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Autoimmunity Reviews 1 (2002) 154–161

AUTOIMMUNITY REVIEWS

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The clearance of apoptotic cells: implications for autoimmunity

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Received 11 February 2002; accepted 11 March 2002

Abstract

Apoptosis has been clearly characterised by the ability to limit the activation of inflammatory responses through the disposal of the apoptotic cell by rapid uptake by phagocytes. The exposure of phosphatidylserine deriving from the loss of plasma lipid asymmetry is the early membrane signal which alerts the phagocyte about the imminent apoptotic death of the cell. Also modifications of membrane carbohydrate groups on apoptotic cells contribute to phagocyte recognition. Soluble proteins such as C1q, mannose-binding lectin, surfactant proteins A and D, C-reactive protein, C3bi, β2-glycoprotein I and growth arrest specific gene-6 bind to apoptotic cells and act as 'opsonins' thus favouring their clearance. A redundant and promiscuous system of receptors including integrins, *scavenger receptors*, CR3 and CR4, calreticulin, CD14 and Mer receptor ensures an efficient and rapid uptake of apoptotic cells. In animal models and in human pathology, single genetic defects of molecules involved in apoptotic cell clearance seem to be the main determinant in the development of autoimmunity. The uptake of apoptotic cells by phagocytes provides an immunomodulatory effect in that it triggers the release of anti-inflammatory cytokines, inhibits the production of inflammatory cytokines and leads to T cell tolerance. Impaired clearance of apoptotic cells or the presence of 'danger' signals may modify the balance between tolerance induction and activation of T cells leading to an effective autoimmune response.

Keywords: Apoptosis; Phospholipid; Phosphatidylserine

1. Introduction

The control of cell number plays a critical role in organ development and in maintaining the integrity of the structural elements and functions in highly integrated systems. Balance between cell proliferation and cell death represents the central aspect of this regulation [1]. The observation that the end of the life of a cell may occur through a variety of death distinct from necrosis, named apoptosis, offered further support to the concept that death is not less important than proliferation in regulation of cell homeostasis [2]. While necrosis is characterised by a disorganised response of the cell to the damage of an external harmful factor and by the release of substances with inflammatory effects, apoptosis has been clearly marked by the ability to limit the activation of inflammatory responses through the rapid disposal of the apoptotic cell itself which is then not allowed to release its dangerous content in the environment.

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1568-9972/02/$ - see front matter
PII: S1568-9972(02)00032-0

The involvement of a defect of apoptosis in the generation of autoimmune phenomena may be twofold. Firstly, it may affect the lymphocyte switch-off system and lead to broken immunological tolerance with survival of B and T clones involved in autoimmune response. Secondly, it may slow down cell apoptosis and/or induce exposure of abnormal amount of apoptosis-related antigens thus favouring the immune response against them [3]. A number of investigations ranging from animal models to human pathology lend support to the view that apoptosis plays a significant role in the development of autoimmunity [4]. In this respect, single genetic defects of molecules regulating apoptosis have been isolated in experimental models and their human counterparts often identified although the relative importance of these defects in the development of most of the naturally occurring human autoimmune diseases is uncertain as yet [5].

As a apoptosis is a cell suicide, i.e. a finely regulated cell event directed by the cells itself in response to a specific 'external milieu', once the cell is dead it requires an efficient 'assistance' to be disposed as rapidly as possible and in the less harmful way for the surrounding environment. Thus, a cell undergoing apoptosis displays specific signals at very early stages of this process to warn specialised cells able to recognize the dying cell and remove it. Since specific genetic defects of molecules involved in these mechanisms have been closely related to the development of autoimmunity, there were a variety of studies which have begun to explore links between abnormalities in the clearance of apoptotic cells and autoimmune phenomena. In this review, we analyse briefly the background to what is known about the clearance of apoptotic cells and focus on the increasing likelihood that abnormalities in this process are a contributory factor to the generation of human autoimmunity.

