The Role of Complement System in Kidney Transplantation

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Complement Activation in Transplant Candidates

Pre Tx : complement-driven kidney diseases

ESRD patients (HD)

Tx : I/R Injury

Post Tx : rejection, recurrence of underlying kidney disease , fibrosis

Ischemia-Reperfusion Injury of Kidney Graft

Humoral Rejection of Kidney Allograft

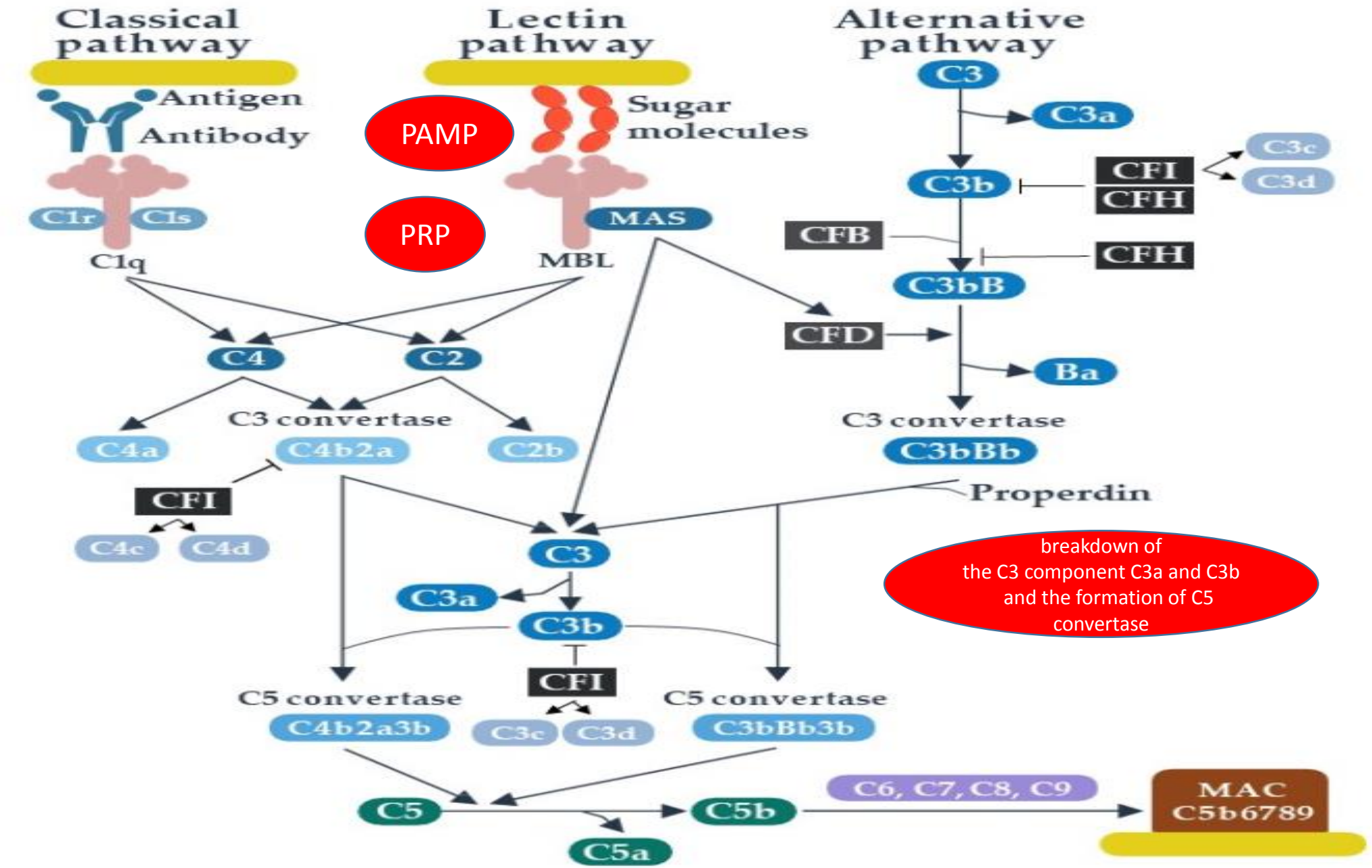
Post-Transplant Thrombotic Microangiopathy (TMA)

The Role of Complement in Kidney Graft Injury

Recurrent Nephropathy in a Transplanted Kidney

Fibrosis

Cellular Rejection of Kidney Allograft


Classical pathway
Antigen
Antibody
C1r
C1s
C1q
Lectin pathway
PAMP
PRP
Sugar molecules
MAS
MBL
Alternative pathway
C3
C3a
C3b
CFI
CFH
C3c
C3d
CFB
CFH
C3bB
CFD
Ba
C3 convertase
C3bBb
Properdin
C4
C2
C3 convertase
C4a
C4b2a
C2b
CFI
C4c
C4d
C3
C3a
C3b
CFI
C3c
C3d
C5 convertase
C4b2a3b
C5 convertase
C3bBb3b
C5
C5b
C5a
C6, C7, C8, C9
MAC
C5b6789
breakdown of
the C3 component C3a and C3b
and the formation of C5
convertase

Overview of the Complement System

Innate

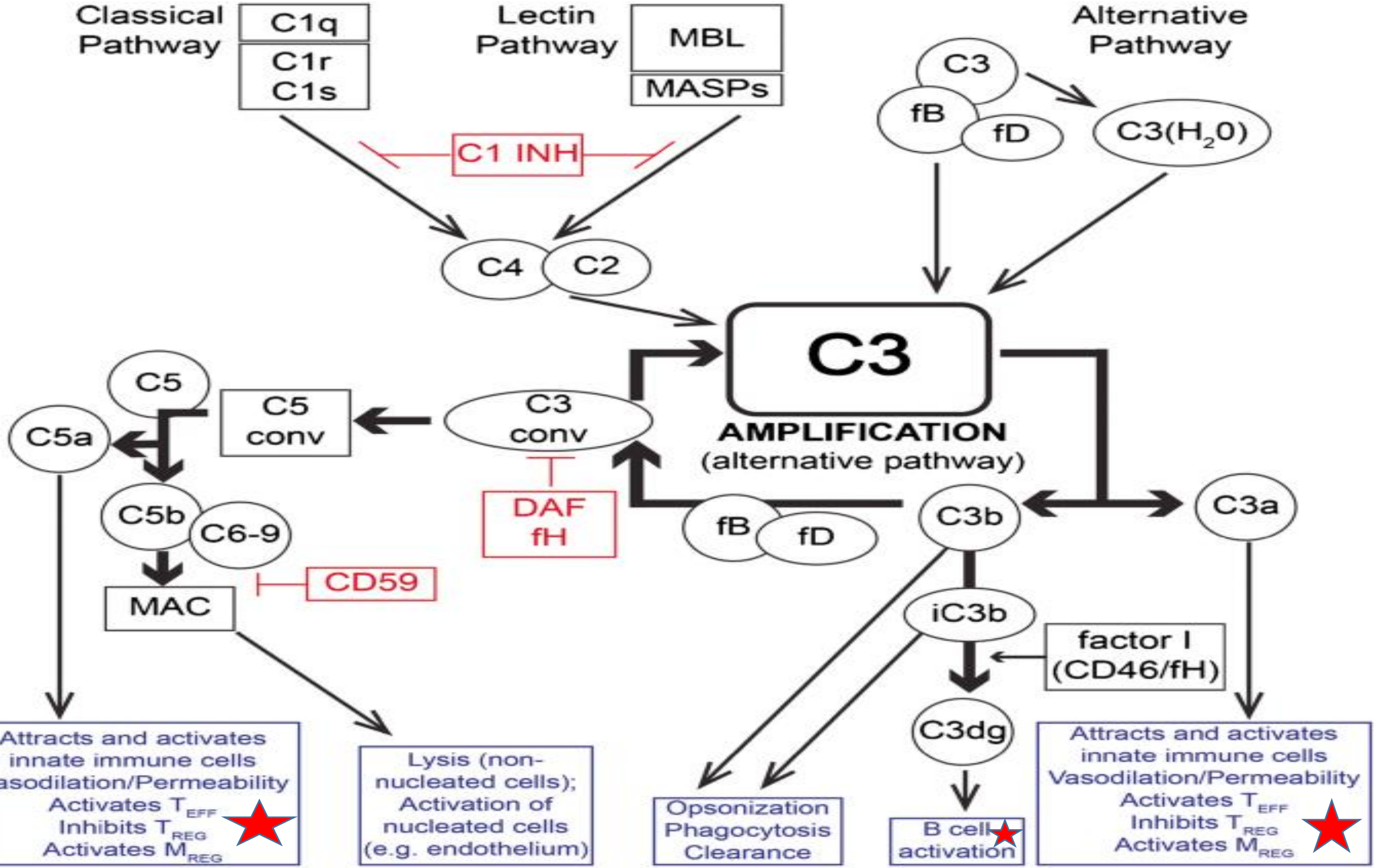
opsonisation of pathogens by C3b, iC3b, C3d, and C4b fragments

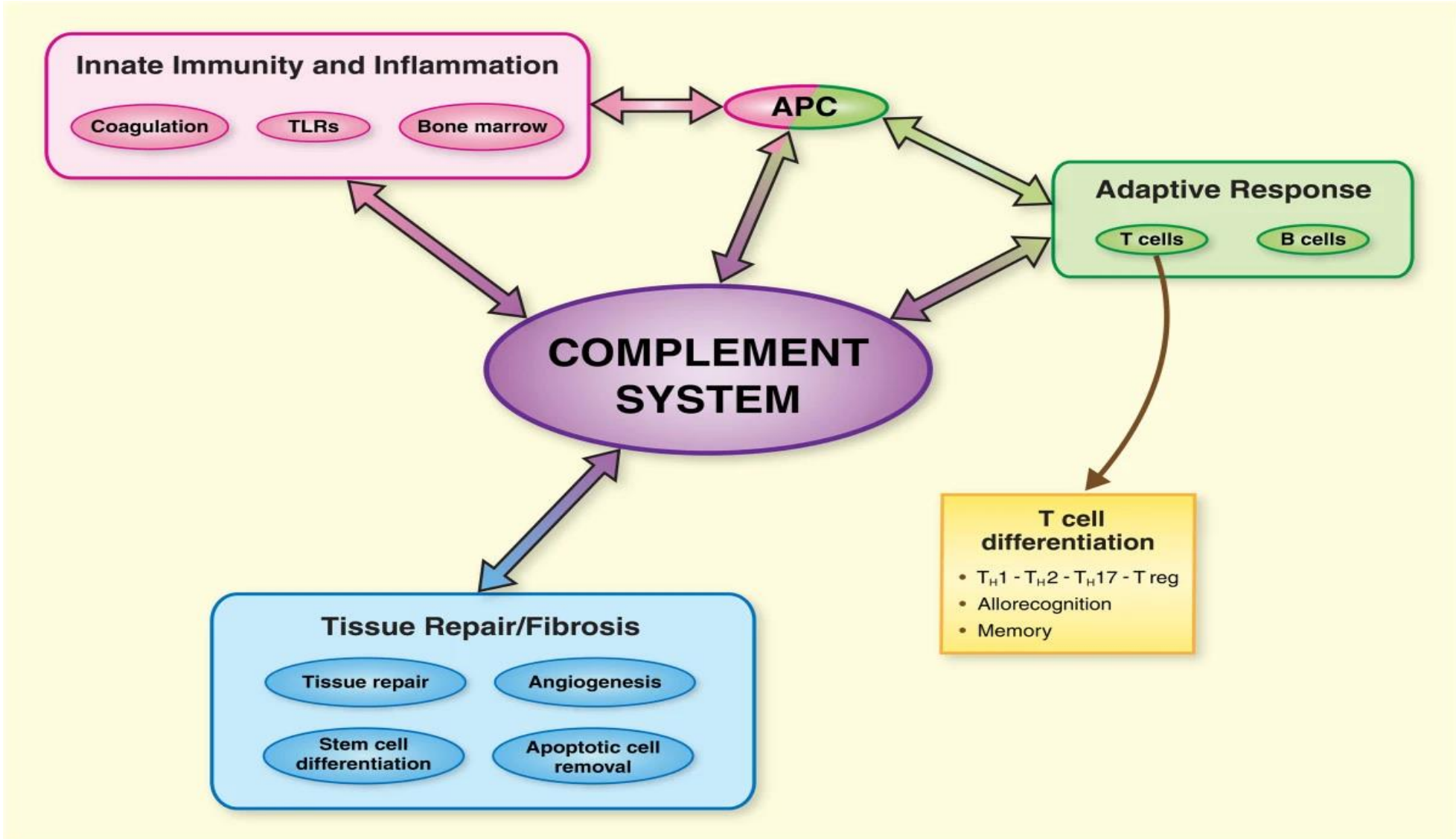
chemotaxis and the activation of leucocytes through the production of potent anaphylatoxins C3a and C5a

direct lysis of bacteria or infected self-cells through the MAC

Adaptive

As a bridge by modulating the activities of APCs, complement can increase antibody responses and strengthen the immunological memory because C3 receptors are on B cells, APC, and FDC


Classical Pathway
C1q
C1r
C1s
Lectin Pathway
MBL
MASPs
Alternative Pathway
C3
fB
fD
C3(H20)
C1 INH
C4
C2
C3
AMPLIFICATION
(alternative pathway)
C5
C5a
C5 conv
C3 conv
DAF
fH
C5b
C6-9
CD59
MAC
fB
fD
C3b
C3a
iC3b
factor I
(CD46/fH)
C3dg
Attracts and activates innate immune cells
Vasodilation/Permeability
Activates T EFF
Inhibits T REG
Activates M REG
Lysis (non-nucleated cells); Activation of nucleated cells (e.g. endothelium)
Opsonization
Phagocytosis
Clearance
B cell activation
Attracts and activates innate immune cells
Vasodilation/Permeability
Activates T EFF
Inhibits T REG
Activates M REG


Innate Immunity and Inflammation
Coagulation
TLRs
Bone marrow
APC
Adaptive Response
T cells
B cells
COMPLEMENT SYSTEM
T cell differentiation
• T_H1 - T_H2 - T_H17 - T reg
• Allorecognition
• Memory
Tissue Repair/Fibrosis
Tissue repair
Angiogenesis
Stem cell differentiation
Apoptotic cell removal

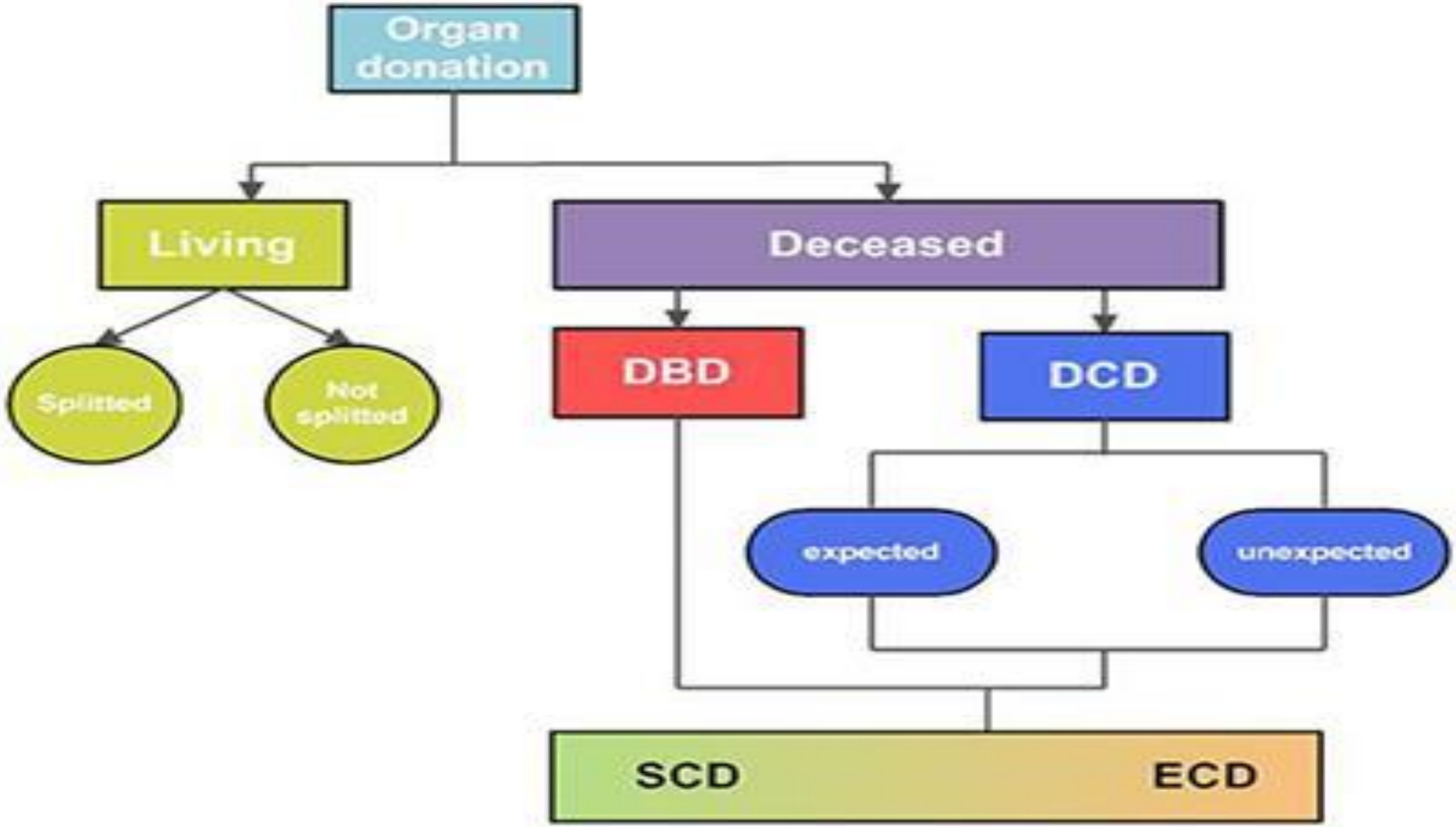
monitoring of allograft function

GFR, Serum Cr, U/A, ultrasound imaging

Kidney biopsy

Despite the progress in the donor-recipient matching, transplant rejection remains a challenge

