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Extracorporeal Photopheresis: From Animal Models to Clinical Practice

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Abstract. Extracorporeal photopheresis (ECP) is an immunomodulatory therapy characterized by the exposure of leukocytes to 8-methoxypsoralen and UV light irradiation, followed by reinfusion of the treated cells into the patient. ECP is considered a safe and well-tolerated procedure that preserves the beneficial aspects of immunity, such as antitumor and antiviral activities, with a low rate of side effects. Currently, ECP is used for the treatment of immune-mediated conditions, such as cutaneous T-cell lymphoma, graft-versus-host disease, solid organ transplant rejection, and autoimmune disorders. ECP is an immunomodulatory therapy characterized by multiple complex events that lead to the modulation of the immune response. Modifying the activity of myeloid antigen-presenting cells with apoptotic cell remnants is key to the therapeutic action of ECP; however, because the pathological roles of macrophages and dendritic cells are context specific, the precise effects of ECP vary between different diseases. Consequently, we need a much better understanding of the immunology and pharmacology of ECP to extend its use in solid organ transplantation and beyond. During the past decades, important advances were made using animal models of ECP, leading to a better mechanistic understanding and its more rational use in many T cell–mediated conditions. This review summarizes the available information on animal models of ECP, providing insights into the mechanisms of action, therapeutic applications, limitations, and translational potential from preclinical animal models to human clinical practice.

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Extracorporeal photopheresis (ECP) is a clinically used cell-based therapy that demonstrated remarkable success rates in the treatment of immune-mediated diseases with T-cell involvement, including cutaneous T-cell lymphoma (CTCL), acute and chronic graft-versus-host diseases (GvHD), autoimmune diseases, organ transplant rejection, and recently checkpoint inhibitor-induced adverse events.[1-4]

ECP is considered to be a safe therapy, as it is not associated with major organ toxicities, infections, or long-term complications, and it preserves the beneficial aspects of antitumor and antiviral immunity.[5,6] ECP involves the collection of peripheral mononuclear blood cells from the patient, through a process called leukapheresis, in which plasma, platelets, and red blood cells are separated from white blood cells (WBCs). The collected WBCs are then treated with a photosensitizing agent, 8-methoxypsoralen (8-MOP), and further exposed to ultraviolet light irradiation (UVA). The treated WBCs are subsequently transfused back into the patient.[7-9] 8-MOP is a naturally occurring inert compound that is activated on exposure to UVA and binds covalently to the pyrimidine bases of DNA, proteins, and cell membrane. Treatment with 8-MOP and UVA cross-links the DNA strands, inhibits DNA replication, and cell cycle arrest, thereby inducing apoptosis.[2,10,11] The immunomodulatory effects induced by ECP include secretion of anti-inflammatory cytokines and chemokines, maturation of dendritic cells (DCs), stimulation of T cells, development of regulatory T cells (Treg), among others.[10,12]

Although advances have been made using ECP as an empiric therapy, its underlying cellular and molecular mechanisms are not fully understood. Thus, understanding the mechanism of ECP and its impact on different diseases is crucial to expand its application to treating other

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disease entities.[1,11] Preclinical models have been shown to play a crucial role in understanding the molecular mechanisms associated with numerous diseases, thereby aiding in the translational potential of new therapies. Indeed, animal models have provided valuable insights into the molecular mechanisms, potential risks, efficacy, and safety profiles associated with ECP.[13,14]

In animal models, ECP can be performed by isolating splenocytes or by extracting blood from donors, and the cells are treated with 8-MOP and incubated, and then exposed to UVA light. Different preclinical models, involving mice and rats, explored diverse treatment regimens, dosages, and time points in accordance with the animal model in use and disease specific (Figure 1). These discrepancies can be attributed to the variability of protocols, such as the number of ECP treatments, the quantity of reinfused cells, and the concentrations of 8-MOP.

In this review, we summarize the literature on preclinical models of ECP in diverse diseases, including cancers, organ transplantation, and autoimmune disorders, and their translational potential.