2. Apoptotic cell surface determinants

It is widely accepted that the sudden loss of normal phospholipid (PL) distribution and the consequent exposure of phosphatidylserine (PS) is an early and quite specific sign of cell commitment to apoptosis which is absolutely required for recognition and engulfment by phagocytes to occur [6]. Under normal circumstances, the lipid composition of the two leaflets of plasma membrane differs. The amino-PL principally PS and phosphatidylethanolamine are mainly localized in the cytoplasmic leaflet, while the outer leaflet comprises mostly choline-PL, essentially sphingomyeline and phosphatidylcholine. Thus, lipid asymmetry observed in quiescent cells is mainly maintained by a lipid transport machinery formed by two independent systems [7]. One, named *translocase*, which is believed to be a 120-kDa Mg^{2+}-dependent ATPase (ATPase II) with four distinct isoforms of this protein identified, shuttles all the PL inward [8]. The other, named *floppase*, promotes the outer movements of both amino- and choline-PL [9]. However, under particular conditions of cell activation, a process referred to as *lipid scrambling* modifies the lipid asymmetry. This process is due to a distinct transporter named *scramblase* partially identified as a protein regulated by intracellular calcium and by phosphorilation by protein kinase Cδ. The *scramblase* promotes a bidirectional movement which involves all major PL classes moving at comparable rates. During apoptosis, *lipid scrambling* occurs but simultaneously the activity of the *translocase* is downregulated mainly by the elevation of Ca^{2+} intracellular levels [10].

Also the oxidation of PS in the course of apoptosis may alter its ability to be transported by the *translocase* [11]. All this perturbation of PL membrane kinetics results in the exposure of PS, a signal which warns the surrounding phagocyte about the imminent apoptotic death of the cell. Again the oxidation of PL which occurs during apoptosis is a critical event resulting in the generation of a recognition ligand for the scavenger receptor of macrophages [12]. The recent description of the exposure of cardiolipin, a molecule normally confined to mitochondria [13], on plasma membrane as an apoptosis-related event, raises the intriguing hypothesis that also this PL in its oxidised form contributes to the interaction with phagocytes. This view has been expanded by the observation that the activity of the ABC1, a transporter which usually shuttles cholesterol and PL from cells to protein acceptor, facilitates *lipid*

scrambling. It is of interest to observe that the activity promoted by ABC1 is also involved in the ability of the macrophage to engulf the apoptotic cell [14].