In clinical practice, the assessment of allograft rejection is not easy


Organ donation
Living
Deceased
Splitted
Not splitted
DBD
DCD
expected
unexpected
SCD
ECD

Ischemia-Reperfusion Injury of Kidney Graft (IRI)

Cell death

HSP

HMGB

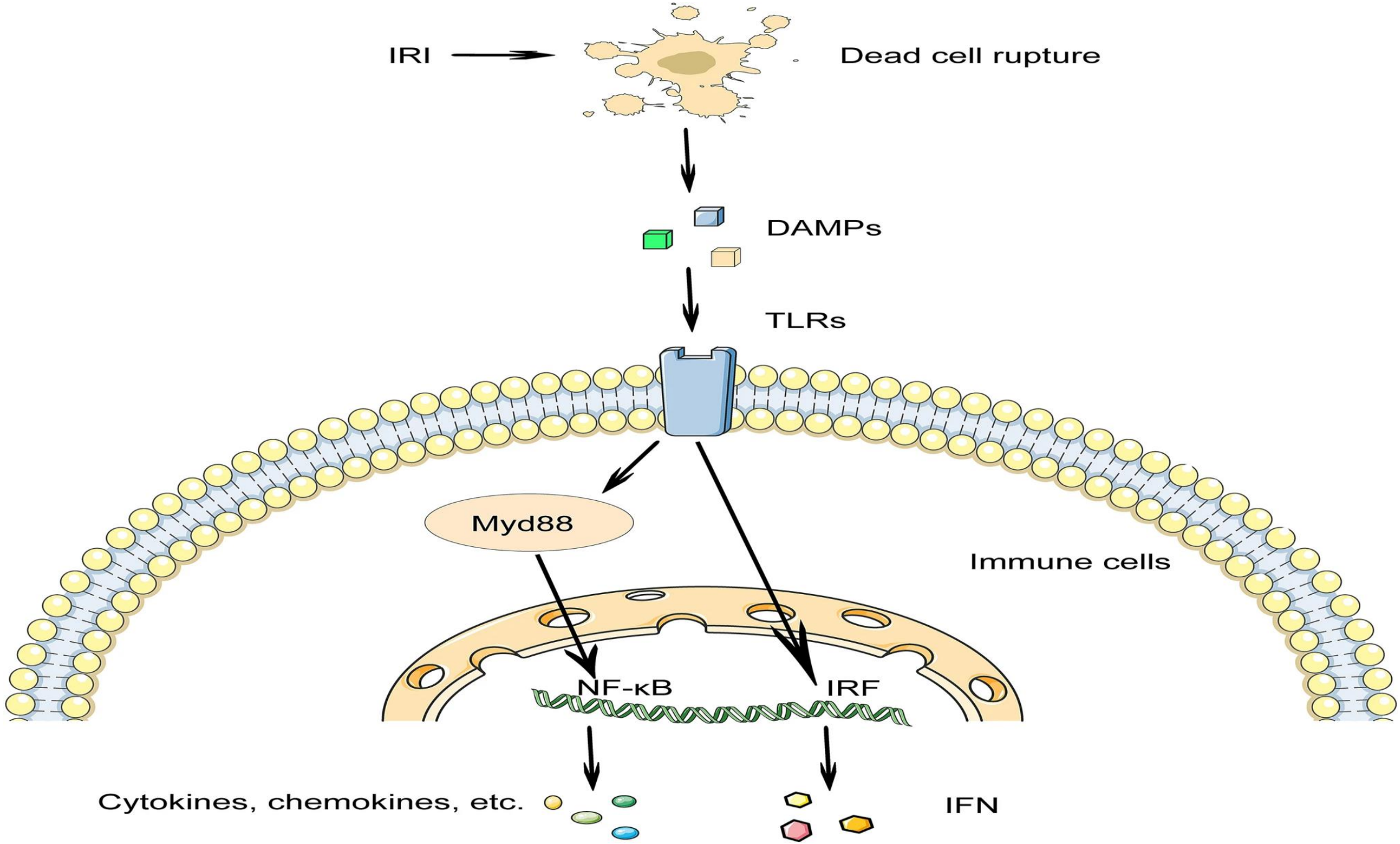
DAMPs

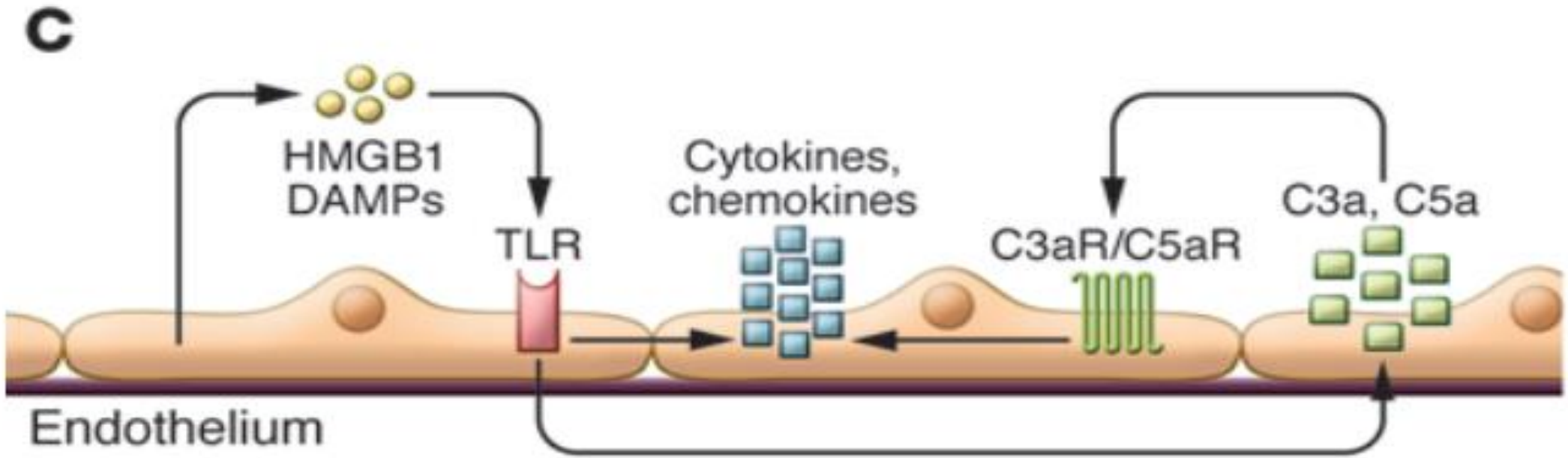
TLRs

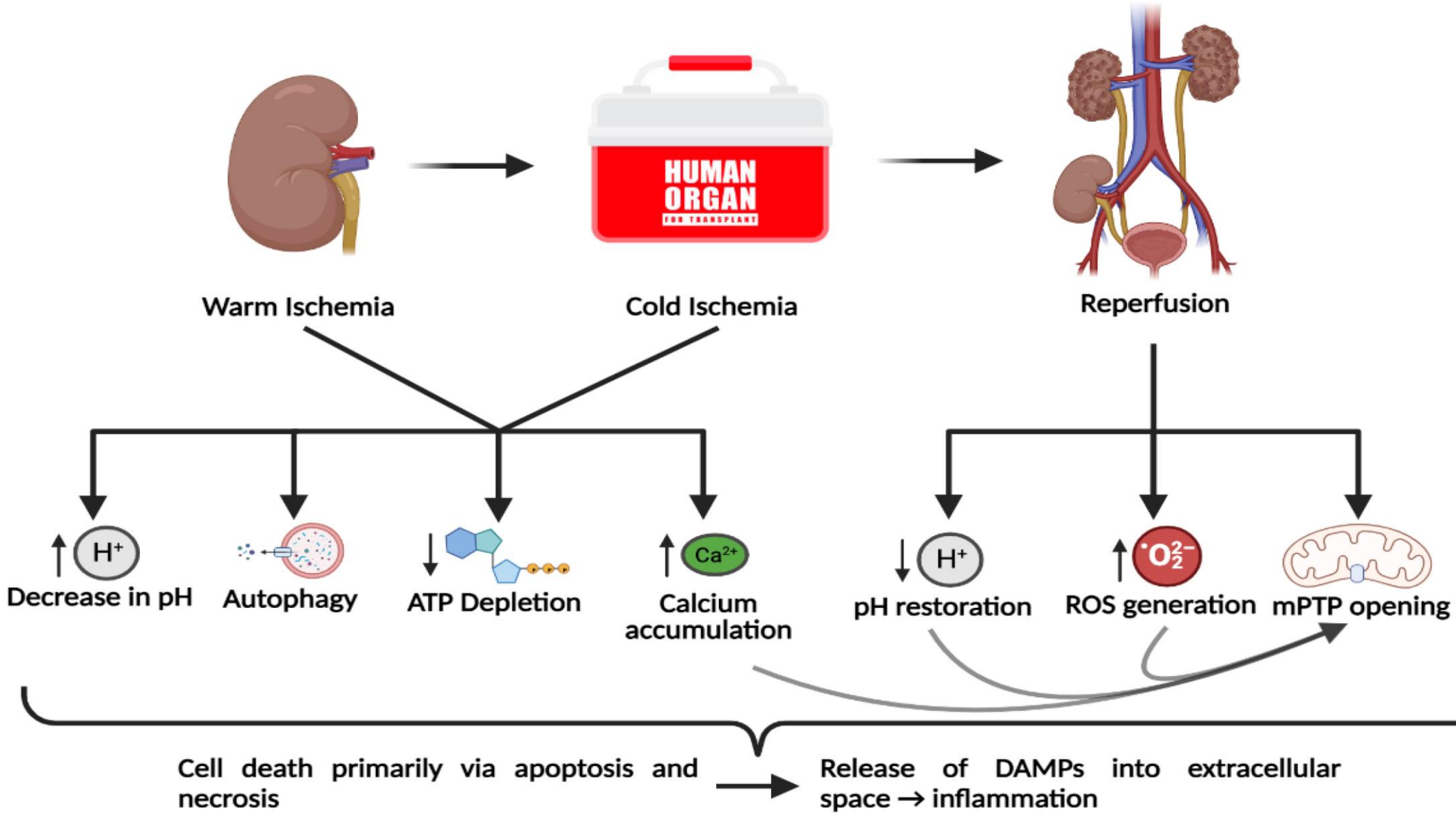
NF-κB signaling pathways

IFN-α/β and IL-1

production of IRI-induced aseptic inflammation


IRI
Dead cell rupture
DAMPs
TLRs
Myd88
Immune cells
NF-κB
IRF
Cytokines, chemokines, etc.
IFN


c
HMGB1
DAMPs
TLR
Cytokines,
chemokines
C3aR/C5aR
C3a, C5a
Endothelium


HUMAN ORGAN
FOR TRANSPLANT
Warm Ischemia
Cold Ischemia
Reperfusion
H+
Decrease in pH
Autophagy
ATP Depletion
Ca2+
Calcium accumulation
H+
pH restoration
O2 2−
ROS generation
mPTP opening
Cell death primarily via apoptosis and necrosis
Release of DAMPs into extracellular space → inflammation

Complement Activation in Donor Kidneys

Activation of C (and coagulation cascade) initiates in donor kidneys following brain death and before the retrieval of the kidneys from the donor

Higher C3 gene expression and increased C3d deposits in the biopsies of kidneys obtained from brain-dead donors as compared to living donors

perioperative levels of sC5b-9 could be used as a clinical biomarker of DGF

Damman, J. Transplantation 2015, 99, 1293–1300

IR/ I of Graft-1

Ischemia: the cells of the transplant are deprived of both oxygen and nutrients, which disrupts the cells' metabolism leading to necrosis.

QUALITY OF donor organ
LRD
BDD
CDD

Duration of ischemia
Organ preservation techniques

IR/I of Graft-2

The subsequent reperfusion exerts further damage to the organ. When circulation is restored to the transplanted organ, necrotic and apoptotic cells activate the innate immune response by stimulating leukocytes and macrophage migration to inflammation sites.

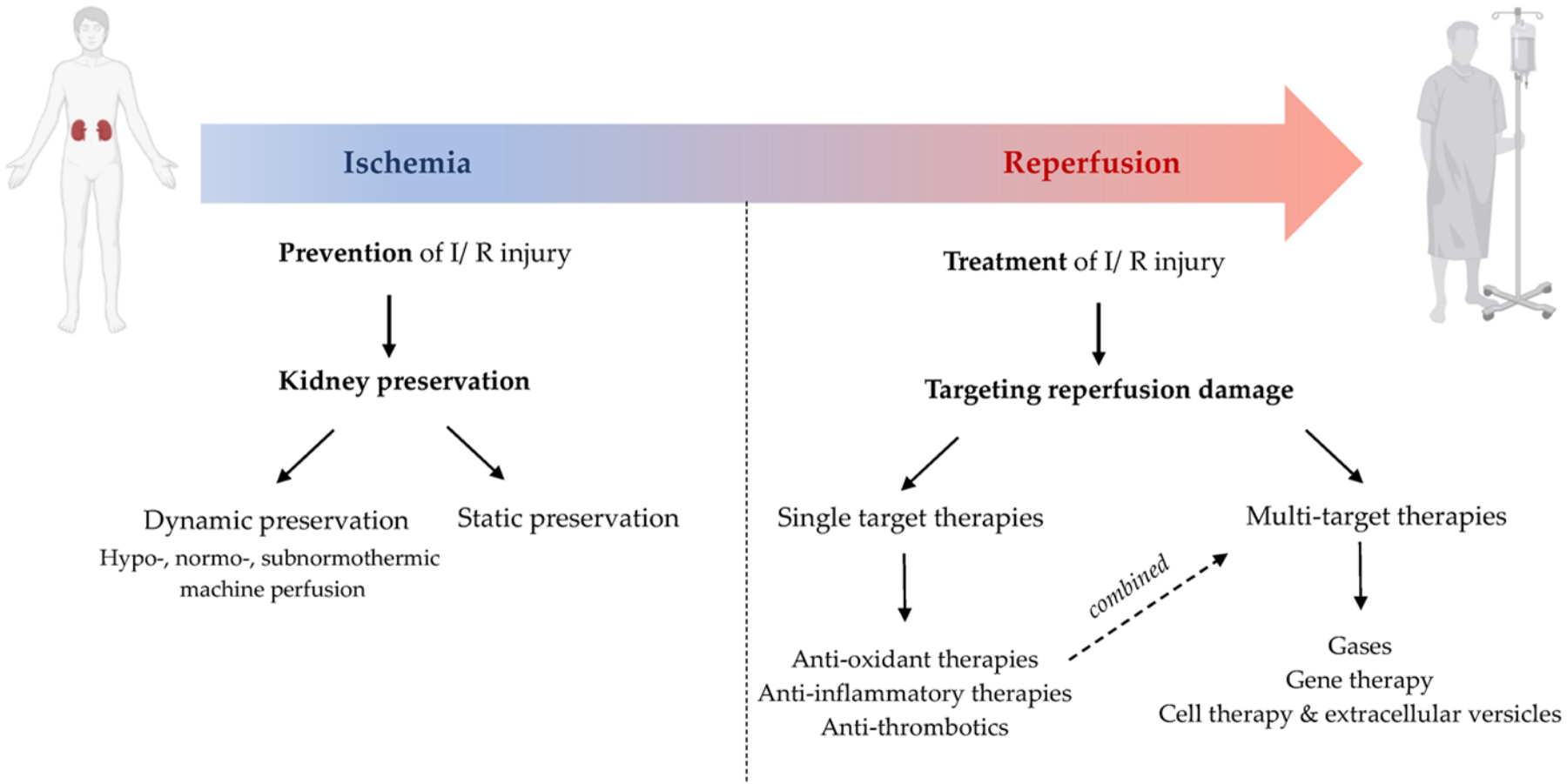
The cytokines, chemokines and reactive oxygen species play a key role in exacerbating the immune and inflammatory response. As (IRI) progresses, DAMPs are generated that perpetuate the cellular inflammatory response and enable the activation of complement activation pathways

C3 activated during transplant reperfusion is a triggering factor of IRI and is associated with late allograft damage and rejection.

