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# Potential Mechanisms of Photopheresis in Hematopoietic Stem Cell Transplantation

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## ABSTRACT

***Immune tolerance*** **describes specific unresponsiveness to antigens. In clinical situations such as graft-versus-host disease it may be useful to capitalize on these pre-existing tolerance mechanisms to treat patients. Extracorporeal photopheresis is a pheresis treatment whereby the approximately $5 \times 10^9$ leukocytes are treated with a photoactivatable compound (8-methoxypsoralen) and UVA light, and immediately returned to the patient in a closed-loop, patient-connected system. This therapy induces apoptosis of virtually all the treated leukocytes. There is growing evidence that infusion of apoptotic cells may trigger certain tolerance mechanisms and, thus, be of therapeutic use in graft-versus-host disease. These apoptotic cells are taken up by phagocytes (antigen-presenting cells) in the body of the patient. Apoptotic cell engagement has been reported to induce several changes and functional activities in the engulfing antigen-presenting cell. These antigen-presenting cells: (1) decrease production of proinflammatory cytokines; (2) increase production of anti-inflammatory cytokines; (3) lower ability to stimulate T-cell responses; (4) delete CD8 T effector cells; and (5) induce regulatory T cells. Any and all of these mechanisms could explain the noted effect in graft-versus-host disease. It is still unclear which one or ones are truly responsible. Ongoing studies in animals and human trials will ultimately unravel these details.**


## KEY WORDS

Photopheresis • Graft versus host disease • Regulatory T cells • Immune tolerance

## INTRODUCTION

The immune system is a collection of organs, cells, and molecules that work in concert to protect higher-order animals from a wide diversity of pathogens such as bacteria, viruses, and parasites. A major component in the initiation of immune responses is the requirement for "danger" signals derived from injured tissue and pathogens [1]. Ways of minimizing nonfunctional or autoreactive activities also evolved to prevent destruction of healthy tissue by immune overreaction. Central mechanisms of tolerance, which occur in the bone marrow and thymus, lead to deletion of autoreactive B and T cells whereas peripheral mechanisms of tolerance can lead to T-cell skewing (e.g. T-helper 1, T-helper 2), suppression (e.g. anti-inflammatory cytokines, regulatory cells), and peripheral deletion (e.g. activation-induced cell death, veto cells). In the majority of cases these tolerance mechanisms help maintain balance between sufficient immunity to fight pathogens and overreaction to self (Figure 1). However, these mechanisms of tolerance are usually not sufficient to overcome complications caused by allogeneic hematopoietic stem cell transplantation.

Graft-versus-host disease (GVHD) is a serious complication of hematopoietic stem cell transplantation leading to significant morbidity and mortality. Current treatment (e.g. steroids, immunosuppressants, T-cell depletion) is based primarily on inhibition of the effector arm of the immune system responds believed to be responsible for the development of GVHD. Although these therapies have decreased the incidence and severity of GVHD, toxic side effects have limited their use. To expand the use of hematopoietic stem cell transplantation, less toxic and more effective therapies for GVHD need to be developed. Recent reports of using tolerance-boosting mechanisms such as adding regulatory T cells or tolerogenic antigen-presenting cells (APCs) have produced promising results in animal models [2-5]. This brief review will discuss one such tolerance-inducing therapy: the