ECP FOR CTCL

CTCL is a clonal T-cell malignancy, characterized by the malignant T cells that are found in the skin and the blood. The most common forms of CTCL include Sézary syndrome and advanced-stage erythrodermic mycosis fungoides.[3,9] ECP emerged as a systemic first-line immunomodulatory therapy in leukemic CTCL and showed to be beneficial in improving overall survival in patients.[15] However, the reports on the effect of ECP on CTCL are mainly patient specific.[3,16] In patients, the ECP mechanism in CTCL is associated with an increase of T helper (Th)-1 cells and subsequent decrease of Th2, toward an anti-inflammatory phenotype, increase of interleukin (IL)-2 produced by monocytes, and upregulation of tumor necrosis factor alpha that facilitates apoptosis of tumor cells.

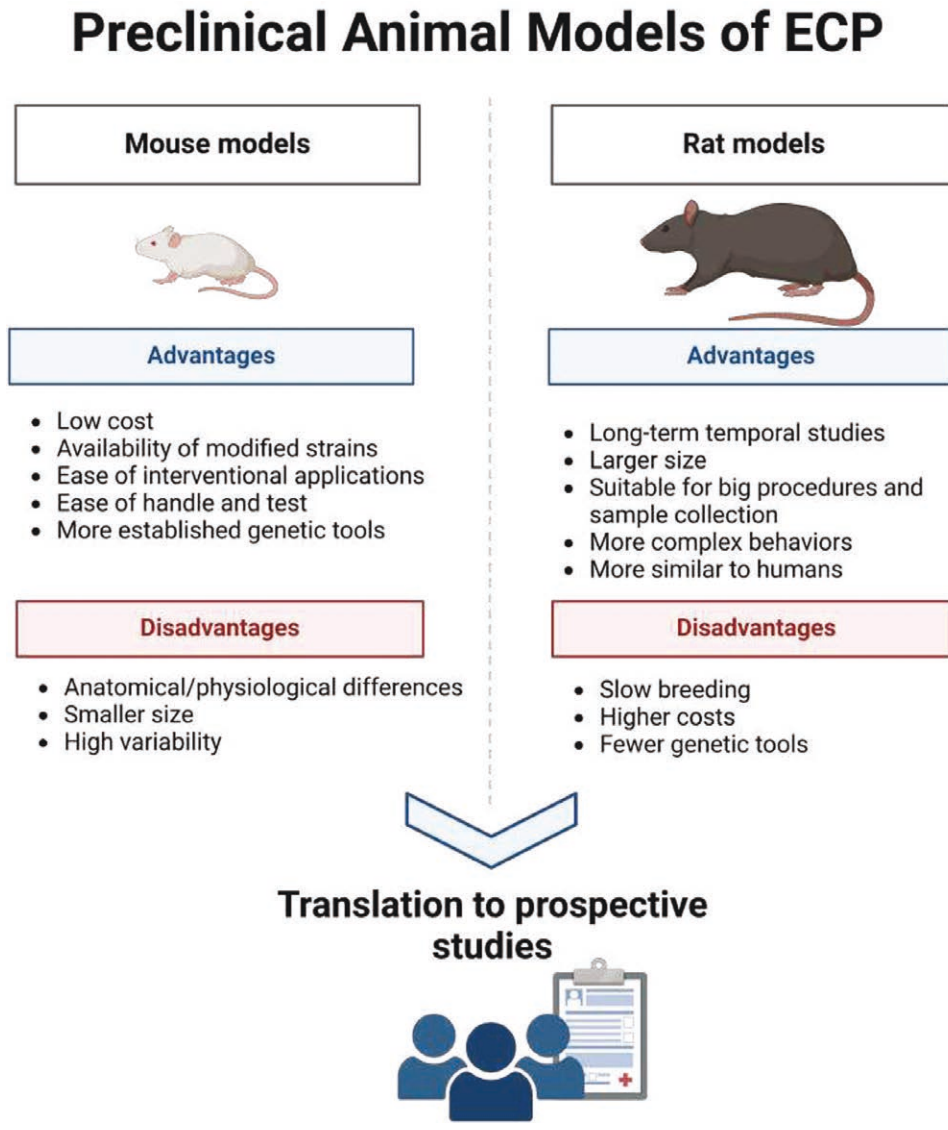

FIGURE 1. Advantages and disadvantages of the different animal models used in ECP. Created with BioRender.com. ECP, extracorporeal photopheresis.