C5a/C5aR signaling has been identified as a profibrotic pathway in the kidney activation of all three complement pathways

The C3 split products (C3c and C3d) detected in kidney biopsies serve as a proof of complement activation regardless of the pathway.

Prevention and treatment of IRI



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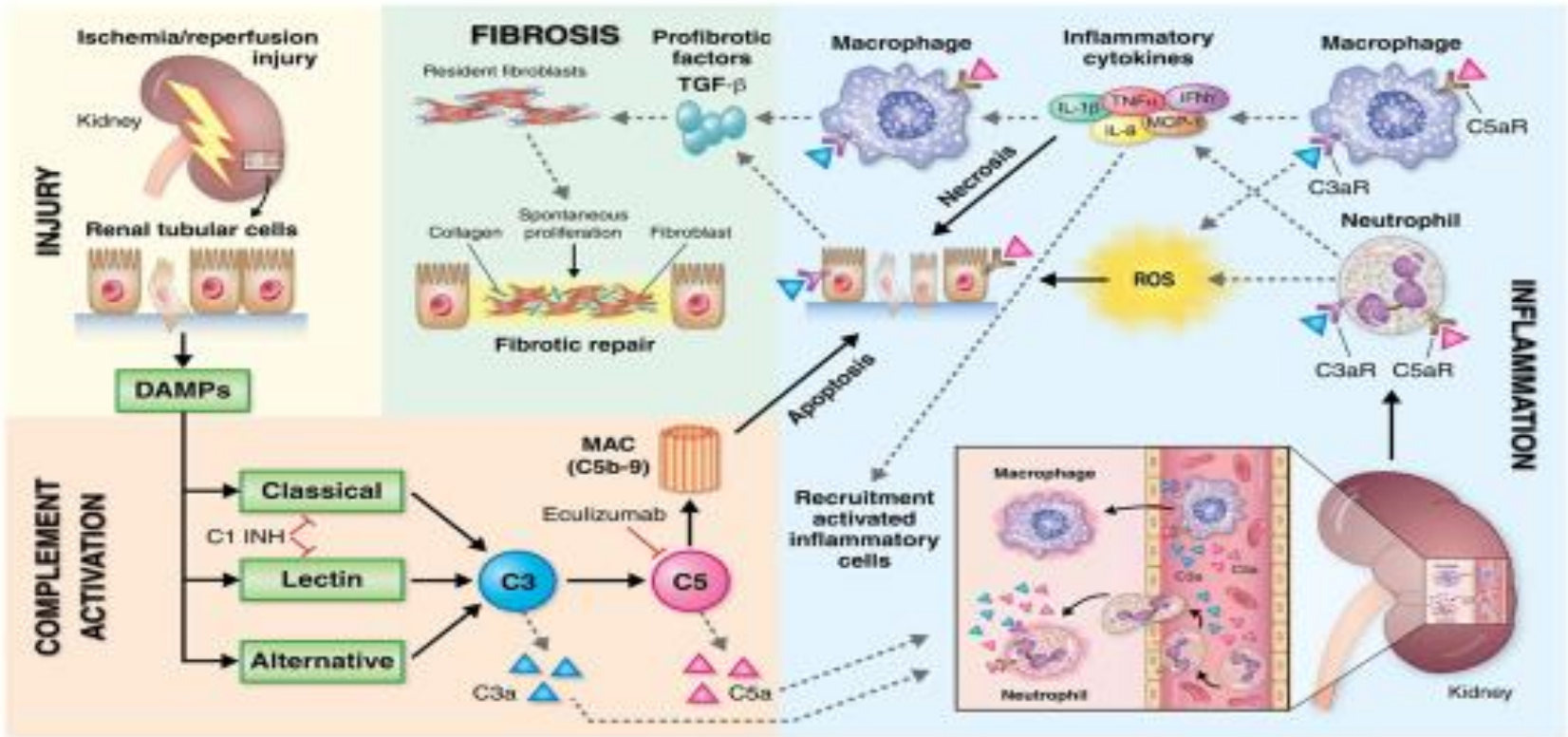

Ischemia/reperfusion injury
Kidney
INJURY
Renal tubular cells
DAMPs
FIBROSIS
Resident fibroblasts
Profibrotic factors TGF-β
Collagen
Spontaneous proliferation
Fibroblast
Fibrotic repair
Macrophage
Inflammatory cytokines
IL-1β
TNFα
IFNγ
IL-8
MCP-1
Macrophage
C5aR
C3aR
Necrosis
Neutrophil
ROS
C3aR C5aR
INFLAMMATION
Apoptosis
MAC (C5b-9)
COMPLEMENT ACTIVATION
Classical
C1 INH
Lectin
Alternative
C3
C5
Eculizumab
C3a
C5a
Recruitment activated inflammatory cells
Macrophage
Neutrophil
Kidney

Targeted therapy

Donor urinary C5a

C5a-C5aR-axis

Upregulation of C5a in the deceased donor

Increased renal tubular expression of the C5aR1

Local immune activation in the deceased renal allograft

Targeted therapy interfering with **local** complement activation before organ **recovery** or during organ **storage**

-Continued

1-C1-INH : is currently tested as a treatment strategy in human DBD donors (NCT02435732)

2- Mirococept

3- Anti-C5 antibody (Ergidina)

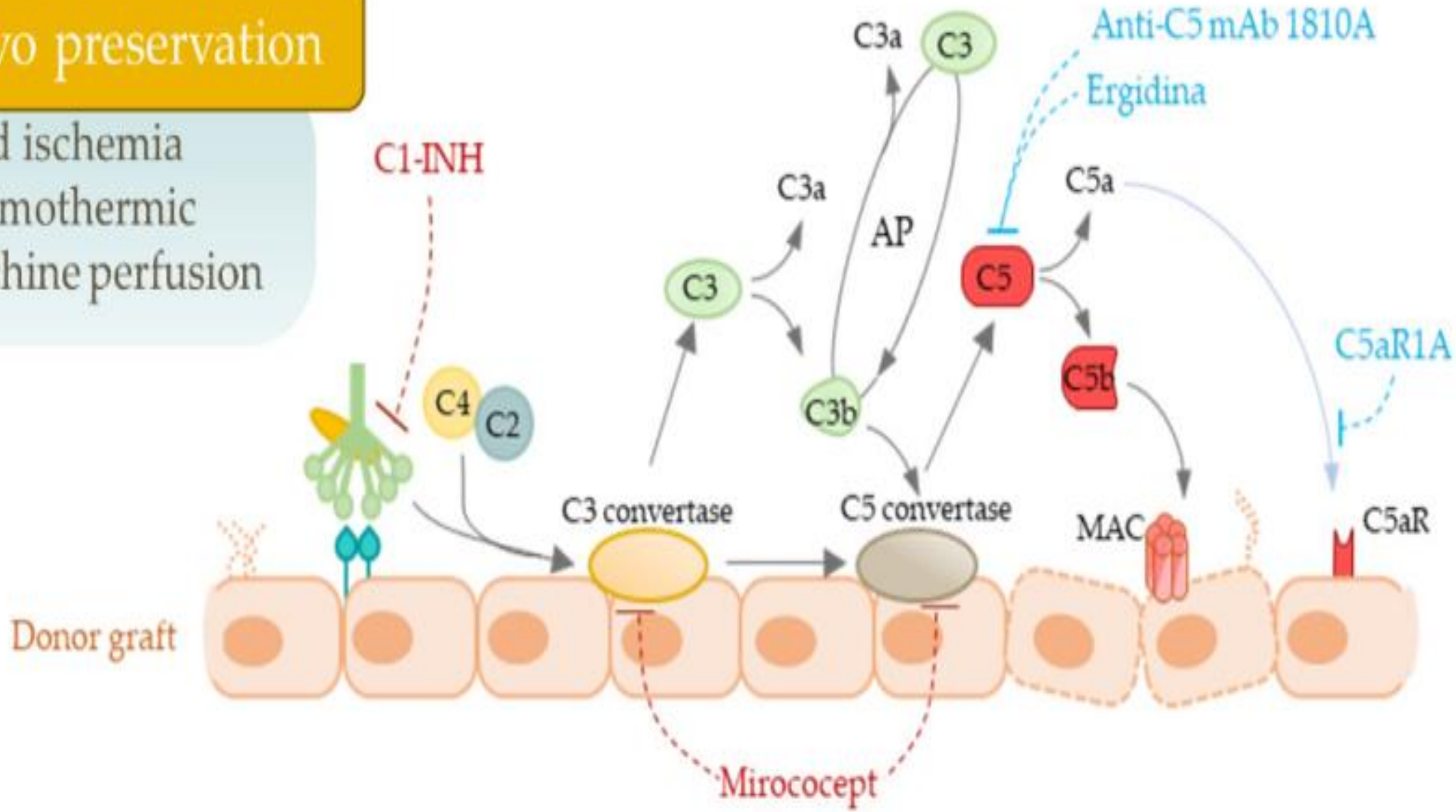
4- TT30 : is a complement receptor 2/factor H fusion protein

Frontiers in immunology , Jan 2020 Vol 10 Article 3029

EARLY PRE-TRANSPLANT PERIOD AND THERAPEUTIC STRATEGIES

Ex-vivo preservation

- Cold ischemia
- Normothermic machine perfusion



Kassimatis et al. Trials (2017) 18:255
DOI 10.1186/s13063-017-1972-x

Trials

STUDY PROTOCOL Open Access

A double-blind randomised controlled investigation into the efficacy of Mirococept (APT070) for preventing ischaemia reperfusion injury in the kidney allograft (EMPIRIKAL): study protocol for a randomised controlled trial

Theodoros Kassimatis[1], Anass Qasem[1], Abdel Douiri[2], Elizabeth G. Ryan[3], Irene Rebollo-Mesa[1,4], Laura L. Nichols[1], Roseanna Greenlaw[1], Jonathon Olsburgh[1], Richard A. Smith[1], Steven H. Sacks[1] and Martin Drage[1,5*]

Abstract

Background: Delayed graft function (DGF) is traditionally defined as the requirement for dialysis during the first week after transplantation. DGF is a common complication of renal transplantation, and it negatively affects short- and long-term graft outcomes. Ischaemia reperfusion injury (IRI) is a prime contributor to the development of DGF. It is well established that complement system activation plays a pivotal role in the pathogenesis of IRI. Mirococept is a highly effective complement inhibitor that can be administered ex vivo to the donor kidney just before transplantation. Preclinical and clinical evidence suggests that Mirococept inhibits inflammatory responses that follow IRI. The EMPIRIKAL trial (REC 12/LO/1334) aims to evaluate the efficacy of Mirococept in reducing the incidence of DGF in cadaveric renal transplantation.

Methods/design: EMPIRIKAL is a multicentre double-blind randomised case-control trial designed to test the superiority of Mirococept in the prevention of DGF in cadaveric renal allografts, as compared to standard cold perfusion fluid (Soltran®). Patients will be randomised to Mirococept or placebo (Pbo) and will be enrolled in cohorts of $N = 80$ with a maximum number of 7 cohorts. The first cohort will be randomised to 10 mg of Mirococept or Pbo. After the completion of each cohort, an interim analysis will be carried out in order to evaluate the dose allocation for the next cohort (possible doses: 5–25 mg). Immunosuppression therapy, antibiotic and antiviral prophylaxis will be administered as per local centre protocols. The enrolment will take approximately 24 months, and patients will be followed for 12 months. The primary endpoint is DGF, defined as the requirement for dialysis during the first week after transplantation. Secondary endpoints include duration of DGF, functional DGF, renal function at 12 months, acute rejection episodes at 6 and 12 months, primary non-function and time of hospital stay on first admission and in the first year following transplant. Safety evaluation will include the monitoring of laboratory data and the recording of all adverse events.

(Continued on next page)

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Wiley Periodicals Inc.

doi: 10.1111/ajt.13797

Targeting Complement Pathways During Cold Ischemia and Reperfusion Prevents Delayed Graft Function

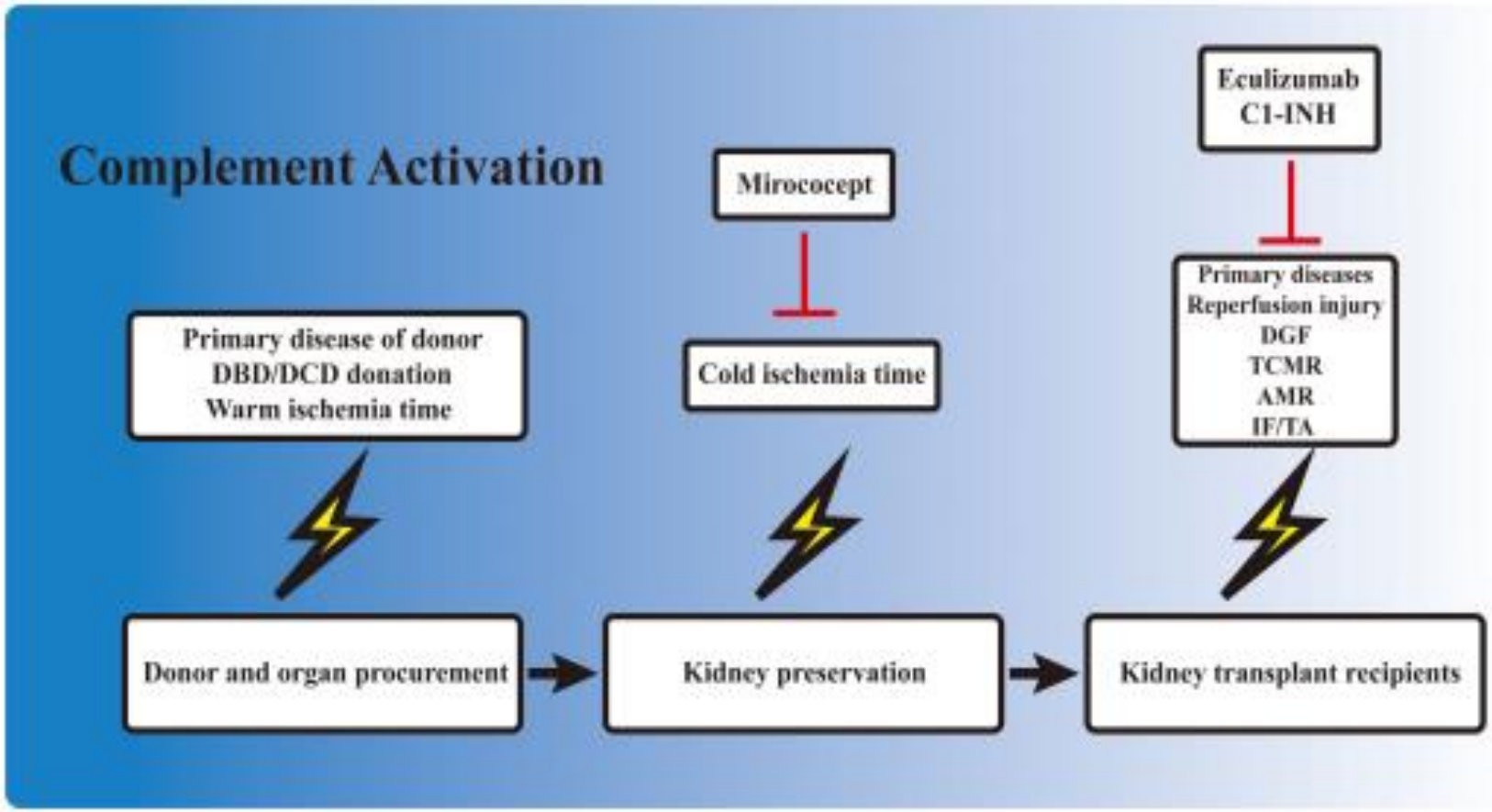
Z. X. Yu[1,*], S. Qi[2], M. A. Lasaro[1], K. Bouchard[1], C. Dow[1], K. Moore[1], Z. Wu[2], A. Barama[2], J. Xu[2], K. Johnson[1], A. J. Marozsan[1] and Y. Wang[1]

