Extracorporeal Photopheresis

Past, Present and future

ESSAY

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فصل مكونات الدم خارج الجسم وتعريضها للأشعة الضوئية في الماضي والحاضر والمستقبل

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Summary

Extracorporeal photopheresis (ECP) is defined as an immuno-modulatory technique that involves removal of peripheral blood, separation of the buffy coat, and photoactivation with a photosensitizer (8-MOP) and ultraviolet A irradiation before re-infusion of cells. It was developed more than 20 years ago by Edleson to treat erythrodermic T cell lymphoma (CTCL).

Most of studies revealed that the mechanism of action of ECP is to induce leucocyte apoptosis, followed by their engulfment by macrophages or other antigen presenting cells, such as immature dendiritic cells in an anti inflammatory cytokin environment. The anti inflammatory cytokine secretion pattern, with a switch from TH1to TH2 for CD4+ lymphocytes, and the engulfment by immature cells without co-stimulatory molecules induces anergy, by deleting effector T- cells that responded to the presented antigens. An increase in regulatory T- cells is also induced after ECP and may contribute to allograft acceptance by the recipient.

However other studies suggest that mechanism of ECP also involves the recruitment and involvement of additional immune cells. Till now it is clear ECP, both activates tumor immunity

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List of abbreviations

Abbrev	*Meaning*
8-MOP	*8-methoxypsoralen*
aGVHD	*acute graft versus host disease*
AMR	*Antibody mediated rejection*
Apaf-1	*Apoptotic protease activating factor 1*
APCs	*Antigen presenting cells*
Apo2l	*Apoptosis ligand 2*
Bad	*Bcl_2 – associated death prompter*
Bak	*Bcl_2 – homologous antagonist killer*
Bax	*Bcl_2 – associated x protein*
BCL- XL	*B cell leukemia X long*
BCL	*B cell leukemia 2*
BH3	*BCL homology*
Bid	*BH_3 domain only death against protein*
Bim	*Bcl_2 interacting mediator*
BIRs	*baculoviral repeats*
Bmf	*Bcl_2 modifying factor*
BRUCE	*BIR repeat containing ubiquitin conjugating Enzyme system*
BOS	*Bronchiolitis obliterans syndrome*
Caspases	*cysteine aspartic acid Specific proteases*
CD4	*Cluster of differentiation*
CELLEXTM	*cell extensible access method*
c-FLIP	*c-FLICE inhibitory protein*

cGVHD	*chronic graft versus host disease*
CHOP	*Cyclo-phosphamide doxorubicin vincristine prednisone*
cIAP	*Cellular IAP*
CMV	*Cytomegalo virus*
CR	*Complete response*
CTA	*Composite tissue allotransplantation*
CTCL	*Cutaneous T cell lymphoma*
DCs	*Dendiritic cells*
DDCs	*Dermal dendiritic cells*
DISC	*Death inducing signaling complex*
DNA	*Deoxyribonucleic acid.*
DR	*Death receptor*
ECP	*Extracorporeal photopheresis*
ECV	*Extracorporeal volume*
FADD	*Fas-associated death domain*
Fas L	*Fas ligand*
FDA	*Food and Drug Administration.*
FoxP3	*Fork head box P3*
GAS6	*Growth arrest specific 6*
GMP	*Good manufacturing practice*
HCV	*Hepatitis C virus*
HLA	*Human leukocyte antigen*
HMGB1	*High mobility group box 1*
HSP	*Heat shock protein*
HSV1	*Herpes simplex virus type1*

IAPs	*Inhibitors of apoptosis proteins*
IgE	*Immunoglobulin E*
ILP	*IAP like protein*
IL10	*Interleukin 10*
INF	*Interferon*
IRF4	*Interferon regulatory factor 4*
LCs	*Langerhans cells*
mDCs	*Myeloid dendiritic cells*
MF	*Mycosis fungoides*
MFG	*Mobile fat globulin*
MLIAP	*Melanoma IAP*
MLR	*Mixed lymphocyte reaction*
NFκB	*Nuclear factor kappa B.*
NIH	*National institutes of health*
NOXA	*Naphthoxy acetic acid*
PAF	*Platelet activating factor*
PBMC	*peripheral blood mononuclear cells*
PCD	*programmed cell death*
pDCs	*plasmacytoid dendiritic cells*
PF	*Pemphigus foliaceus*
PI	*Propidium iodine*
Pre-PCD	*Pre programmed cell death*
PRP	*Pityriasis rubra pilaris*
PS	*Phosphatidylserine*
PUMA	*P_{53} Upregulated modulator of apoptosis*
PUVA	*Psoralen ultraviolet A irradiation*