Mature DCs present the tumor antigens to T cells, thus increasing antitumor activity and response.[9,10] Nonetheless, CTCL patients with CTCL become refractory to ECP over time and second-line therapies such as mogamulizumab, a monoclonal antibody targeting CC chemokine receptor (CCR) type 4, are used. Recent data indicate that combining mogamulizumab and ECP is an effective therapy against CTCL with a good safety profile.[17] The clinical efficacy of ECP in the treatment of CTCL has been extensively and well documented. However, preclinical studies in animal models are lacking. To date, no published studies have demonstrated the use of ECP in animal models for CTCL. A recent publication highlighted the importance and proposed the use of an animal model to assess the therapeutic potential of ECP as a combined therapy and the underlying mechanism in CTCL.[18]

ECP for GvHD

Allogeneic hematopoietic stem cell transplantation is a well-established treatment option for hematological malignancies. One of the main clinical challenges of this treatment is the development of GvHD, which is a major contributor to morbidity and mortality.[19,20] GvHD can be categorized into acute or chronic, with chronic GvHD occurring in 30%–70% of patients who have undergone allotransplantation.[21,22] Corticosteroids are the first-line treatment of choice for both acute and chronic GvHD but are accompanied by significant toxicity, with steroid-refractory disease having a dismal prognosis.[1,13] ECP is recommended as a second-line therapy for treating steroid-refractory GvHD, as it is associated with great tolerance and minimal toxicity.[11,12,23] The mechanism of action of ECP on mitigating GvHD is associated with the induction of a tolerogenic phenotype, characterized by activation of T cells and differentiation into Treg, and a shift toward a Th2 immune response, with an increase of anti-inflammatory cytokines, interleukin (IL)-10, IL-4, and transforming growth factor beta (TGF-β) and a decrease of proinflammatory mediators tumor necrosis factor alpha, IL-12, and IL-1β.[22,24] Recent data support the combination of ECP and ruxolitinib for patients with refractory chronic GvHD.[25]

Prior studies reported that ECP-induced apoptotic cells, isolated from mice splenocytes and exposed ex vivo to 8-MOP and UVA, have potent immunomodulatory effects that can enhance hematopoietic engraftment and ameliorate GvHD. Moreover, macrophages and Treg, were identified as important mediators of tolerogenic potential after ECP treatment.[26] Gatza et al treated donor-derived splenocytes with 8-MOP and UVA and observed that ECP reversed GvHD and its effect extended beyond apoptosis induction. The suggested mechanism is implicated with an increase of Treg and a reduction of donor effector lymphocytes, indicating a broader impact on the immune environment.[27] Other studies showed that ECP-treated splenocytes attenuated GvHD in a murine model regardless of disease status of the donor, with increased Treg and IL-10 production. Using IL-10-deficient bone marrow, ECP-treated cells lost their therapeutic effect, showing that IL-10 production by bone marrow is crucial for the effect of ECP.[28] Florek et al[29] observed that prophylactic ECP significantly improved the survival after bone marrow transplant and inhibited the initiation phase of acute GvHD. They isolated splenocytes from donor mice, and after ex vivo treatment with 8-MOP and UVA irradiation, the splenocytes were injected into recipient mice, which led to a reduction of activation of DCs and proliferation of T cells, together with an increase in Treg and the IL-10 levels. The immunomodulatory and protective effect of ECP was directly associated with increased IL-10 levels and Treg.[29] Budde et al[30] concluded that the standard ECP setup was effective in alleviating acute GvHD in a mouse model. However, ECP-treated leukocytes that were isolated from healthy mice did not yield significant therapeutic effects in vivo. Conversely, ECP-treated cells from healthy donors reduced GvHD symptoms in chronic GvHD and third-party HLA-mismatched donor cells increased the survival.[31]

Although there are contradictory reports on the therapeutic efficacy of ECP treatment in relation to donor types, future studies using animal models are needed to decipher the disease-dependent mode of action of ECP.