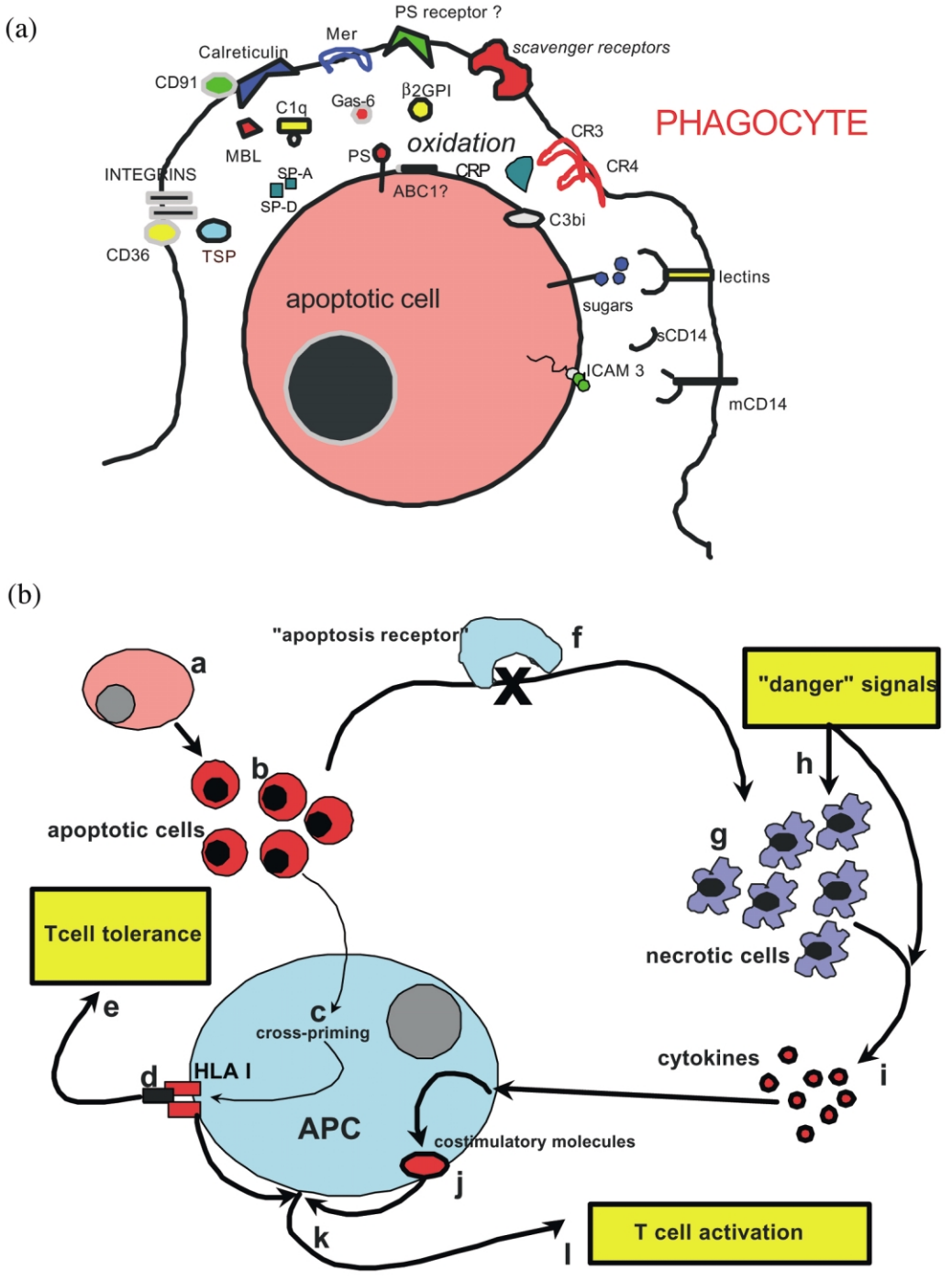
The alteration of carbohydrate groups on apoptotic cells represents another signal for the lectin-like molecules expressed on macrophage surface [15]. It has also been suggested that apoptosis may result in the exposure of carbohydrate groups on ICAM3 which can then engage CD14 in its capacity as a lectin [16]. Following the loss of PL asymmetry, several soluble proteins generally referred to as *collectins* display the property of binding to apoptotic cells in aggregated patterns. Among these molecules, a primary role is attributed to the first component of the complement C1q which binds to apoptotic cells in an antibody-independent way [17], to the mannose-binding lectin (MBL) [18] and to the surfactant proteins A and D (SP-A, SP-D) [19]. It has also been shown that apoptotic cells fix complement leading to the deposition of C3bi on their surface and this capacity is likely to be involved in their clearance [20].

A revisited role of C-reactive protein (CRP) would suggest that this protein, traditionally regarded as a marker of systemic inflammation, is in reality an efficient system to dispose apoptotic cells. Indeed, CRP binds to apoptotic cells in a Ca^{2+}-dependent manner, enhances the classical pattern of complement activation but prevents the assembly of the terminal complement components on the cells [21]. β2-glycoprotein I (β2-GPI), a PL-binding plasma protein which is considered one of the main autoantigens in the Antiphospholipid Syndrome, has been shown to bind to apoptotic cells and to be involved in the interaction with phagocytes and the clearance of apoptotic cells at least when targeted by specific autoantibodies [22]. Growth arrest specific gene-6 (Gas-6) a ligand of receptor tyrosine kinase Axl is known to promote cell proliferation and prevent cell death. Besides this function, recent experimental evidence suggests that this molecule also specifically binds to PS and thereby links Axl-expressing cells to PS-coated surfaces. Thus, it is likely that Gas-6 helps phagocytes recognize cells with PS exposed on their surface [23] (Fig. 1A).