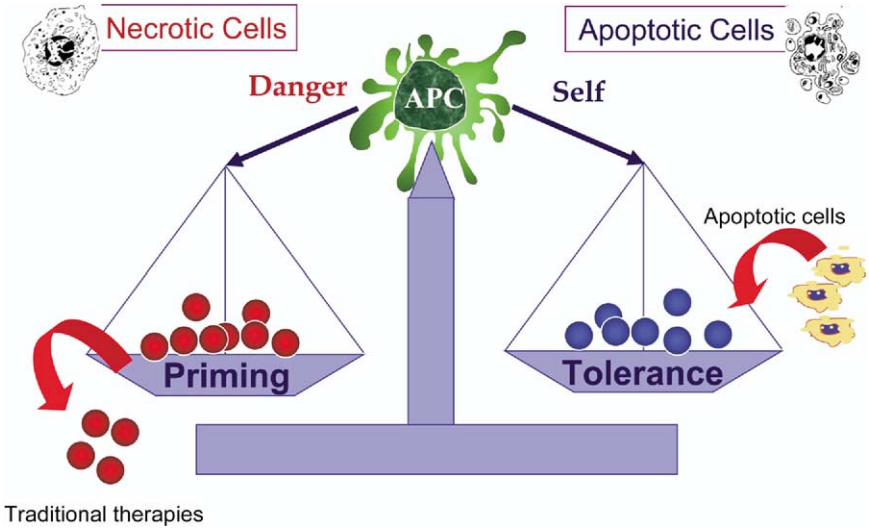


**Figure 1.** The immune system is a careful balance between priming effector function to fight pathogens and tolerance to inhibit overzealous immune responses. Traditional therapies act primarily via inhibition of the effector arm of the immune response. Therapies such as ECP may add clinical value by targeting the tolerance side of the immune balance, offering a novel way to treat disease and possibly synergize with traditional therapies.

infusion of apoptotic cells (ACs) generated by extracorporeal photopheresis (ECP).

## EXTRACORPOREAL PHOTOPHERESIS

Extracorporeal photopheresis has been used clinically for almost 20 years as an approved therapy for the palliative treatment of cutaneous T-cell lymphoma (CTCL). ECP instruments reside in many major academic institutions in Europe and North America. This therapy is an apheresis-based process whereby approximately $5 \times 10^9$ autologous leukocytes are treated with a photoactivatible compound, 8-methoxypsoralen, followed by exposure to ~1.5 J/cm$^2$ of Ultraviolet A light and reinfused. This occurs in a point-of-care, patient-connected, sterile, closed-loop system. As a result of ECPs demonstrated efficacy and safety profile in CTCL, physicians applied ECP treatment to a wide variety of diseases that respond to immunosuppression [6] including GVHD [7-9]. The history of ECPs development for CTCL is well documented [10]. During the last two decades several mechanisms have been proposed as the mode of action of ECP. Unfortunately, none are completely satisfying from a scientific standpoint, especially in the absence of convincing data. From the beginning it was clear that the therapeutic effect of ECP could not be explained solely by destruction of malignant cells, because only a small proportion of the circulating pathogenic T cells are treated during an ECP treatment cycle. This led to the hypothesis that a systemic and specific immune-mediated antitumor activity may be involved in the clinical activity of ECP [11]. The possibility that ECP induces a generalized immunosuppression is unlikely because patients with CTCL undergoing long-term ECP therapy have not demonstrated a higher risk of developing infections or malignancies [12] and respond normally to both novel and recall antigens [13]. This review summarizes the recent work concerning the mechanism of action of AC infusion.

## IMMUNE REGULATION BY ECP: AC CLEARANCE

ECP induces the cell death of most of the treated leukocytes within 24 to 48 hours [14-16]. What is the consequence of infusing patients with a bolus of ACs?

It has been known since the time of Metchnicoff that cellular debris is removed from complex organisms by phagocytes. Many cell types in the body can remove apoptotic and cellular debris from tissues; however, the professional phagocyte, or APC, has a higher capacity to do so. The recognition of ACs occurs by a series of evolutionarily conserved, AC-associated molecular-pattern receptors on APCs that recognize and bind corresponding AC-associated molecular patterns found on ACs. These receptors recognize ligands such as phosphotidyl serine and oxidized lipids found on ACs. The full description of the receptor systems involved in AC clearance is beyond the scope of this article and has been reviewed in detail [17,18]. The vast majority of ECP-treated cells are retained in the spleen and liver after infusion where they are presumably engulfed by APCs [14,19].

Multiple laboratories using a variety of methods and models both in vitro and in vivo have now reported that AC clearance by APCs regulates immune responses [17]. This immune modulation appears to