[1]*Pre-Clinical Sciences, Alexion Pharmaceuticals, Inc., Cheshire, CT*
[2]*Research Centre, Centre Hospitalier de l'Université de Montréal, Department of Surgery, Hôpital Notre Dame and Université de Montréal, Montréal, Quebec, Canada*
**Corresponding author: Zhao-Xue Yu, yuz@alxn.com*

The complement system plays a critical role in ischemia–reperfusion injury (IRI)–mediated delayed graft function (DGF). To better understand the roles of complement activation pathways in IRI in kidney transplantation, donor kidneys were treated *ex vivo* with terminal complement pathway (TP) inhibitor, anti-rat C5 mAb 18A10, or complement alternative pathway (AP) inhibitor TT30 for 28 h at 4°C pretransplantation in a syngeneic kidney transplantation rat model. All 18A10- and 67% of TT30-pretreated grafts, but only 16.7% of isotype control-pretreated grafts, survived beyond day 21 ($p < 0.01$). Inhibitor treatment in the final 45 min of 28-h cold ischemia (CI) similarly improved graft survival. Systemic posttransplant treatment with 18A10 resulted in 60% increased graft survival beyond day 21 ($p < 0.01$), while no TT30-treated rat survived > 6 days. Our results demonstrate that AP plays a prominent role during CI and that blocking either the AP or, more effectively the TP prevents ischemic injury and subsequent DGF. Multiple complement pathways may be activated and contribute to reperfusion injury;

Introduction

Delayed graft function (DGF) is an early and serious complication of renal transplant affecting approximately 25% of deceased-donor kidney transplant patients (1–3). To date, no approved treatments for DGF are available (3,4). DGF is generally considered to be the result of ischemia–reperfusion injury (IRI). Although a large body of literature has suggested that activation of the complement cascade during ischemia and/or reperfusion plays a critical role in the development of IRI (5–8), the relative contribution of each complement activation pathway in the pathogenesis of IRI and DGF remains controversial (9–13). The complement system is activated through the classical, lectin, and alternative pathways (APs), but can also be activated through the coagulation activation pathway (14). All of these pathways share a common terminal complement pathway that includes the complement component C5, its breakdown products C5a and C5b, and the membrane attack complex. Results of numerous studies indicate that the AP plays a critical role in IRI, including studies in factor B–deficient mice (15) and studies of the beneficial effects of factor H constructs targeted to the tissue surface (16), whereas other studies support the role of the lectin pathway in IRI (17,18). Many of these studies have utilized models of warm-IRI, which, arguably, may not replicate the pathogenesis of DGF in the setting of life-supporting organ transplantation (9,10,12,13,19). The primary aim of this study was to dissect the exact contribution of the various complement activation pathways in cold ischemic injury or reperfusion injury in a clinically relevant DGF model. We have utilized specific blockers of AP and terminal complement path-


Complement Activation
Eculizumab
C1-INH
Mirococept
Primary diseases
Reperfusion injury
DGF
TCMR
AMR
IF/TA
Primary disease of donor
DBD/DCD donation
Warm ischemia time
Cold ischemia time
Donor and organ procurement
Kidney preservation
Kidney transplant recipients

Antibody-mediated rejection (ABMR)

Patel and Terasaki - 1969 (CDC)

Feucht -1991 (C4d positivity)

C1q - binding DSAs

C3d - binding DSAs

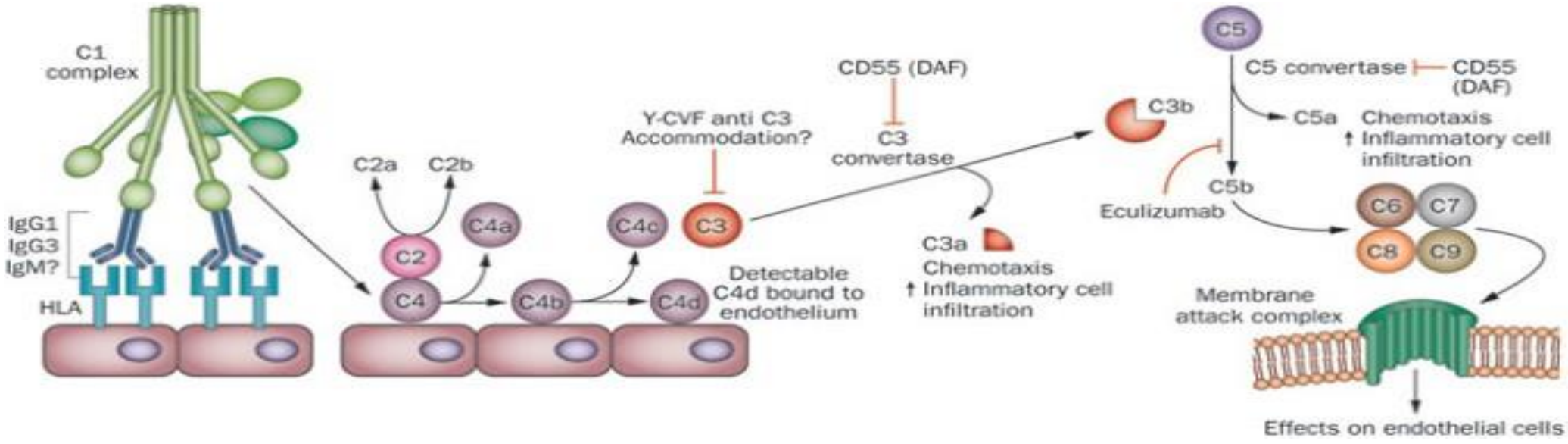
C3a

Małgorzata Kielar, Biomolecules 2021, 11, 773

Humoral Rejection of Kidney Allograft

- leading cause of late or chronic transplant rejection
- 30–50% of acute rejection episodes occur due to AMR
- The recipient’s alloantibodies bind the antigens exposed on the endothelial cells of the graft
- bind C1q complement component, leading to the activation of the classical complement pathway.
- DSAs

-continued


C1
complex
IgG1
IgG3
IgM?
HLA
C2a
C2b
C2
C4a
C4
C4b
C4c
C4d
Y-CVF anti C3
Accommodation?
C3
Detectable
C4d bound to
endothelium
CD55 (DAF)
C3
convertase
C3b
C3a
Chemotaxis
↑ Inflammatory cell
infiltration
C5
C5 convertase
CD55
(DAF)
C5a
Chemotaxis
↑ Inflammatory cell
infiltration
C5b
Eculizumab
C6
C7
C8
C9
Membrane
attack complex
Effects on endothelial cells

I/RI and Adaptive immunity

Induces mechanisms of innate immunity

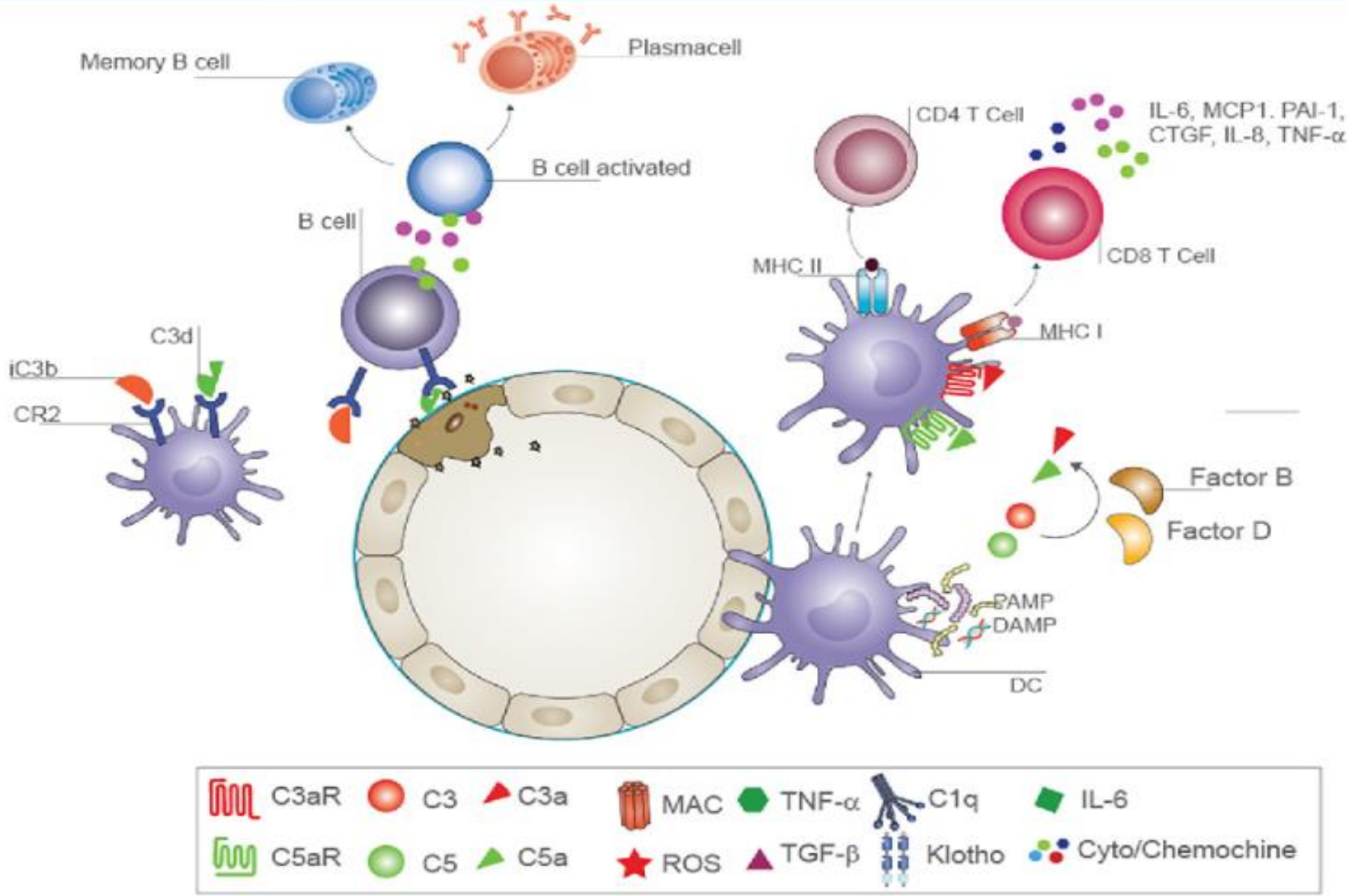
Enhances antigen presentation and stimulates B and T-cell mediated adaptive immunity.

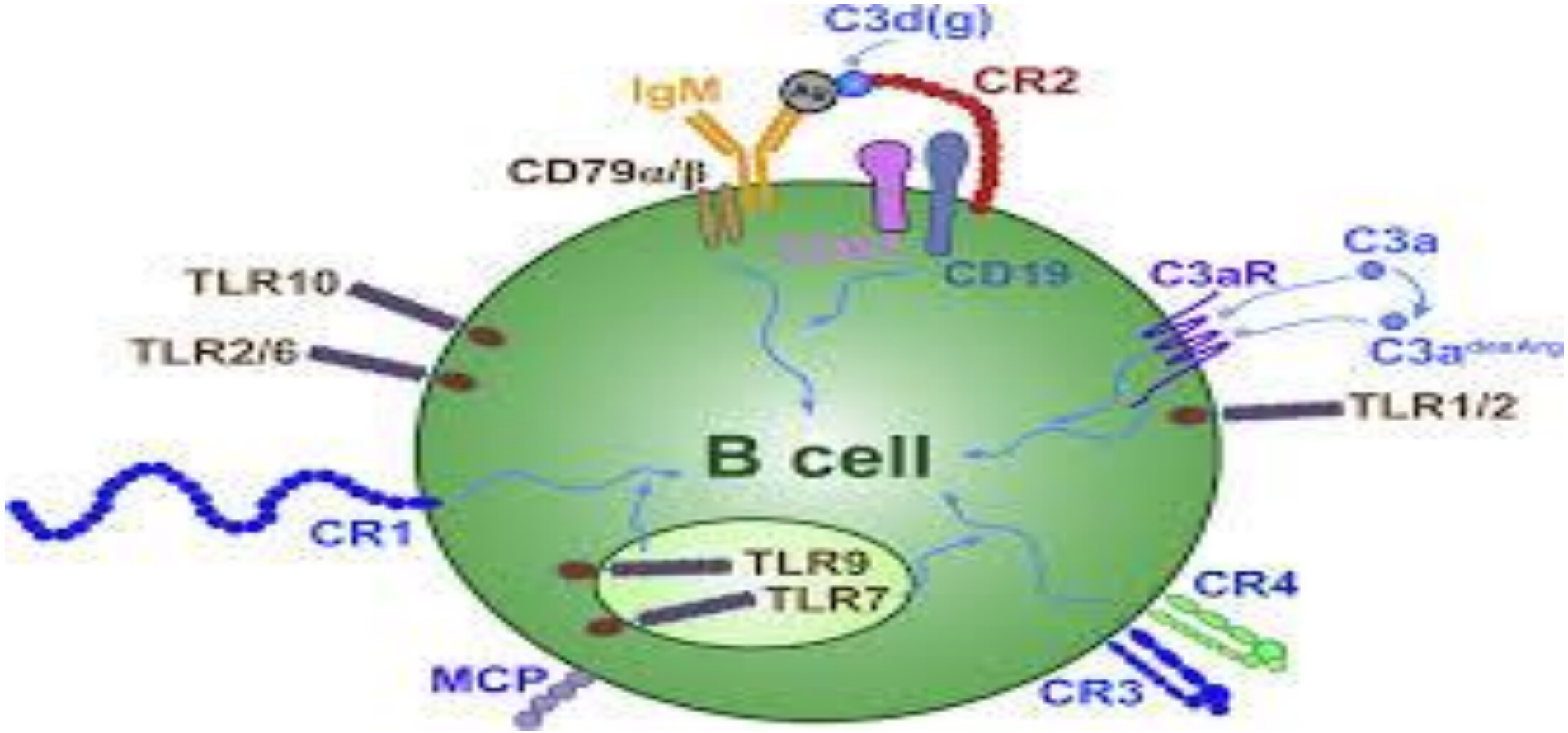
CR2 signaling increase B cell response to antigens present on C3d-opsonized cells .

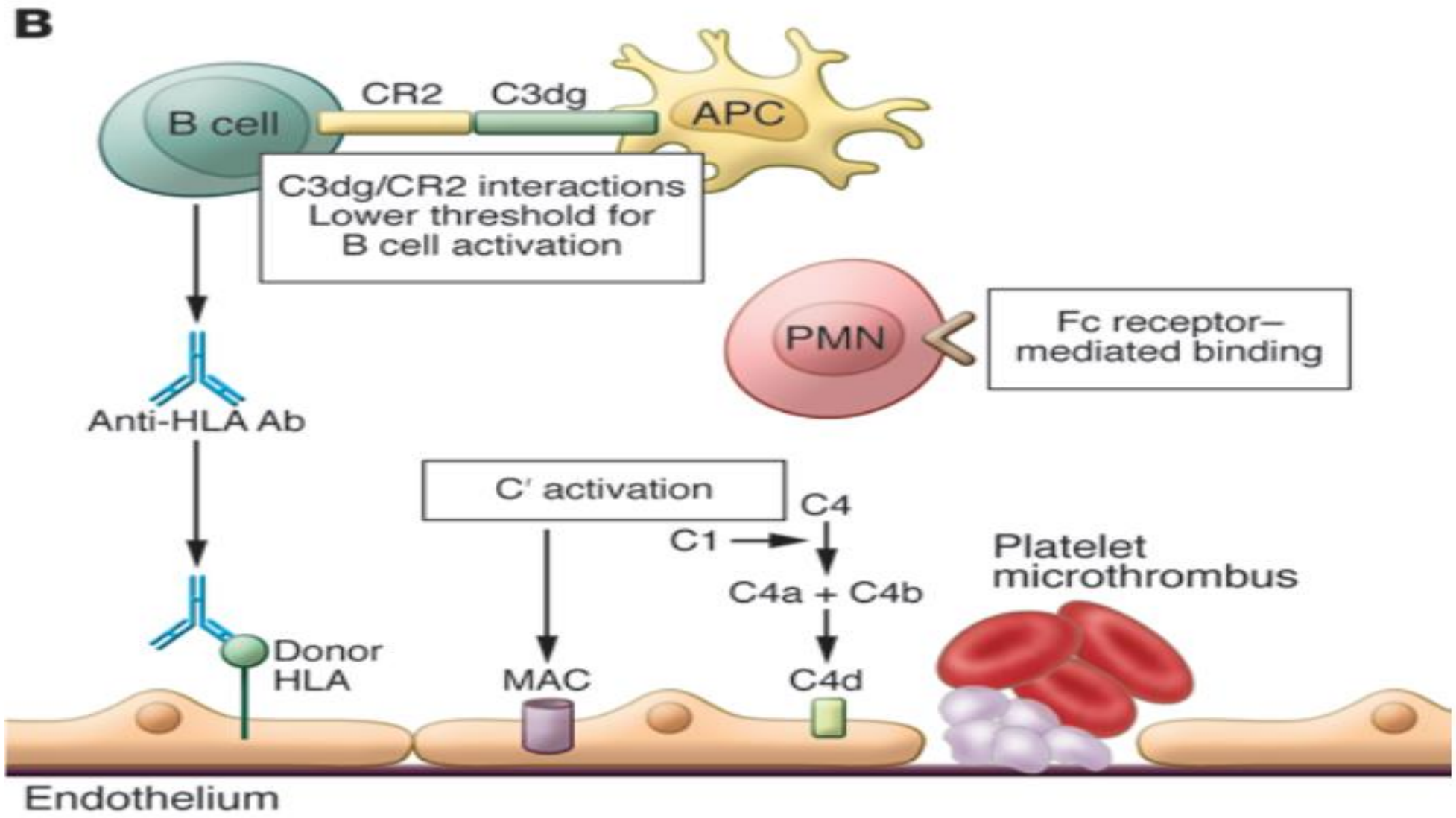
CR 2–4 are present on myeloid cells, including B and T-cells, and their activation by C3b fragments increase cytokine production and phagocytosis

Donata, Cells 2023, 12, 791

Immune cells and complement




C3d(g)
IgM
CR2
CD79α/β
CD19
TLR10
TLR2/6
C3aR
C3a
TLR1/2
B cell
CR1
TLR9
TLR7
CR4
MCP
CR3


B
B cell
CR2
C3dg
APC
C3dg/CR2 interactions
Lower threshold for
B cell activation
PMN
Fc receptor–
mediated binding
Anti-HLA Ab
C′ activation
C4
C1
C4a + C4b
Platelet
microthrombus
Donor
HLA
MAC
C4d
Endothelium

> J Immunol. 1998 Jun 1;160(11):5273-9.