3. Apoptotic cell receptors

Although tissue macrophages are the most efficient at phagocytosis of apoptotic cells, other cell types such as hepatocytes, endothelial cells, glomerular mesangial cells and fibroblasts also take part in their removal. It has been shown that a sialoglycoprotein receptor/mannose receptor and a mannose-fucose receptor are responsible for phagocyte recognition of changes in the surface carbohydrates on apoptotic cells [15]. The integrin $a_v b_3$(vitronectin receptor) cooperates with the macrophage cell receptor CD36 to the phagocytosis of apoptotic cells inasmuch as this molecule is able to bind to a sequence of three aminoacids. Thrombospondin, a protein bearing this sequence acts as a molecular bridge in that is also able to bind to CD36 on macrophage surface [24]. Several other *scavenger receptors* including the CD36 analog SR-BI, scavenger receptor A, the oxLDL receptor CD68/macrosialin and LOX1 have been involved in this mechanism [25]. Although most of these receptors show some degree of interaction with PS especially in its oxidized form which enables them to bind to oxidized lipoproteins, the real nature of a more specific 'PS-receptor' remains unclear given that many inhibition experiments would suggest additional complexity. In this concern, the role potentially played by β2-GPI in facilitating apoptotic cell uptake by phagocytes has been outlined. Following previous studies showing that this plasma glycoprotein is able to bind to apoptotic cells after the exposure of PS [26] and that this interaction apparently leads to the exposure of a unique epitope [27], experimental data indicate that human macrophages use a specific receptor to interact with β2-GPI only after the binding of this glycoprotein to its lipid ligand [28].

The activation of the alternative complement pathway and the subsequent participation of complement to apoptotic cell clearance requires receptors such as CR3 (CD11b/CD18) and CR4 (CD11c/CD18) [20]. The contribution of C1q to these mechanisms is unique and of pivotal importance in that requires a specific mechanism of


(a)
PS receptor ?
Mer
Calreticulin
scavenger receptors
CD91
β2GPI
Gas-6
C1q
PHAGOCYTE
oxidation
CR3
MBL
PS
CR4
INTEGRINS
SP-A
CRP
SP-D
ABC1?
C3bi
CD36
TSP
apoptotic cell
lectins
sugars
sCD14
ICAM 3
mCD14
(b)
"apoptosis receptor"
f
a
"danger" signals
h
b
apoptotic cells
g
Tcell tolerance
necrotic cells
e
c
cross-priming
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i
d
HLA I
APC
costimulatory molecules
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T cell activation
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Fig. 1.

interaction and engulfment by the phagocytes. Quite interestingly, this property is shared with MBL, another member of *collectin* family and implies that these two molecules bind through a collagenous tail to a multifunctional receptor, calreticulin, which in turns is bound to the endocytic receptor protein CD91 [29].

mCD14 is a plasma membrane-anchored molecule on the surface of macrophages where it is able to recognize lipopolysaccharide (LPS), an interaction which normally activates a transductional signal leading to cell activation and an inflammatory response to microorganisms. However, this molecule also acts as a receptor for recognition and engulfment of apoptotic cells. It is still a matter of debate whether mCD14 expressed by monocytes, granulocytes and fibroblasts or the soluble form of this molecule (sCD14) exerts a similar function. Anyway, mCD14 molecule provides a remarkable example of how a single molecule may be involved in both the non-inflammatory clearance of apoptotic cells and the highly inflammatory response to a bacterial product such as LPS. The engagement of two distinct partner-receptors on membrane surface and the activation of two distinct transductional pathways is the most likely explanation for this phenomenon [16]. The Axl/Mer/Tyro3 receptor tyrosine kinase family comprises Mer a receptor which recognizes the product of Gas-6 gene, a soluble PS-binding protein [30] (Fig. 1A).

4. The clearance of dead cells regulates immune homeostasis and response

The coexistence of such an articulated and complex system of membrane determinants, receptors and 'opsonins' would suggest that the efficiency of uptake and clearance of apoptotic cells is guaranteed by high levels of redundancy. However, redundancy is accompanied by hierarchy in that the different molecules involved in these mechanisms do not apparently have the same relevance. As suggested by the study of the naturally occurring human genetic defects and animal models, while single genetic defects of some molecules lead to the development of autoimmunity in its clinical and/or serological expressions, the lack of other molecules does not significantly affect the immune response or does affect it only in the presence of a genetically-defined autoimmune-prone background.

