in life-threatening situations and for non-responders to standard systemic immunosuppression. Unfortunately, randomised controlled trials evaluating new drugs are still missing and difficult to perform because systemic autoimmune diseases are rare and heterogeneous. In addition, there is also need for alternative topical anti-inflammatory therapeutic modalities in patients with autoimmune diseases, and newly developed immunomodulators have been shown to be active also in a topical formulation with enormous potential to change the way that skin lesions are treated and managed.

Most traditional therapeutic concepts for patients with systemic autoimmune diseases are based on data received from case reports and small trials using systemic agents approved for other indications, for example *cyclosporin A*

(CSA), which is mostly used in organ transplantation. Although CSA has shown promising results in various diseases with disturbed immunoregulation, controlled studies in SLE are limited after nearly 20 years of experience. The largest and longest experience in lupus nephritis is documented by Dostal *et al*. (11) reporting a clear reduction in proteinuria and disease activity with a complete remission in 5 of 11 patients of a group suffering mostly from nephrotic syndrome. CSA is mostly well tolerated and reasons for discontinuation are side effects, such as hypertension, tremor, and nephrotoxicity. However, the multiple interferences of CSA with further drugs have to be taken in mind before its application. *Tacrolimus* (FK 506), initially administered to prevent graft rejection in a liver-transplant patient, is currently used as an immunosuppressive agent in many kinds of organ transplantations. However, the experience with the systemic use of tacrolimus in autoimmune diseases is limited to some severe cases. In the 1990s, tacrolimus was introduced as a topical agent producing favourable results in atopic dermatitis (12). In single case reports, tacrolimus ointment has also been shown to be effective in treating skin lesions of patients with SLE (13) and a multicenter study is ongoing to confirm the results.

Methotrexate, the most often used medication in patients with rheumatoid arthritis (RA), is also applied to patients with non-organ threatening systemic connective tissue diseases (14). In patients with SLE, a conclusive profile for an indication of methotrexate is not obvious and the risk of accumulation in impaired kidney function has to be taken into consideration. More recently, *mycophenolate mofetil* (MMF) has been introduced as an alternative in SLE mainly for patients refractory to other treatments and for lupus nephritis (15-17). In a variety of other SLE manifestations, such as thrombocytopenia, haemolytic anaemia, and uncontrolled disease activity, MMF has also been reported to be successful. The results of 86 patients with SLE using MMF in various indications were recently published demonstrating an overall reduction of disease activity, an increase in complement values, and a decrease in antibody titers (18). Next to the consequences of general immunosuppression, the limitations of MMF are gastrointestinal side effects, accompanied by a hemorrhagic colitis in severe cases.

In recent years, a number of further therapeutic agents have been developed for various indications and need to be evaluated for patients with autoimmune diseases by clinical successful application (22). For example, *rituximab*, a chimeric anti-CD20 antibody, is approved in B-cell lymphoma and was documented to be safe in more than 300,000 treatments. There are several case reports indicating the efficacy of rituximab in refractory autoimmune haemolytic anemia, thrombocytopenia, polymyositis, antiphospholipid-syndrome, and CNS involvement in SLE (26). In a recent published trial, Sfikakis *et al*. (20) focused the evaluation of anti-CD20 therapy to patients with type III and IV lupus nephritis. Using rituximab in combination with steroids, 8 of 10 patients responded at least partially after 2 months. Analysis of lymphocyte subsets in these patients revealed a reduction of T-lymphocyte activation, reflected by a decrease of surface expression of CD40L, CD 69, and HLA DR on $CD4^+$ lymphocytes. These data suggest that B cells promote autoimmunity in humans by directly influencing T cells and are important in further understanding the pathophysiological process in SLE. A further promising agent was *LJP 394*, a molecule shown to have high affinity to anti-DNA antibodies and to decrease anti-oligonucleotide antibody formation in mice through induction of B-cell tolerance. Multicenter clinical trials with LJP 394 exhibited efficacy on the rate of renal relapses in patients with high-affinity antibodies to its DNA epitope (21). However, this hypothesis could not be confirmed in the following trial. The most significant finding with LJP 394 treatment was the improvement in health-related quality of life in patients with SLE.

In summary, the above mentioned substances are examples of new therapeutic options in the treatment of patients with systemic autoimmune diseases indicating the enormous development in this area. However, randomised clinical trials are urgently needed taking in account the heterogeneous expression and the lack of proven standardized therapy for specific organ manifestations, such as CNS and skin.

New biological agents for the treatment of autoimmune diseases

Strategies for the effective treatment of autoimmune diseases of the skin are complex and are frequently associated with side effects. Therefore, there is urgent need to search for novel efficient therapies with a favourable safety profile. Accordingly, the recent improvement in our understanding of the underlying pathomechanisms and the major advances in biotechnology resulted in the development of several novel agents and strategies for the treatment of inflammatory and autoimmune diseases. Current approaches focus on autoantigen recognition and autoantibody production, cytokine function and production, tolerance induction, and gene transcription (22, 23).