Expression of complement receptors 1 and 2 on follicular dendritic cells is necessary for the generation of a strong antigen-specific IgG response

Y Fang [1], C Xu, Y X Fu, V M Holers, H Molina

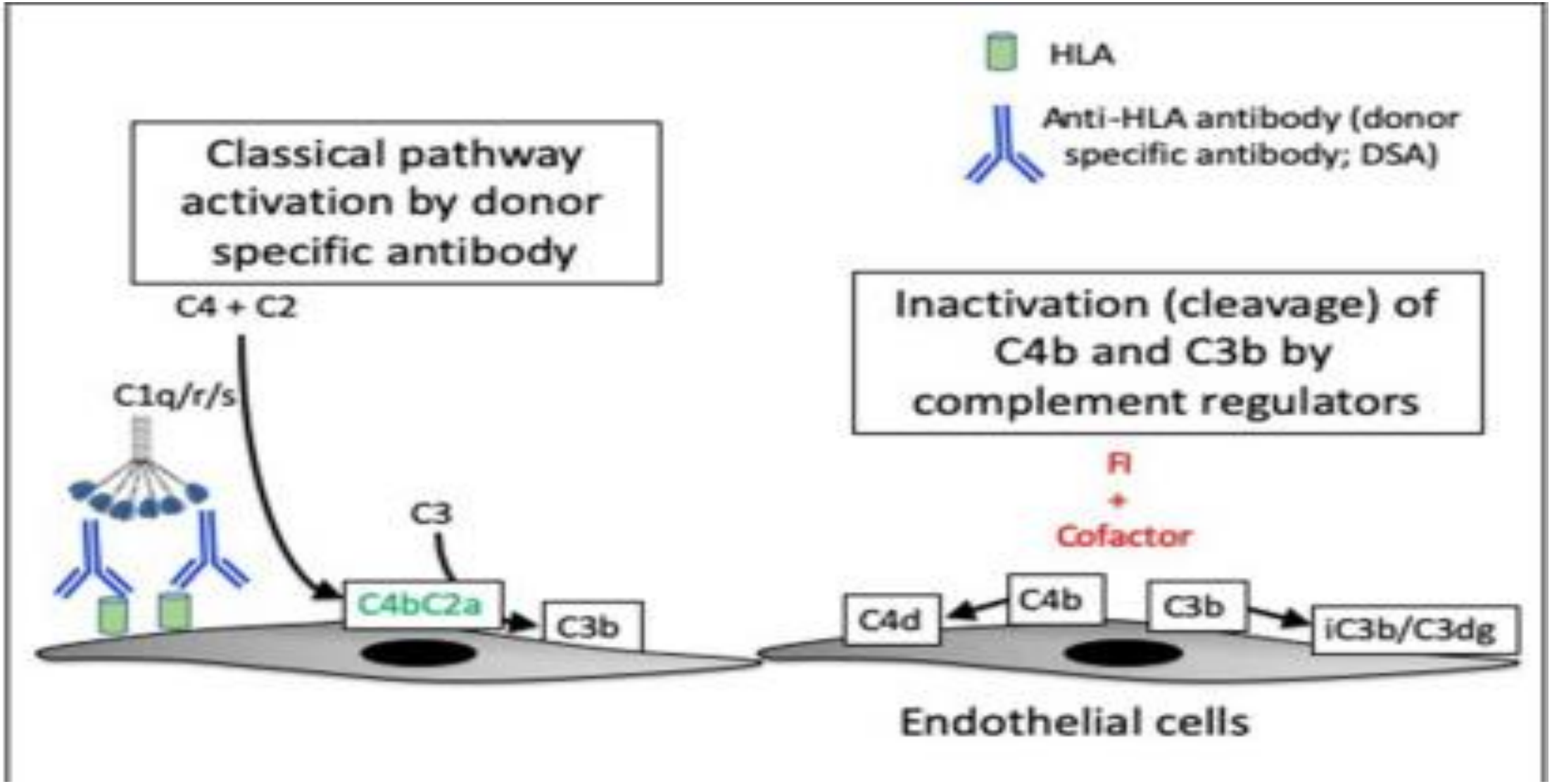
Affiliations + expand

PMID: 9605124

Abstract

Two mechanisms could account for the impaired humoral immune response found in Cr2-/- mice. The absence of complement receptors 1 and 2 (CR1, CR2) on B cells could affect their activation. Alternatively, impaired Ag trapping by follicular dendritic cells (FDC) could affect B cell maturation into Ig-secreting or memory B cells. To compare the roles of CR1 and CR2 on B cells vs FDC in this abnormal response, bone marrow (BM) chimeric mice were generated and immunized with specific T-dependent Ags. The primary and secondary Ab response was measured. Cr2+/+ animals reconstituted with a Cr2-/- BM generated a diminished but detectable humoral immune response compared with controls. When injected with preformed immune complexes (IC), these mice maintained follicular IC localization. Cr2-/- animals reconstituted with a Cr2+/+ BM had an initial rise in the Ab titer, but were unable to maintain it as shown by a pronounced decrease in the IgG titer. This defect persisted during the secondary immune response. Follicular IC trapping was also impaired. Despite the abnormal Ab response, germinal center formation was retained in all of the chimeric animals. These experiments are the first to demonstrate an absolute requirement for CR1 and CR2 expression on FDC in the generation of a normal humoral immune response.

Complement activation in antibody-mediated rejection



TCMR

- C3a or C5a regulation of APC maturation and function
- C3a and C5a could be produced locally at the APC-T cell interface, where reciprocal cognate interactions appeared to upregulate the expression of anaphylatoxin receptors in both partners, suggested that complement might have direct effects on the functional co-stimulation and differentiation of naive CD4+ T cells.
- Extracellular / intracellular stores of complement components and receptors (e.g., anaphylatoxin receptors and their ligands; C3b,
- factor B, factor H)
- George hajishengalis , Nat Immunol. 2017 November 16; 18(12): 1288–1298

> Nat Med. 2002 Jun;8(6):582-7. doi: 10.1038/nm0602-582.

Local synthesis of complement component C3 regulates acute renal transplant rejection

Julian R Pratt [1], Shamim A Basheer, Steven H Sacks

Affiliations + expand

PMID: 12042808 DOI: 10.1038/nm0602-582

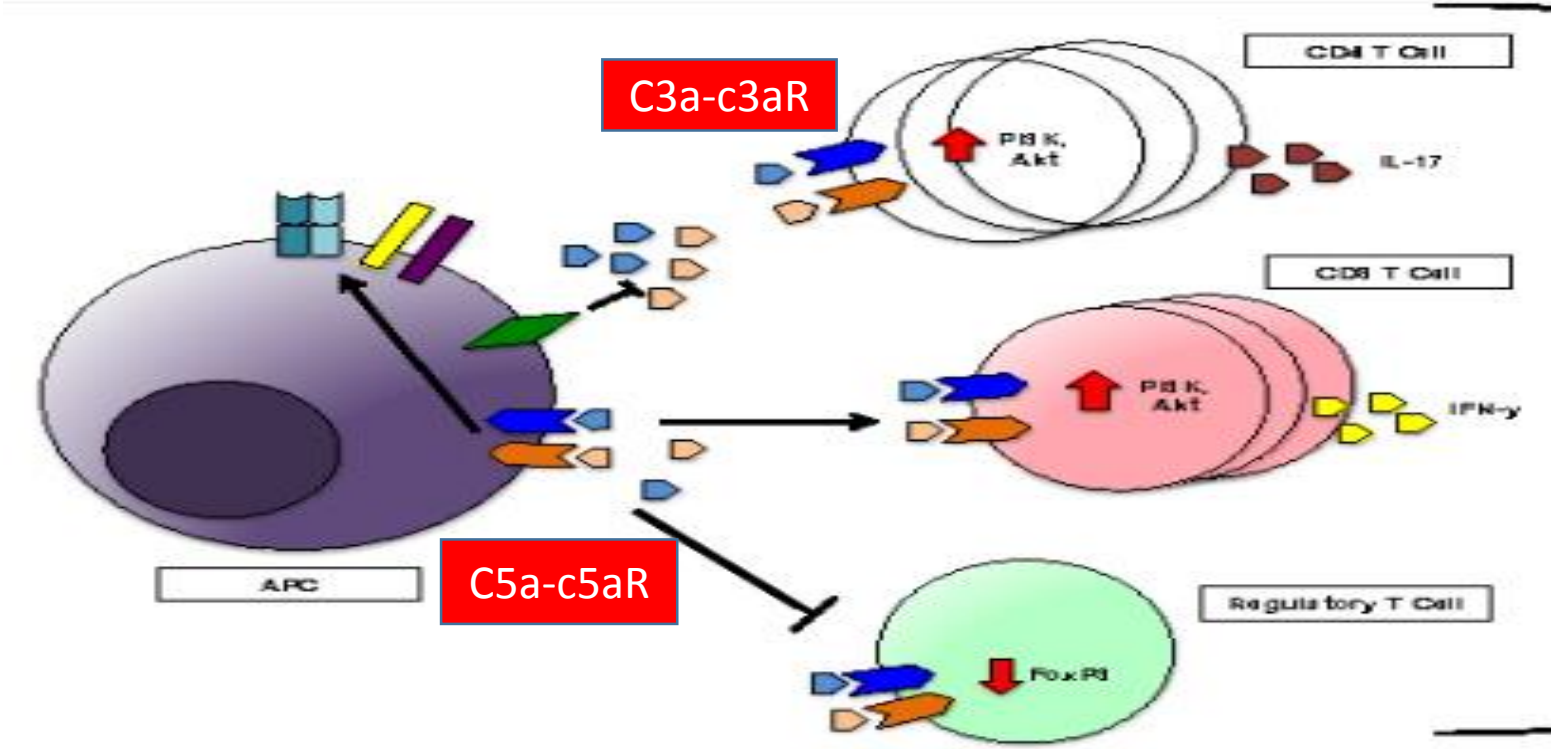
Abstract

Accumulating evidence suggests that innate immunity interacts with the adaptive immune system to identify potentially harmful antigens and eliminate them from the host. A central facet of innate immunity is complement, which for some time has been recognized as a contributor to inflammation in transplant rejection but without detailed analysis of its role in what is principally a T cell mediated process. Moreover, epithelial and vascular tissues at local sites of inflammation secrete complement components; however, the role of such local synthesis remains unclear. Here we show that the absence of locally synthesized complement component C3 is capable of modulating the rejection of renal allografts in vivo and regulating T-cell responses in vivo and in vitro. The results indicate that improved success in kidney transplantation could come from therapeutic manipulation of innate immunity in concert with T cell directed immunosuppression.

The Local and Intracellular Role

kidney tubular cells

Intracellular synthesis of C3a and C5a in T-cells is required for survival of CD4+ T-cells.



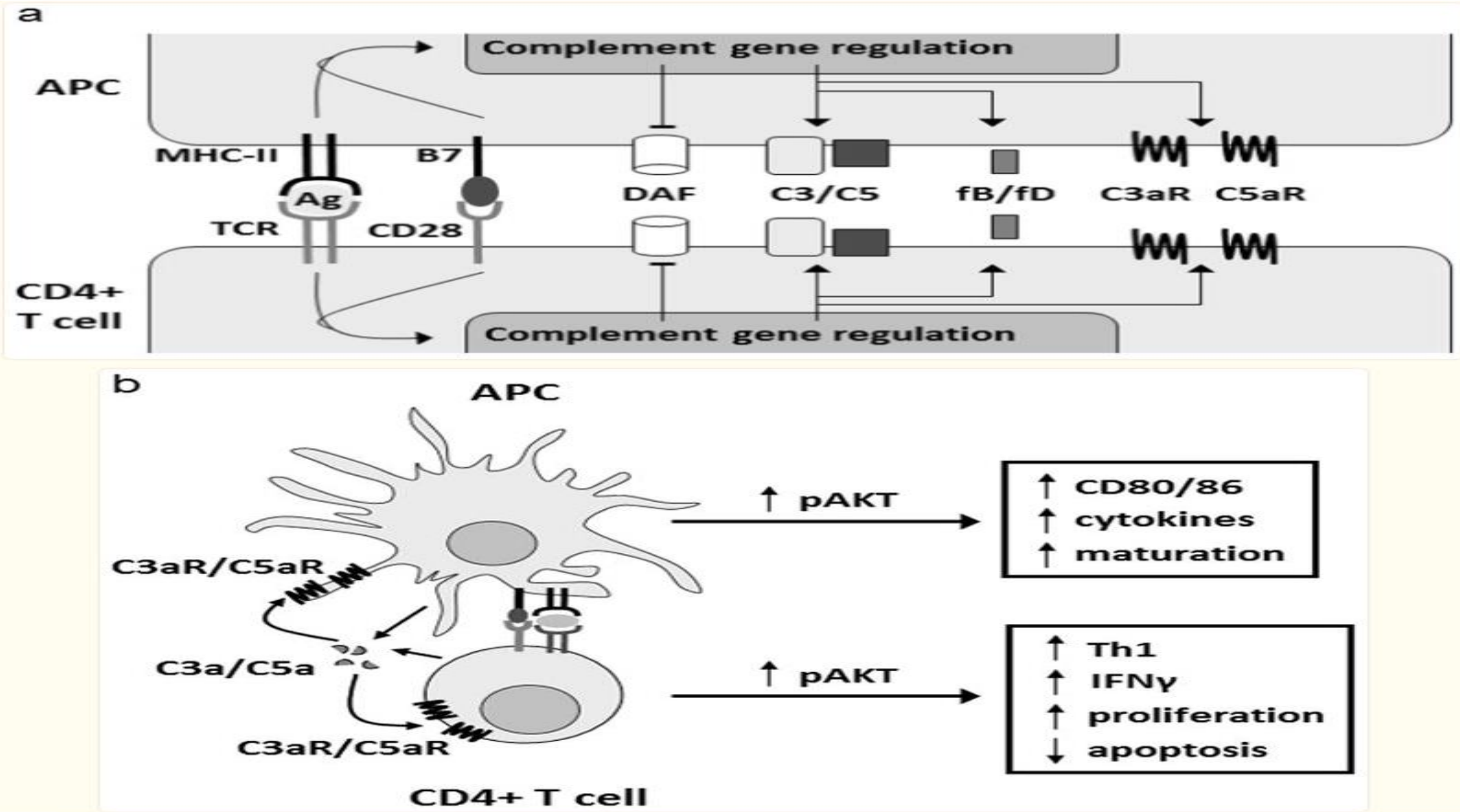
Małgorzata Kielar Biomolecules 2021, 11, 773