ECP FOR ORGAN TRANSPLANTATION

Solid organ transplantation is an important intervention for patients with organ damage and is usually associated with allograft rejection.[1,32] Current strategies to avoid allograft organ rejection include the use of immunosuppressive agents, which minimize rejection and mortality, and are also associated with significant side effects, including cytopenias, gastrointestinal and hematological complications, and risk of infection.[32,33] Therefore, there is an unmet medical need for new treatments in patients undergoing organ transplantation to provide graft tolerance and improve survival while minimizing the side effects. ECP is recommended as a treatment for the prevention and management of heart and lung transplant rejection.[34-37]

Preclinical studies, using splenocytes isolated from mice and treated ex vivo with 8-MOP and UVA irradiation, suggest that ECP improved the cardiac allograft survival rates by increasing the frequency of Treg, $CD4^+CD25^+FoxP3^+$ cells, and adoptive transfer of $CD4^+CD25^+$ T cells from ECP-treated animals extended graft survival after heart transplantation. This suggests that Treg play a key role in the immunomodulatory effects of ECP and that the mechanism and beneficial effects of ECP on graft survival are mediated by induction of Treg rather than by eliminating alloreactive T cells.[38] Moreover, infusion of DCs that had phagocytosed ECP-treated splenocytes from donor mice inhibited cardiac allograft rejection in an antigen-specific manner and induced the expression of Treg. These findings suggest that DCs can act as negative immune regulators and inducers of immune-tolerance, which can help improve outcomes by inducing tolerance to donor antigens.[39]

ECP has also been used after lung transplantation and has been shown to be a promising strategy for patients with acute graft rejection. ECP is used in the treatment of bronchiolitis obliterans (BOS) and fibrosis, which are major threats that often lead to graft failure and poor outcomes after lung transplantation.[36,37,40] Researchers found that ex vivo ECP treatment using donor rat peripheral blood was beneficial; however, it did not significantly attenuate fibrosis in a rat model of pulmonary fibrosis. Remund et al[41] isolated splenocytes from donor mice, and after ex vivo treatment with 8-MOP and UVA irradiation, they reported that ECP led to a higher expression of IL-10, TGF-β, and interferon-γ in the lung tissue of treated animals, indicating a beneficial

effect in pulmonary fibrosis. Further studies in a lung transplant model, using apoptotic splenocytes from donor mice, showed that ECP reduces alloimmune responses and inhibits BOS by reprogramming alveolar macrophages to secrete decorin, an antagonist of TGF-β, thereby reducing TGF-β availability. In untreated animals, high TGF-β stimulates alveolar macrophages to produce CC chemokine ligand 2, which attracts a population of $CCR2^+$ monocytes and promotes BOS. This study identified alveolar macrophages as modulators of TGF-β networks and $CCR2^+$ monocytes recruitment and differentiation to the fibrotic process and BOS.[42,43]

Several studies suggest that ECP is effective in the management of associated side effects after kidney and liver transplantations.[44] However, these findings were limited to case studies and provided limited mechanistic inputs.[32-34,45] In addition, ECP cells from peripheral blood and splenocytes from previously transplanted donor mice significantly improved graft survival and reduced donor-specific antibodies in a full-mismatch rat model of kidney transplant. Moreover, ECP improved the survival of kidney graft.[46]