PV	*Pemphigus vulgaris*
RBCs	*Red blood cells*
RCTs	*Randomized controlled trials*
SLE	*Systemic lupus erythematosus*
SMAC	*Second mitochondria derived activator of caspases.*
SS	*Se'zary syndrome*
Sulfo Lac Nac (slan)	*sulfo N acetyllactosamine*
TAM	*Tyr 3, axl, mer*
TBV	*Total blood volume*
TGF-B1	*Transforming growth factor B1*
Th	*T-helper*
TIM4	*T cell immunoglobulin mucin 4*
TLR	*Toll-like receptor*
TNF	*Tumor necrosis factor*
TPE	*Therapeutic plasma exchange*
TRAIL	*Tumor necrosis factor related apoptosis inducing ligand*
UVA	*Ultraviolet A*
UVADEX	*Brand name of methoxsalen*
UVAR –XTS	*Ultra violet Auto blood Radiation xytex tissue services.*
UVAR	*Ultraviolet A radiation*
UVB	*Ultraviolet B*
WBCs	*White blood cells*
XIAP	*X-linked inhibitor of apoptosis protein*

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Introduction

Extracorporeal photopheresis (ECP) also known as extracorporeal photochemotherapy, it is an immunomodulatory technique based on pheresis of light sensitive cells. It is consists of exposure of peripheral blood mononuclear cells (PBMC), collected by aphaeresis, to ultraviolet A light in the presence of the DNA-intercalating agent 8-methoxypsoralen. The treated cells undergo apoptosis and are readily reinjected into the patient, leading to antigen-specific immunomudulation ***(Aubin and Mousson, 2004)***. This technique is reported by Edleson et al in 1987 to treat erythrodermic cutaneous T cell lymphoma ***(Edleson et al., 1987)***

However it has been reported later on to be effective for a wide variety of disease such as acute graft versus host disease (GVHD), solid organ transplant rejection, crohn's disease, scleroderma, diabetes mellitus, multiple sclerosis, systemic sclerosis, bullous pemphigoid, pemphigus vulgaris, pityriasis rubra pilari, nephrogenic systemic fibrosis. Pemphigus foliaceus, systemic lupus erythromatosis, psoriatic arthritis, psoriasis vulgaris, rheumatoid arthritis, atopic dermatitis, juvenile dermatomyositis, scleromyxedema, and most widely in steroid refractory chronic graft versus host disease (cGVHD).***(Maeda, 2009; Chiesa-Fuxench and Gonzalez Chavez, 2010)***

Further more, the use of ECP in some of these conditions may allow a significant reduction in the use of systemic steroid and other immunosuppressant , reducing long term morbidity, and mortality ***(Knobler et al., 2009)***

The advantage of the photopheresis treatment is the low frequency of side effects such as vasovagal syncope or infection, the disadvantages however are the practical efforts required and the high treatment cost ***(Meada, 2009)***

Extracorporeal photopheresis is performed using the UVAR XTS Photopheresis System developed by Therakos, the process is performed through one intravenous access port and has 3 basic stages: (1) leukapheresis, (2) photoactivation, and (3) reinfusion. The process takes 3-4 hours to complete.

- One 16-gauge peripheral intravenous line or central venous access is established in the patient.
- Blood (225 mL) is passed through 3 cycles of leukapheresis, or 125 mL of blood is passed through 6 cycles, depending on the patient's hematocrit value and body size. At the end of each leukapheresis cycle, the red blood cells and plasma are returned to the patient.
- The collected WBCs (including approximately 5% of the peripheral blood mononuclear cells) are mixed with heparin, saline, and 8-methoxypsoralen (8-MOP), which intercalates into the DNA of the lymphocytes upon

exposure to UVA light and makes them more susceptible to apoptosis when exposed to UVA radiation.

- The mixture is passed as a 1-mm film through a sterile cassette surrounded by UVA bulbs for 180 minutes, resulting in an average UVA exposure of 2 J/cm^2 per lymphocyte.
- The treated WBC mixture is returned to the patient. ***(Camile et al., 2011)***

It has been suggested that ECP therapy, unlike other immunosuppressive regimens, does not cause global immunosuppression, but induces immune tolerance. Recent clinical and animal studies demonstrate that ECP therapy induces antigen-specific regulatory T cells, including CD4, CD25, FoxP3, T cells and IL-10-producing Tr1 cells, that may arise secondarily to the induction of tolerogenic antigen-presenting cells (APCs) by infusion of apoptotic cells. It has also been suggested that ECP therapy may induce IL-10-producing regulatory B cells and regulatory CD8 T cells. Finally, several recent studies, which examined the cellular elements involved in the uptake of apoptotic cells, demonstrated that apoptotic cells modulate APCs through binding to specific receptors, particularly TAM receptors that provide inhibitory signals that block APC activation**.** ***(Chang-Qing Xia et al., 2009)***