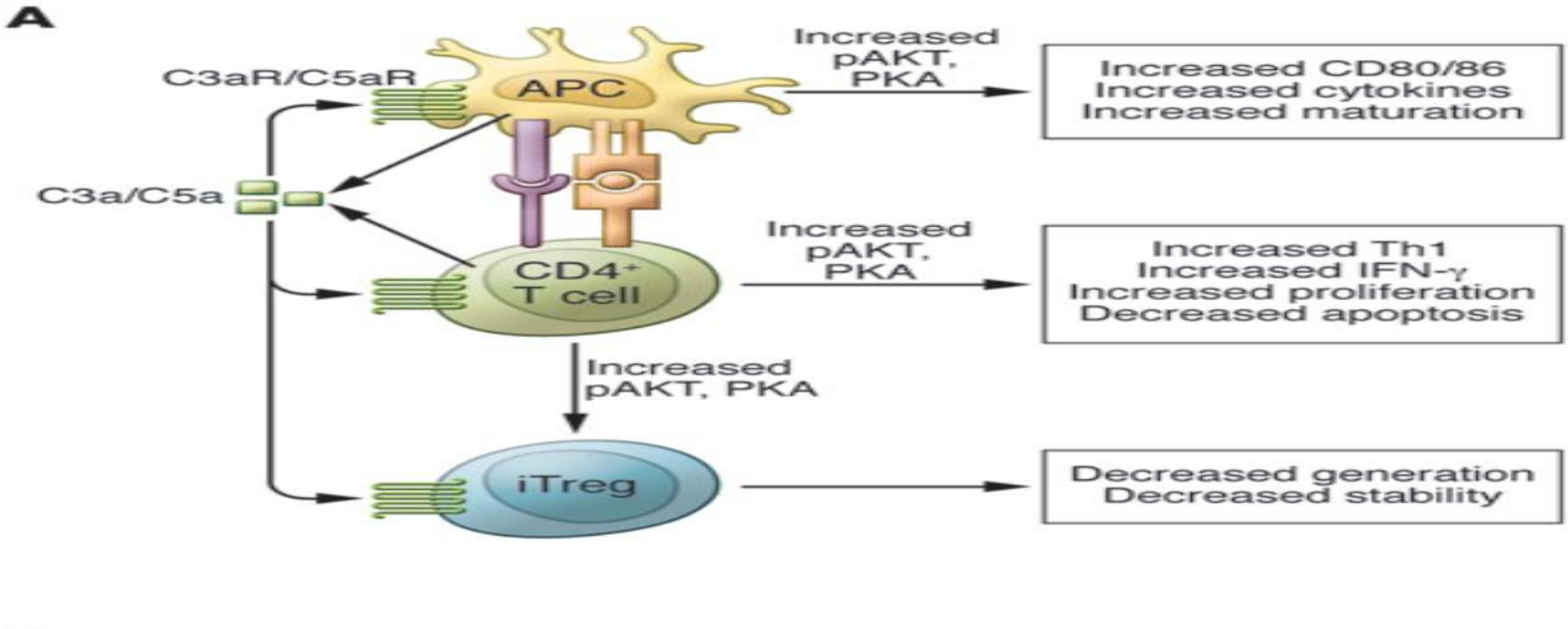
During a cognate interaction between APC and T cell, signaling through B7 costimulatory moleules and CD28 triggers local complement component production and release by both cells (~1000 fold more is produced by the APC) along with a transient downregulation of cell surface DAF and upregulation of C3aR/C5aR.

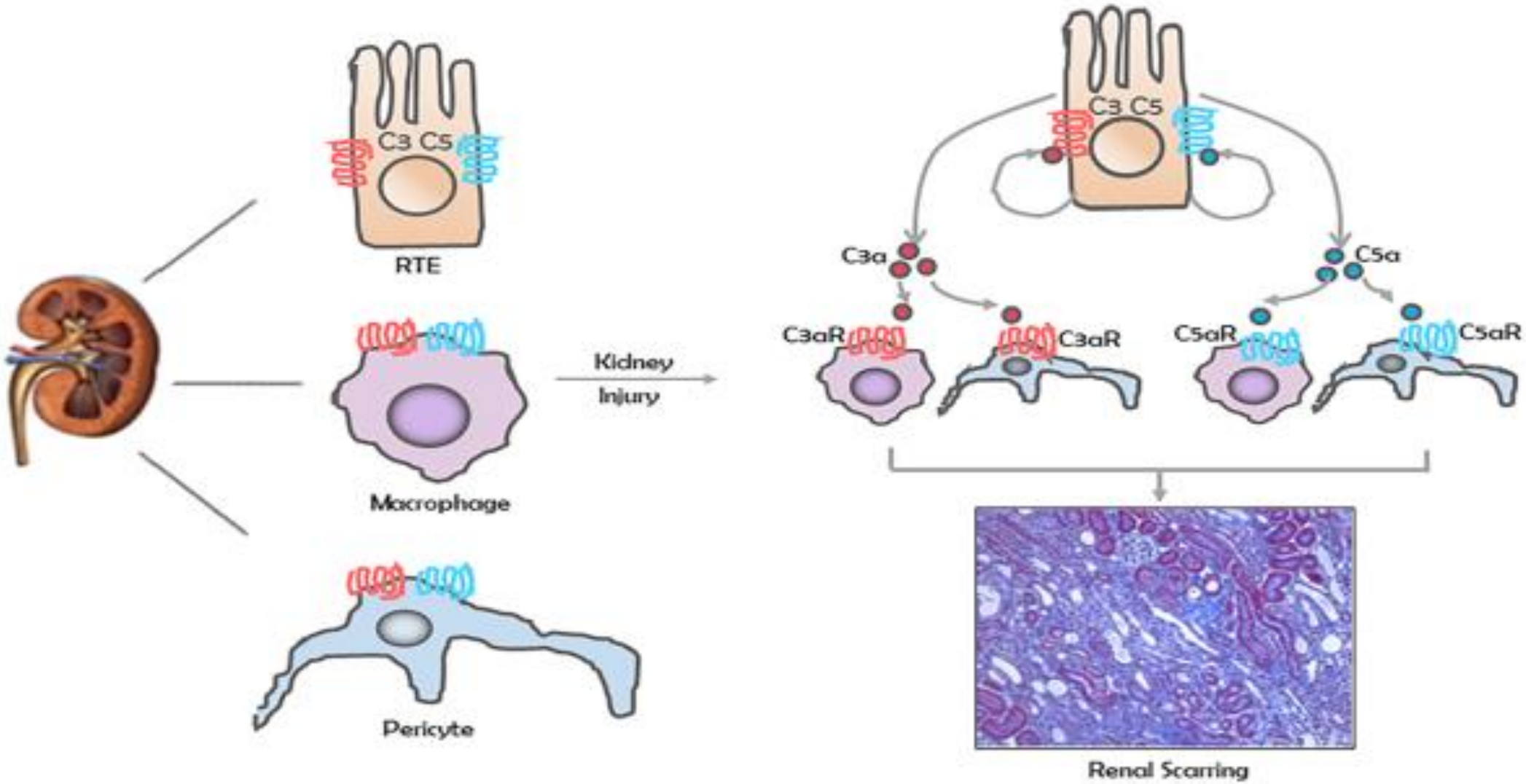
These conditions favor the local, spontaneous, activation of complement by the alternative pathway. Consequently, local levels of C3a and C5a increase which stimulate both partners through their respective receptors. C3aR/C5aR signaling on both APC and T cells activates the AKT pathway by phosphorylation

AKT activation on the APC stimulates maturation, cytokine production, and B7 costimulatory molecule expression. AKT activation on the T cell directly promotes IFNγ secretion, reduces susceptibility to apoptosis, and promotes cell proliferation. In this manner, C3aR/C5aR stimulation directly and indirectly promotes T cell maturation with an expanded effector repertoire.

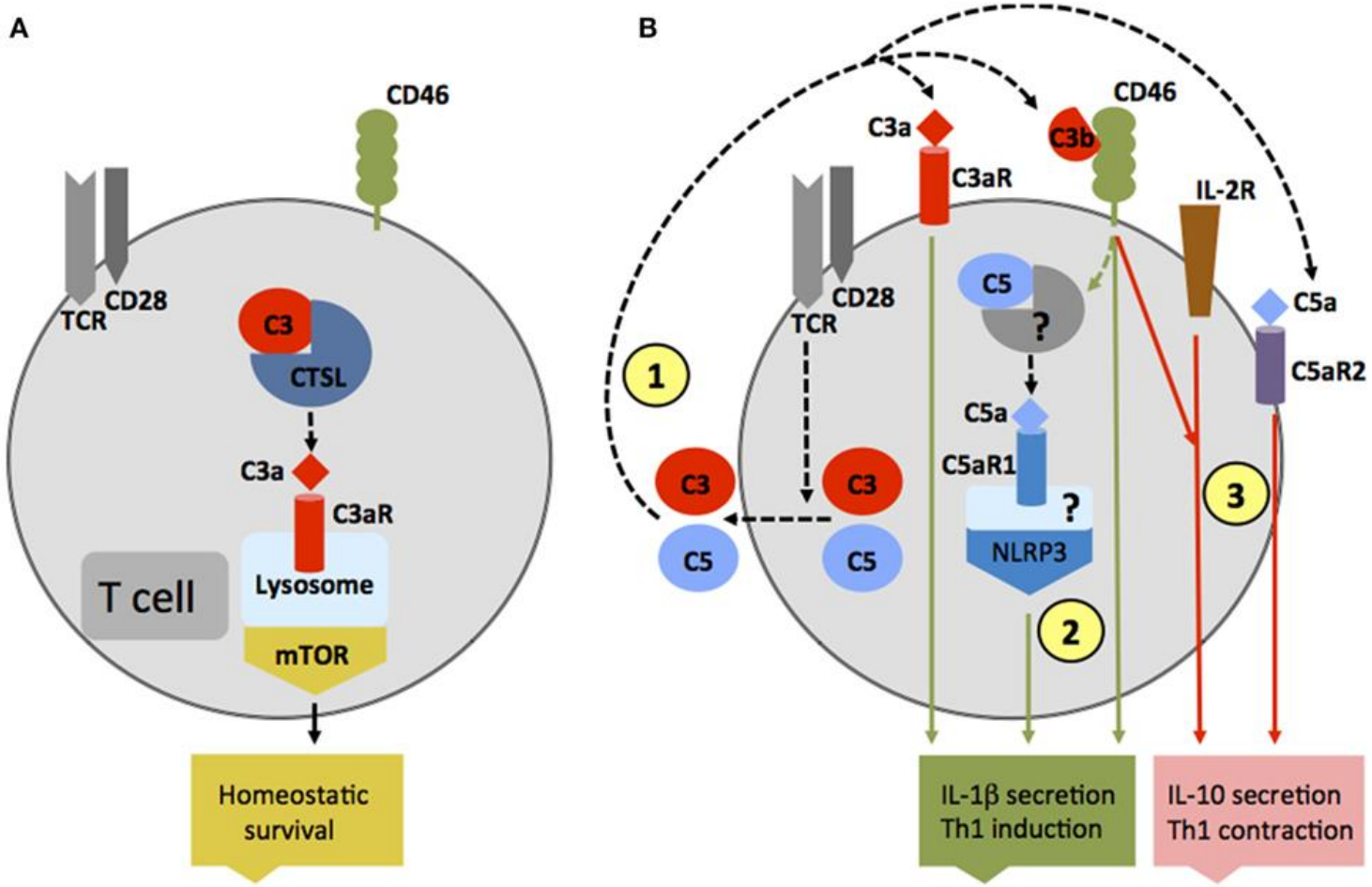
Anna B, Curr Opin Organ Transplant. 2019 December ; 24(6): 659–663


a
APC
Complement gene regulation
MHC-II
B7
Ag
TCR
CD28
DAF
C3/C5
fB/fD
C3aR
C5aR
CD4+
T cell
Complement gene regulation
b
APC
C3aR/C5aR
C3a/C5a
C3aR/C5aR
CD4+ T cell
↑ pAKT
↑ CD80/86
↑ cytokines
↑ maturation
↑ pAKT
↑ Th1
↑ IFNγ
↑ proliferation
↓ apoptosis


A
C3aR/C5aR
APC
Increased pAKT, PKA
Increased CD80/86
Increased cytokines
Increased maturation
C3a/C5a
CD4+ T cell
Increased pAKT, PKA
Increased Th1
Increased IFN-γ
Increased proliferation
Decreased apoptosis
Increased pAKT, PKA
iTreg
Decreased generation
Decreased stability


C3 C5
RTE
Macrophage
Pericyte
Kidney
Injury
C3a
C5a
C3aR
C3aR
C5aR
C5aR
Renal Scarring