In this concern, two examples, one from human pathology, the other from animal models are remarkable as they show that a single genetic defect of a molecule involved in apoptotic cell clearance seems to be the main determinant in the development of autoimmunity. In human pathology, the complete lack of C1q, as observed in the homozygous form of this genetic defect, is per se sufficient to the development of a form of cutaneous lupus [31]. In an animal model, named Mer^{kd} mouse which brings the cytoplasmic truncation of the recently identified Mer receptor, the

Fig. 1. (A) The cell displays a complex and articulated membrane signal system to warn the phagocyte about its imminent apoptotic death. These signals include the flipping out of phosphatidylserine (PS) on the outer surface of plasma membrane as a result of the loss of lipid asymmetry and the cooperation of ABC-1 transporter, changes of carbohydrate groups, modification of ICAM3 molecule. *Collectins*, a groups of soluble proteins including complement factor C1q, mannose-binding lectin (MBL) and surfactant proteins A and D (SP-A, SP-D), C-reactive protein (CRP), C3bi (split fragment of complement C3), β2-glycoprotein I (β2-GPI), the product of growth arrest specific gene-6 (Gas-6), bind to apoptotic cells and act as 'opsonins'. A redundant and promiscuous set of receptors expressed by phagocytes including integrins acting with the cooperation of thrombospondin (TSP), *scavenger receptors*, a 'PS-receptor', CR3 and CR4 (complement receptors), calreticulin, mCD14 and Mer, carry out adhesion and engulfment of the apoptotic cell. (B) Under normal conditions (a) when a cell undergoes apoptosis (b) the uptake by antigen-presenting-cells (APC) results in *cross-priming* (c) with peptides associated with HLA class I molecules (d). In the absence of costimulatory signals, the interaction with T cell induces tolerance (e). If apoptotic cell clearance is impaired (f) apoptotic cells will turn into secondary necrosis (g) with the possible contribution of other 'danger' signals such as a viral infection (h). The production of inflammatory cytokines will ensues (i). The inflammatory stimula will induce APC to express costimulatory molecules (j). If a certain rate of apoptosis coexists, the HLA class I-associated presentation of apoptosis-derived peptides and the expression of enough costimulation (k) will lead to broken immunological tolerance with T cell activation and response (l).

development of autoimmune phenomena have been reported [30]. It is reasonable to assume that the pathogenic mechanism underlying these two models is based on the increased availability of potentially immunogenic material to the immune response. These observations raise the fundamental question as to whether the apoptotic cells are per se immunogenic. Immunization experiments provided evidence that syngenic apoptotic cells are more immunogenic than syngenic viable or necrotic cells [32]. However, in stark contrast with this observation, it has been shown that the binding of PS-exposing apoptotic cells to the 'PS-receptor' triggers the release of anti-inflammatory cytokines such as TGFβ and IL10 and inhibits the production of proinflammatory cytokines such as TNFα [33].

In addition, also dendritic cells phagocytose apoptotic cells although not as efficiently as macrophages. Although data on whether dendritic cells can mature and present antigens from apoptotic cells are conflicting, most of investigations clearly indicate that uptake of apoptotic cells does not lead to dendritic cell maturation and effective T cell stimulation. Dendritic cells process protein antigens from apoptotic cells and shuttle peptides to the class I MHC molecules which are then exposed on the surface of the cell to be recognized by specific T cells. This mechanism, named *cross-priming*, is of primary importance since in normal conditions the only peptides that are displayed on class I MHC molecules are those deriving from the inner cellular route such as self-antigens. Thus, peptides presented through *cross-priming* on class I MHC will not be capable of inducing T stimulation because of lack of costimulation [34]. On the contrary, the uptake of necrotic cells especially tumor cells results not only in presentation of peptides but also in the expression of costimulatory molecules by dendritic cell [35]. It is reasonable to postulate that this mechanism can easily be perturbated when a 'danger' signal, such a viral infection, occurs. In this case, apoptosis-derived antigens will follow the same intracellular route as viral antigens leading to class I MHC presentation. Which is more important is that the viral infection per se or if associated to a certain rate of cell necrosis will generate, through the production of cytokines such as INFγ, enough costimulatory stimula to provide an effective response to both viral and apoptosis-derived antigens. In this setting, the coexpression of viral and self-antigens in the apoptotic bodies raises the intriguing hypothesis that apoptosis may play a crucial role in the molecular mimicry between viral and self-antigens [36]. This observation reinforces the concept that uptake and processing of 'necrotic' and/or 'apoptotic' antigens may be one of the critical event modulating the balance between immune homeostasis and inflammation, and activation versus tolerance induction of T cells [37].