Among non-specific biological agents intravenous immunoglobulins which exert a variety of immunomodulating activities according to several case reports and smaller clinical trials have been successfully used for the treatment of autoimmune-mediated skin diseases such as SLE, dermatomyositis, scleroderma, bullous autoimmune diseases, chronic autoimmune urticaria, and several forms of vasculitis (24).

Agents targeting T cells include antibodies directed against several surface molecules of T- or B-cells. For example, antibodies directed against CD4 were found to be useful for the treatment of discoid lupus erythematosus (22). Antibodies against the interleukin (IL)-2Rα chain (daclizumab, basiliximab, and inolimomab) as well as against T-cell markers and IL-2/toxin fusion proteins are currently being investigated in many T-cell mediated diseases. There is some evidence for the efficacy of anti-IL-2 strategies in the treatment of psoriasis and cutaneous T-cell lymphomas (22). Targeting B lym-

phocytes with antibodies directed against CD 20 (tositumomab, rituximab) or CD 22 (epratuzumab) is not only an effective way to treat B-cell lymphomas, but also appears to be a promising approach for the treatment of some autoimmune diseases (see above).

Furthermore, among several proinflammatory cytokines tumor necrosis factor-α (TNF-α) has been recognized as a key molecule mediating inflammation and autoimmunity. Accordingly, targeting TNF-α with antibodies such as infliximab, adalimumab or a fusion protein of the TNFα RII fused with a humanized immunoglobulin fragment (etanercept) have been successfully used for the treatment of psoriasis, psoriatic arthritis, RA, ankylosing spondylitis, and Crohn's diseases. However, from these applications it is well known that TNF-α inhibition may lead to the formation of antinuclear and also anti-dsDNA antibodies, a finding that prevented the early use of these substances in autoimmune diseases, such as SLE. Recently, a pilot study was published by Aringer *et al*. (25) investigating the safety of TNF-α blockade in patients with SLE. *Infliximab* was given to 6 patients in addition to standard immunosuppression. The arthritis in 3 patients came to remission and the lupus nephritis in 4 patients improved by a reduced proteinuria, already after 1 week of treatment. Overall, infliximab did not lead to adverse events concerning disease activity, although autoantibody titers increased as expected. Randomised controlled trials are in the pipeline to further evaluate the benefits and risks of TNF-α blockade in SLE, and compounds such as pegylated anti-TNF (certolizumab) are currently being investigated (22, 23, 27, 29). Targeting IL-1 (anakinra) or IL-6R (atlizumab) may represent a further promising approach for the treatment of RA and related diseases (28, 30).

The capacity of certain immunomodulating cytokines such as IL-4, IL-10, and IL-11 to shift the immune response from Th1 towards Th2 has initiated several clinical trials. First studies concentrated on the investigation of their efficacy in psoriasis which like RA is regarded as an immune-mediated inflammatory disease. According to first small clinical trials IL-4 and IL-10 appear to have a potential for the treatment of psoriasis and SLE (28, 31).

Cytokines of the interleukin-12 (IL-12) family including IL-12, IL-23, and IL-27 are known to regulate Th1-cell responses (32). A monoclonal antibody to the human interleukin-12 p40 subunit (anti-IL-12p40) which is shared with IL-23 has been developed for the treatment of autoimmune diseases. In a first clinical trial, this antibody proved to be very effective for the treatment of psoriasis (32). Antibodies against costimulatory molecules such as CD80 (IDEC-114, galiximab) are also being exploited and were found to be promising, safe and well tolerated for the treatment of psoriasis in some first clinical trials (33). Moreover, antibodies against CD40-ligand (anti-CD154, IDEC-131, ruplizumab) are currently under evaluation for the treatment of SLE (34).

Abatacept (CTLA-4Ig) is a fusion protein of the extracellular domain of CTLA-4 with the Fc portion of IgG1 which serves as a soluble receptor. Therefore, this molecule prevents CTLA-4/B7 interaction by blocking T-cell activation and T-cell dependent B-cell functions *in vivo*. In animal studies, treatment of NZB/W mice resulted in an improved survival rate as well as regression of nephritis. Clinical studies with CTLA-4Ig in patients with lupus nephritis are being initiated and one compound (BMS-188667) currently is investigated in clinical trials for patients with RA and psoriasis (35). Preliminary data indicate that treatment with a monoclonal antibody designed to interfere with complement C5 function decreased proteinuria and improved survival in treated NZB/NZW mice. Moreover, in first clinical trials patients with SLE have been treated successfully with a humanised anti-C5 monoclonal antibody (pexelizumab) (36).

In summary, the introduction of biologics has significantly increased our therapeutic armamentarium for the treatment of many inflammatory and autoimmune diseases. Use of biologics, moreover, may help to identify novel effector and target molecules being crucially involved in the pathogenesis of these diseases. The successful and safe use of already available compounds has finally prompted the development of many new and modified biological agents.

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