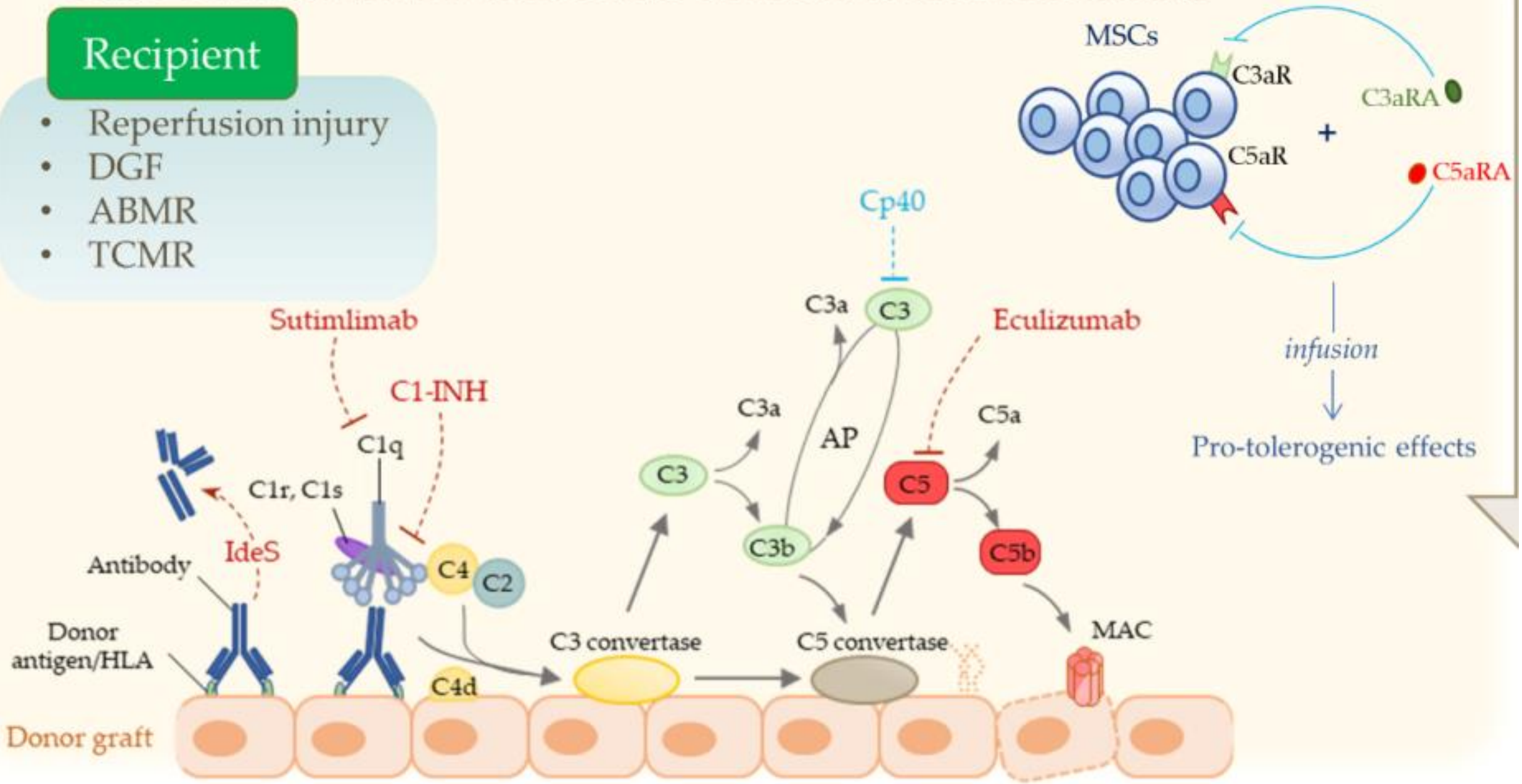
-Continued

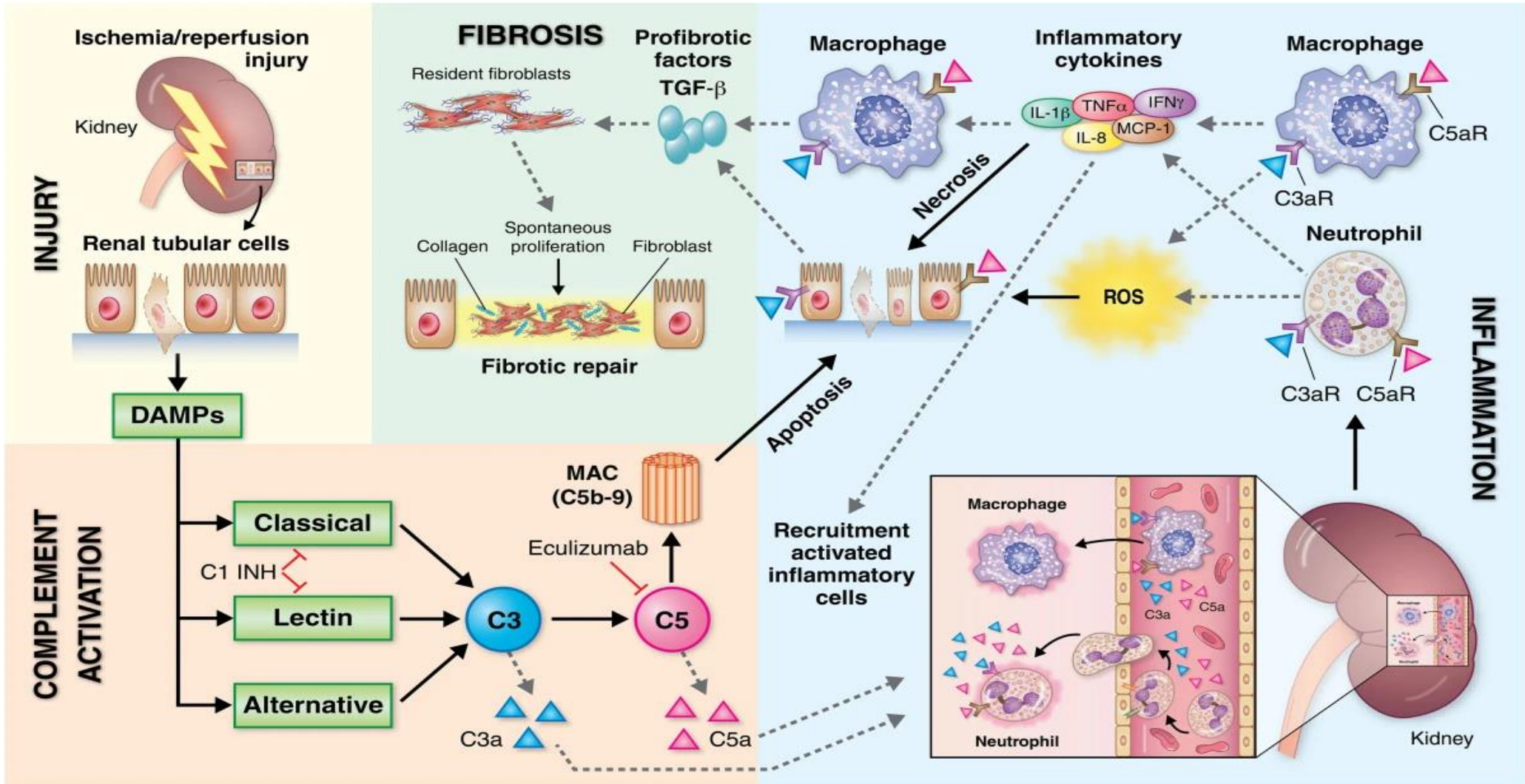

A
CD46
TCR
CD28
C3
CTSL
C3a
C3aR
T cell
Lysosome
mTOR
Homeostatic survival
B
C3a
C3b
CD46
C3aR
IL-2R
C5
?
C5a
C5aR2
TCR
CD28
1
C3
C3
C5
C5
C5a
C5aR1
?
NLRP3
3
2
IL-1β secretion
Th1 induction
IL-10 secretion
Th1 contraction

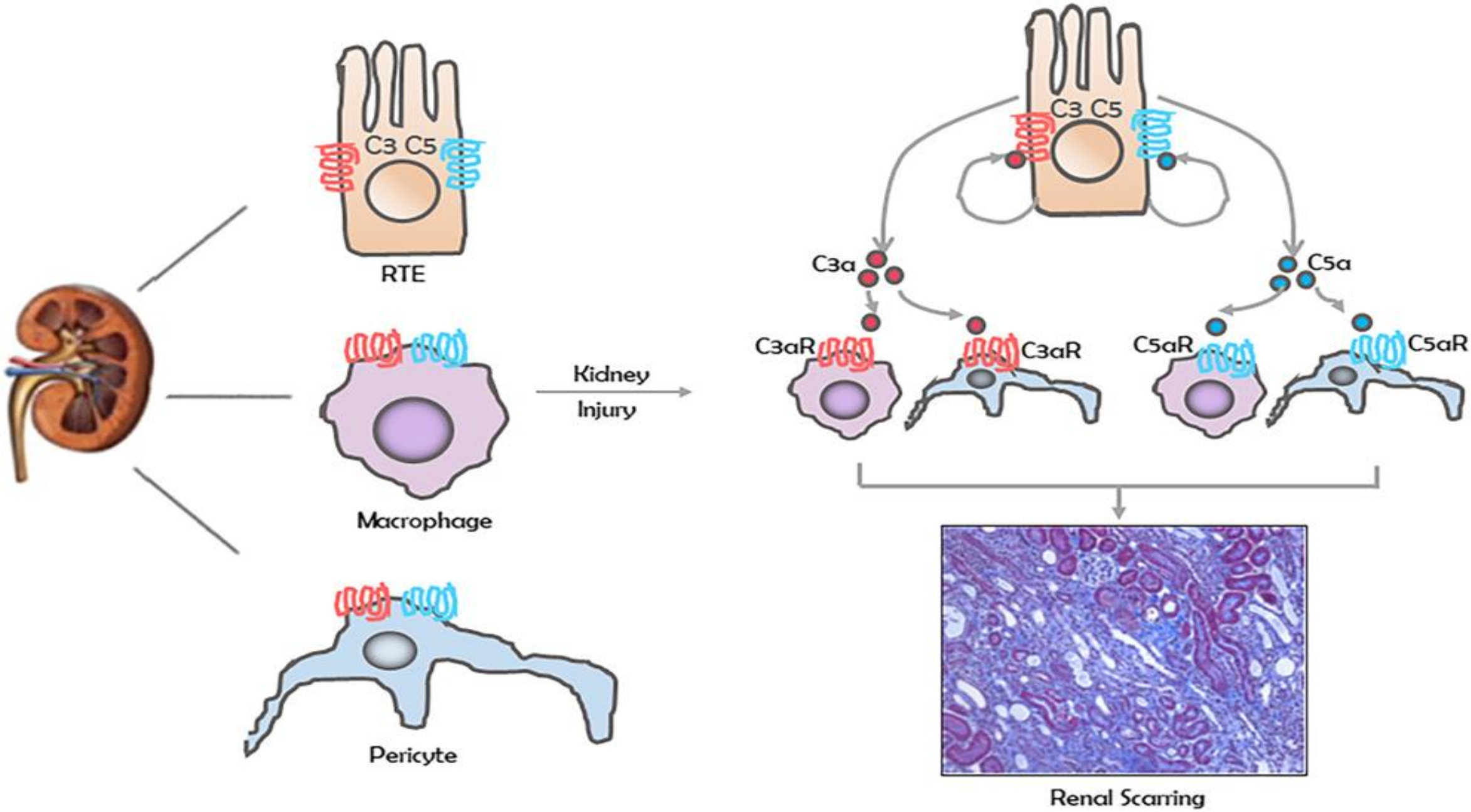
POST-TRANSPLANT PERIOD AND THERAPEUTIC STRATEGIES

Recipient

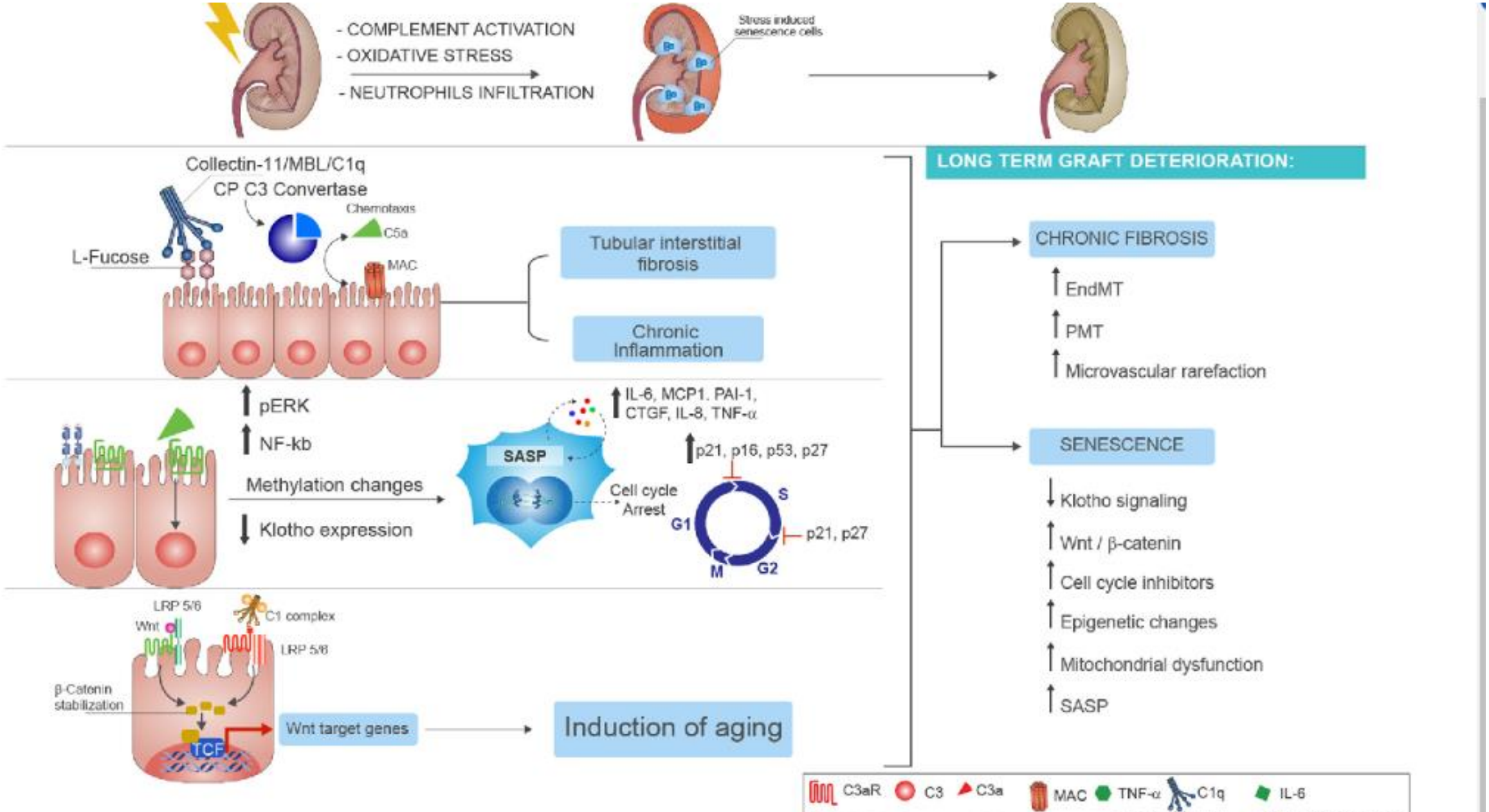
- Reperfusion injury
- DGF
- ABMR
- TCMR




INJURY
Ischemia/reperfusion injury
Kidney
Renal tubular cells
DAMPs
FIBROSIS
Profibrotic factors
TGF-β
Resident fibroblasts
Collagen
Spontaneous proliferation
Fibroblast
Fibrotic repair
Macrophage
Inflammatory cytokines
IL-1β
TNFα
IFNγ
IL-8
MCP-1
Macrophage
C5aR
C3aR
Necrosis
Neutrophil
ROS
C3aR
C5aR
Apoptosis
INFLAMMATION
COMPLEMENT ACTIVATION
Classical
C1 INH
Lectin
Alternative
C3
C5
MAC (C5b-9)
Eculizumab
C3a
C5a
Recruitment activated inflammatory cells
Macrophage
C3a
C5a
Neutrophil
Kidney


C3 C5
RTE
Macrophage
Pericyte
Kidney
Injury
C3 C5
C3a
C5a
C3aR
C3aR
C5aR
C5aR
Renal Scarring

Long term – Fibrosis



Innate

Pre-existing, ready to mobilize and fight allograft

- Phagocytes
- Dendritic cells,
- NK cells,
- Proteins
- Receptors

Adaptive

Combat when activated

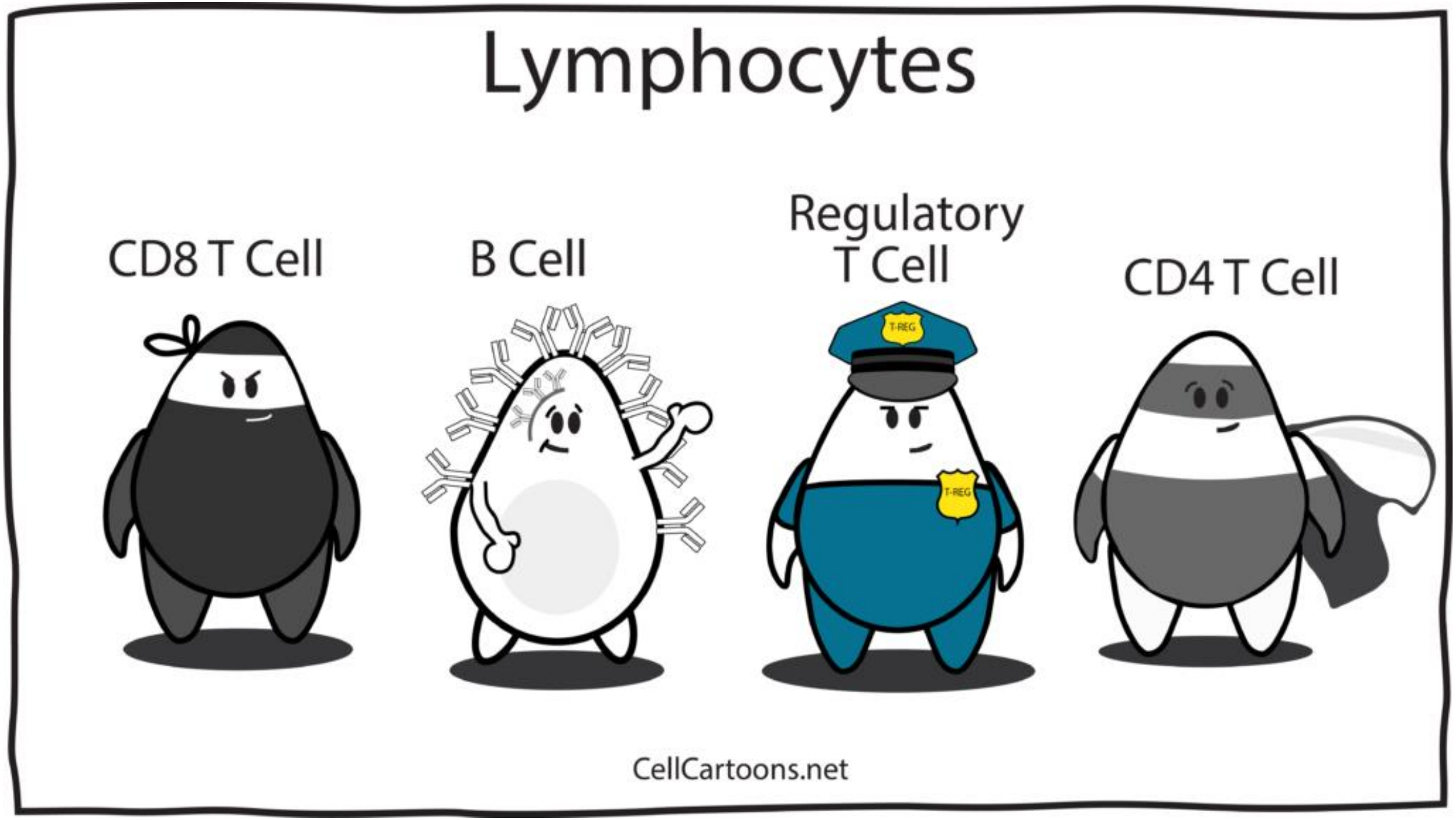
- Naïve B Cells directed antibody-mediated
- Naïve T Cells directed cell-mediated