If the normal mechanism of apoptotic cell clearance is impaired or overloaded with an excessive rate of apoptosis or affected by abnormal production of cytokines such as in the course of a viral infection, apoptotic cells will turn into secondary necrosis which may imply a clearance through a different inflammatory and more immunogenic route (Fig. 1B). Once the immune response is triggered specific autoantibodies against molecules involved in the clearance of apoptotic cells such as β2-GPI antibodies may shift the physiological apoptotic receptor-mediated to an antibody/Fc receptor-mediated clearance with profound effects on dendritic cell maturation and immune response [38]. New avenues of apoptosis research have opened up as the relationship between the defect of clearance of apoptotic cells and autoimmune diseases has come under increasing scrutiny. Advances in this field should be rapid and exciting from this point on.

Acknowledgments

The financial support of Telethon – Italy (Grant no. E.1170), MURST ex 60%, and MURST 40%, is gratefully acknowledged.

Take-home messages

- The exposure of PS resulting from the perturbation of plasma lipid asymmetry is the early membrane signal which warns the phagocyte about the imminent apoptotic death of the cell.
- Changes of membrane carbohydrate groups are apoptosis-related events which contribute to phagocyte recognition.

- Different groups of soluble proteins including *collectins* (C1q, MBL, SP-A and SP-D) CRP, C3bi, β2-GPI and Gas-6 bind to apoptotic cells and act as 'opsonins' thus favouring their clearance.
- A redundant and promiscuous system of receptors including integrins, *scavenger receptors*, CR3 and CR4, calreticulin, CD14 and Mer receptor ensures rapid and efficient disposal of apoptotic cells.
- These receptors display multiligand properties and/or the property to discriminate between different ligand through the engagement of partner receptors and the activation of distinct transductional pathway.
- Single genetic defects of molecules involved in apoptotic cell clearance are main determinant in the development of autoimmunity.
- The phagocytosis of apoptotic cells by phagocytes triggers the release of anti-inflammatory cytokines and inhibits the production of inflammatory cytokines.
- Although apoptotic cells are immunogenic in experimental models, uptake of apoptotic cells by dendritic cells does not lead to dendritic cell maturation and effective T cell stimulation.
- Impaired clearance of apoptotic cells or the presence of 'danger' signals may modify the balance between tolerance induction and activation of T cells.

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The World of Autoimmunity; Literature Synopsis

Plasmapheresis versus cyclophosphamide in lupus nephritis

Lupus nephritis represents one of the major clinical manifestations of SLE. Intravenous cyclophosphamide in combination with steroids is considered a standard therapy for proliferative lupus nephritis. In a recent study, Nakamura et al. (Clin Nephrol 2002;57:108) examined whether reduction of autoantibodies and circulating immune complexes by double-filtration plasmapheresis (DFPP) could be more beneficial in treating patients with diffuse proliferative Lupus nephritis. In their study, 10 patients were treated with intravenous cyclophosphamide (0.75–1.0 g/m^2 body surface area) pulse therapy, given as boluses once a month for 6 consecutive months, combined with oral corticosteroid (up to 1 mg/kg/day). Ten other patients were treated with a combination of DFPP (performed 1–2 times weekly) and corticosteroid in the same amount. In both groups proteinuria significantly decreased at evaluation after 6 months, as well as the amount of urinary podocytes, and no significant differences were noted between groups. The authors concluded that both treatment regimens were as effective in the treatment of podocyte injury in patients with diffuse proliferative lupus nephritis.