Perez et al[47] showed that ex vivo ECP-treated splenocytes from donor mice could inhibit rejection of skin allografts and prolong the survival by suppressing the immune response through the induction of Treg and other immunomodulatory mechanisms.[47] A recent study in skin allograft models found that ECP treatment, using splenocytes from donor mice exposed to 8-MOP and UVA irradiation ex vivo, induced the generation of regulatory $CD19^+$ B cells that express high levels of the anti-inflammatory cytokine IL-10. Infusion of ECP-treated cells prolonged survival of recipient skin allograft mice and was associated with an increase in the frequency of $CD19^+IL\text{-}10^+$ B cells, indicating that regulatory B cells are crucial for inducing tolerance and immunomodulatory effects.[48]

Altogether, these data indicate that ECP has a potential role in organ transplantation as immunomodulatory treatment, with no impact on graft survival and no risk of infection or significant side effects. Nevertheless, there is a lack of evidence and further understanding of organ types is mandatory to understand the mechanism of action of ECP, to support and develop new protocols and guidelines for future prospective clinical trials.

ECP IN AUTOIMMUNE DISEASES

AIDS are characterized by dysregulation of the immune system, immunodeficiency, and organ damage and are usually associated with high morbidity and mortality. AIDS encompass multiorgan, heterogenous clinical presentations, and the current treatments include prolonged systemic immunosuppression, which leads to side effects, increased risk of infection, or ineffective. ECP has emerged as a promising approach, with a high safety profile and fewer side effects.[4,49,50]

A study in a preclinical model of rheumatoid arthritis, isolated splenocytes from donor mice, and after 8-MOP and UVA irradiation ex vivo exposure, showed that ECP treatment resulted in a decrease of arthritis scores, with a decrease in the frequency of Th cells. However, ECP-treated cells isolated from a healthy donor had no impact on controlling arthritis progression compared with ECP-treated cells from arthritic mouse donors. These findings indicate that ECP can effectively manage arthritis, supporting the potential of ECP in the treatment of rheumatoid arthritis in human patients.[51]

Moreover, studies showed that ECP reduced the progression of arthritis in mice by alleviating the symptoms, inflammation, and preventing cartilage damage. ECP ex vivo treatment using splenocytes and venous blood isolated from mice donors and exposed to 8-MOP and UVA irradiation led to an increase of Treg and a decrease of Th17 cells and proinflammatory cytokines, such as IL-6 and IL-17, which resulted in a reduction of inflammation. In this study, monocytes were identified as important mediators of ECP, as depletion of monocytes worsened the symptoms and increased proinflammatory cytokines in arthritis models. ECP was proven to be effective in treating rheumatoid arthritis by modulating the immune system, promoting a shift from Th cells to Treg, and development of tolerogenic DCs.[52] Previous studies investigated the role of ECP on the prevention and management of type 1 diabetes in nonobese diabetic mice, by using splenocytes isolated from donor mice and treated with 8-MOP and UVA irradiation ex vivo. It was reported that ECP delayed the onset of diabetes, increased the expression of Treg and suppressed antigen-specific T-cell responses without causing immunosuppression, leading to the conclusion that ECP therapy provides a safe and effective approach for the prevention of type 1 diabetes.[53]

Preclinical murine model of dermatitis, provided important insights into the potential mechanisms of ECP, suggesting that apoptotic cells isolated from donor mice spleens and exposed to 8-MOP and UVA irradiation ex vivo, are associated with the induction of antigen-specific Treg that can suppress specific immune responses.[54] Most recently, an ex vivo murine model using mice splenocytes from donor mice previously sensitized for apoptosis induction, reported that the generation of IL-10 and induction of Treg are the key mechanisms by which ECP inhibits contact hypersensitivity. These 2 mechanisms may explain the clinical benefits of ECP and provide insights into how ECP is effective in treating diverse immune-mediated diseases.[55] A preclinical rat model of experimental allergic encephalomyelitis, used peripheral blood from donor rats to induce apoptosis of cells ex vivo, showed that ECP treatment reduced the incidence of relapses and was more effective after multiple treatments. Moreover, it was observed that ECP may be more effective at preventing relapses than reducing disease severity. In this study, it was shown that ECP may have beneficial effects in reducing relapses in autoimmune disorders.[56] However, another study in an ex vivo rat model showed that ECP treatment did not enhance immune system resistance in an animal model of experimental allergic encephalomyelitis, leading to the conclusion that intensive ECP protocols could have adverse effects, including the risk of relapse after discontinuing the treatment. This study emphasizes the need to establish new protocols for the use of ECP that would reduce the T-cell pathogenicity while preserving their immune effects.[57] Finally, a recent study, in an ex vivo murine model used peripheral blood mononuclear cells from donor mice, identified a possible mechanism of action of ECP in melanoma. ECP-induced differentiation of monocytes into DCs, and these DCs further process and present tumor antigens from apoptotic tumor cells. Moreover, it was demonstrated that T cells demonstrated a protective role against the tumor. This study identified important cellular contributors to the immunotherapeutic effect of ECP.[58]

In a recent study, Braun et al explored the therapeutic potential of ECP in managing immune-related adverse events induced by immune checkpoint inhibitors in cancer patients. Using different murine models of colitis, ECP was performed by isolating the splenocytes from previously treated mice, exposing the splenocytes ex vivo to 8-MOP and UVA irradiation, and subsequently reinfusing the apoptotic cells in the recipient mice. They demonstrated that ECP preserves antitumor immunity and identified the ECP-adiponectin axis as a key mediator of the ECP mechanism. They observed increased levels of adiponectin, which in turn reduced proinflammatory T cells in the colon and decreased the activation of tissue-resident memory T cells in the colon, showing that ECP immunosuppression is localized to the site of inflammation. Furthermore, they also conducted a phase 1b/2 clinical trial, where ECP showed low toxicity and safety, resulting in a 92% overall response rate with 100% remission of colitis.[59]

CHALLENGES AND FUTURE DIRECTIONS

Although ECP depicted notable success rates in the treatment of diverse immune-mediated diseases, such as CTCL and GvHD, the mechanism of action of ECP and its influence on disease pathophysiology remain unanswered. More preclinical studies are needed to identify the underlying molecular mechanism and biomarkers that would aid in extending this application to other disease entities. Additionally, unraveling the synergistic effect of ECP combined with other approved therapies could benefit the patients. Due to significant differences in the immune system between animal models and patients, standardized protocols across different models that enhance their reproducibility and translation potential are needed (Figure 1).

A relevant animal model of ECP should reflect the type of disease studied, to mimic the immunological context and key aspects of the human clinical scenario. The recommended model for ECP should involve the use of donor-derived splenocytes or peripheral blood mononuclear cells from syngeneic healthy controls or diseased animals. Following red blood cell lysis, leukocytes should be incubated with 8-MOP and exposed to UVA light. After UVA exposure, cells should be washed thoroughly and injected intravenously into recipient animals. According to the previous animal studies stated here, the typical dose ranges from 10 to 20×10^6 cells per cycle; however, this may change depending on the model. The number and frequency of ECP treatments should be adapted to each disease model to best resemble the clinical setting.

Further research using preclinical models is important to assess the impact of different ECP treatment approaches on efficacy and outcomes of the therapy, the combination of ECP with other therapies, and to standardize protocols across different models.

CONCLUSIONS

In summary, ECP has been proven to be a successful therapeutic approach in the treatment of immune-mediated disorders, with no significant side effects, high safety profile, and feasibility. In recent years, promising results have been published, establishing ECP as an immunomodulatory therapy with a high potential for inducing immune-tolerance, most likely through maturation of DCs, reduction of proinflammatory molecules, upregulation of anti-inflammatory cytokines, and increase of B and regulatory T cells. Further research is needed to address remaining unanswered questions, specifically to identify the underlying therapeutic mechanisms of ECP and to predict the type of response and associated factors in different diseases. In this review, we highlighted the importance of preclinical animal models to study ECP and its translation potential to the human setting. Animal studies that can be extrapolated to early prospective controlled clinical trials are necessary and crucial to better determine the role of ECP as a potential standard therapy for the treatment of other immune-mediated conditions.

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