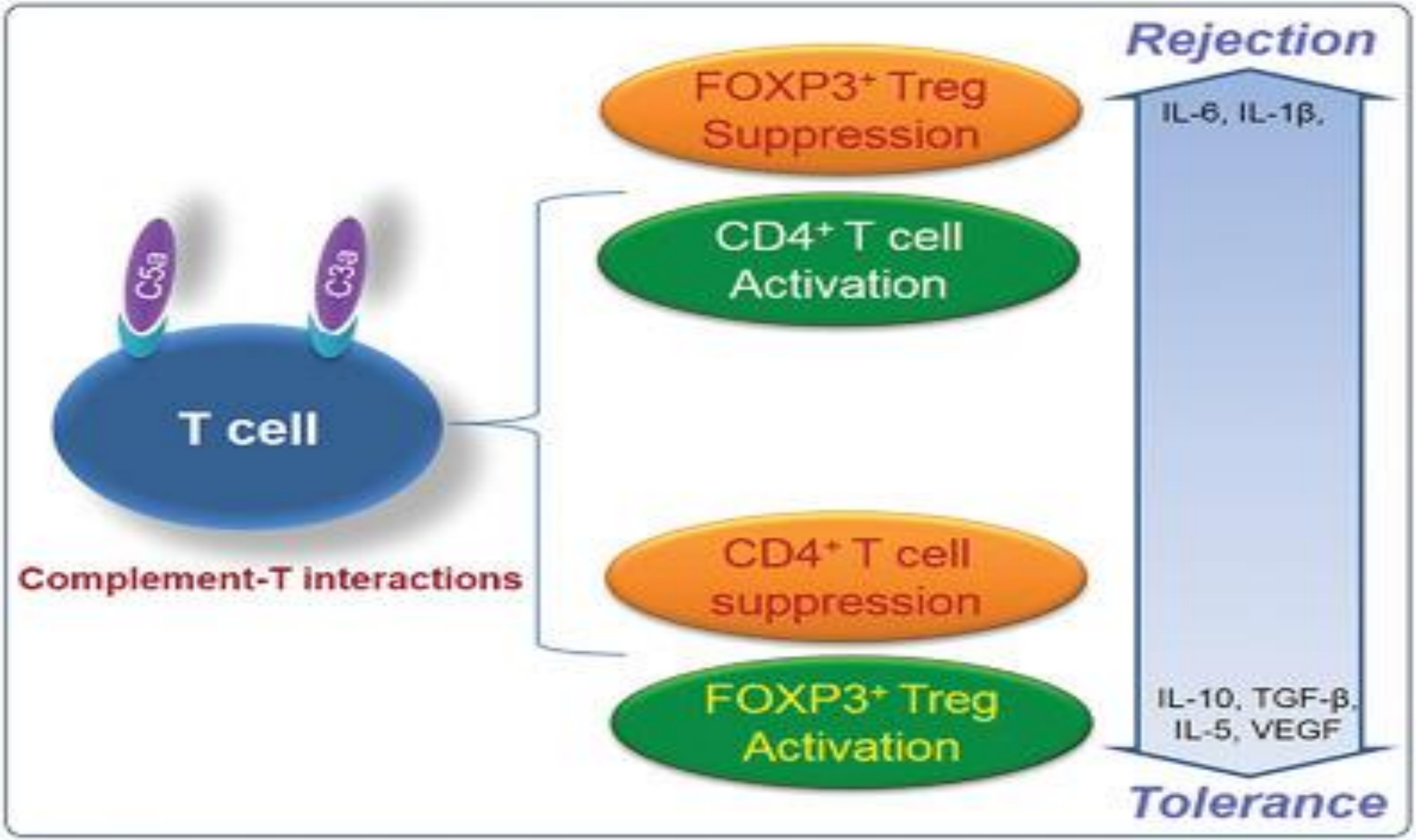
Combined

Initial innate responses condition the resistance to tolerance

- Donor-derived antigen-presenting cells
- Orchestrated storm: antibody-complement-FcγRs-endothelium

Complement and Tolerance

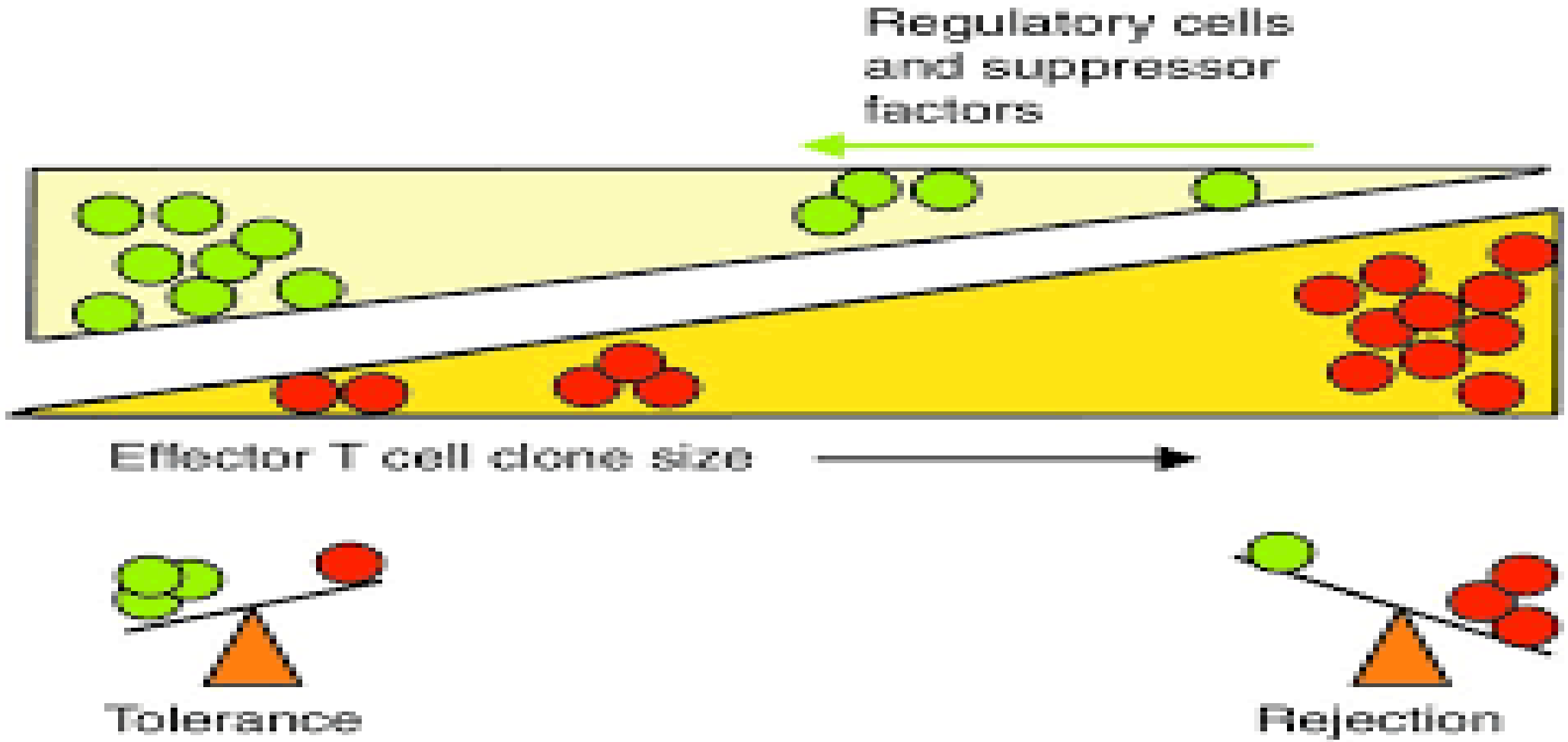



Rejection
FOXP3+ Treg Suppression
CD4+ T cell Activation
IL-6, IL-1β,
C5a
C3a
T cell
Complement-T interactions
CD4+ T cell suppression
FOXP3+ Treg Activation
IL-10, TGF-β, IL-5, VEGF
Tolerance

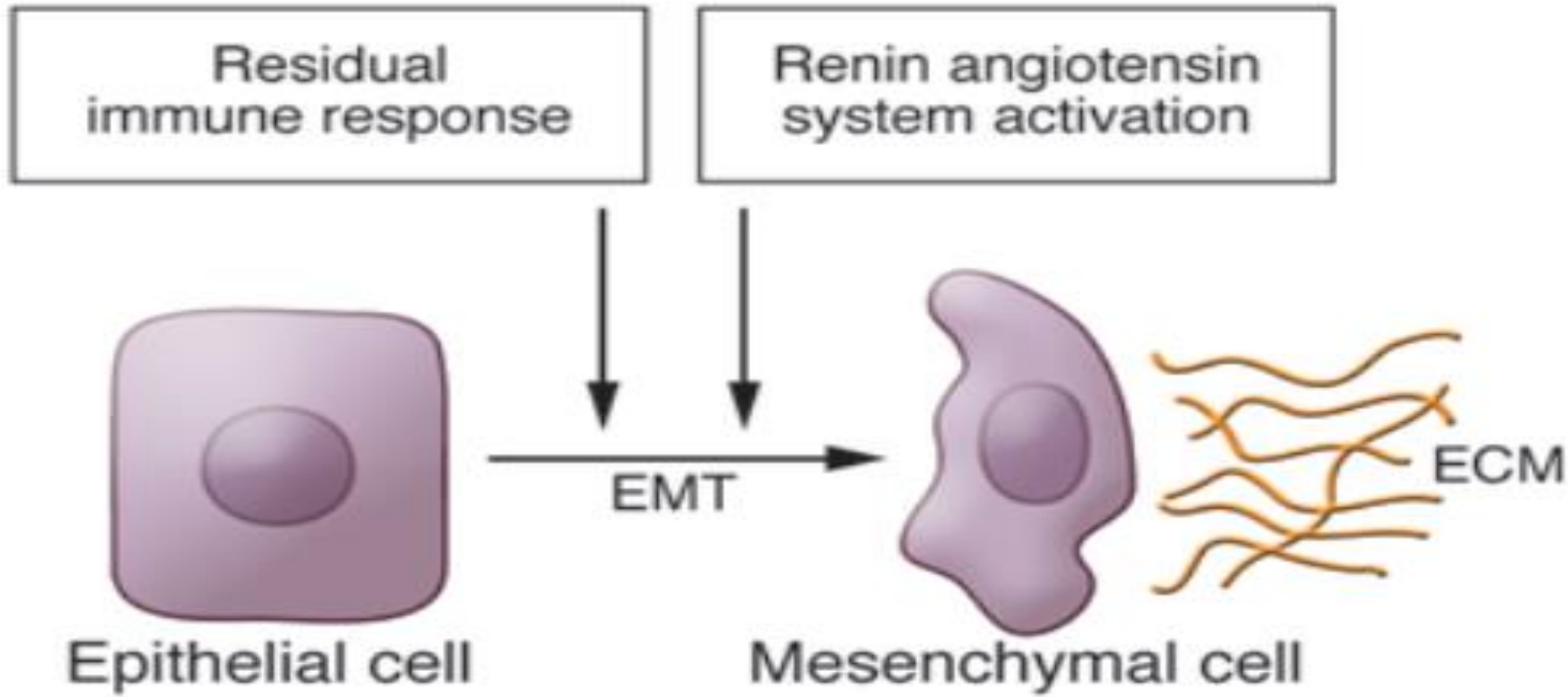
-Continued

Regulatory T cells (Tregs) are a subset of T cells that suppress immune activation and limit autoimmunity in the periphery

A number of cell types with immune-regulatory function have been characterized as Tregs, though the one best understood, at present, are the CD4+FOXP3+ Tregs. These either arise in the thymus (tTregs) or develop from peripheral CD4+ T cells that convert into CD4+FOXP3+ Tregs as peripherally derived Tregs (pTregs)


Regulatory cells
and suppressor
factors
Effector T cell clone size
Tolerance
Rejection

D


Residual immune response
Renin angiotensin system activation
EMT
ECM
Epithelial cell
Mesenchymal cell

Role of Complement System in Kidney Transplantation: Stepping From Animal Models to Clinical Application

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Kidney transplantation is a life-saving strategy for patients with end-stage renal diseases. Despite the advances in surgical techniques and immunosuppressive agents, the long-term graft survival remains a challenge. Growing evidence has shown that the complement system, part of the innate immune response, is involved in kidney transplantation. Novel insights highlighted the role of the locally produced and intracellular complement components in the development of inflammation and the alloreactive response in the kidney allograft. In the current review, we provide the updated understanding of the complement system in kidney transplantation. We will discuss the involvement of the different complement components in kidney ischemia–reperfusion injury, delayed graft function, allograft rejection, and chronic allograft injury. We will also introduce the existing and upcoming attempts to improve allograft outcomes in animal models and in the clinical setting by targeting the complement system.

Keywords: complement activation, kidney transplantation, ischemia–reperfusion injury, delayed graft function, T-cell-mediated rejection, antibody-mediated rejection, eculizumab, C1-INH

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The role of complement inhibition in kidney transplantation

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Review

The Complement System in Kidney Transplantation

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Abstract: Kidney transplantation is the therapy of choice for patients who suffer from end-stage renal diseases. Despite improvements in surgical techniques and immunosuppressive treatments, long-term graft survival remains a challenge. A large body of evidence documented that the complement cascade, a part of the innate immune system, plays a crucial role in the deleterious inflammatory reactions that occur during the transplantation process, such as brain or cardiac death of the donor and ischaemia/reperfusion injury. In addition, the complement system also modulates the responses of T cells and B cells to alloantigens, thus playing a crucial role in cellular as well as humoral responses to the allograft, which lead to damage to the transplanted kidney. Since several drugs that are capable of inhibiting complement activation at various stages of the complement cascade are emerging and being developed, we will discuss how these novel therapies could have potential applications in ameliorating outcomes in kidney transplantations by preventing the deleterious effects of ischaemia/reperfusion injury, modulating the adaptive immune response, and treating antibody-mediated rejection.

Keywords: complement activation; kidney transplantation; ischaemia/reperfusion injury; delayed graft function; alloresponse; antibody-mediated rejection; complement therapeutics

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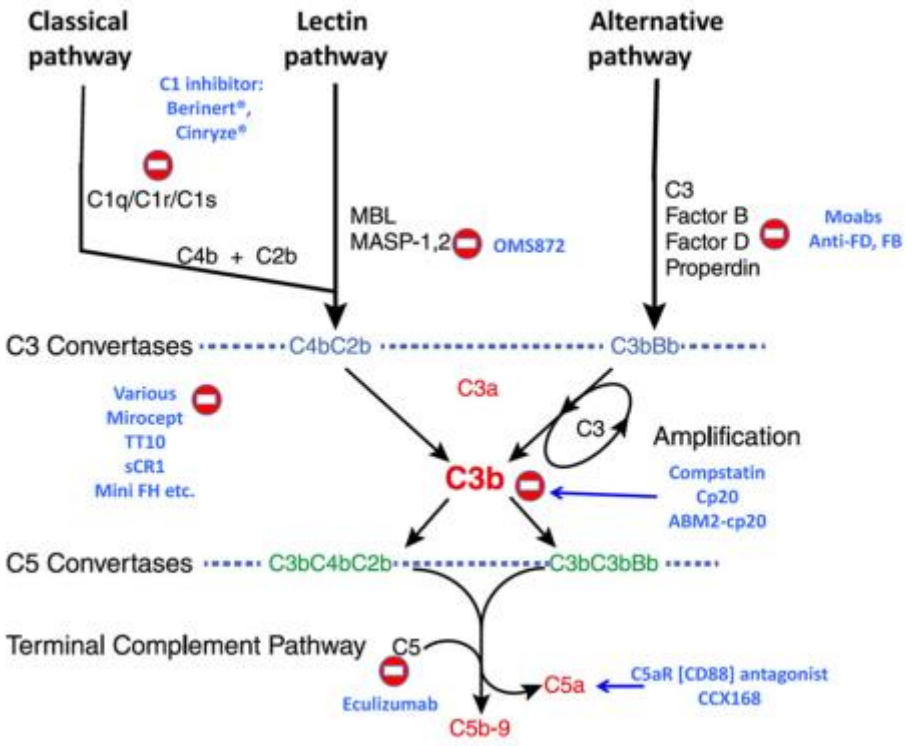
Classical pathway
Lectin pathway
Alternative pathway
C1 inhibitor: Berinert®, Cinryze®
C1q/C1r/C1s
C4b + C2b
MBL
MASP-1,2
OMS872
C3
Factor B
Factor D
Properdin
Moabs
Anti-FD, FB
C3 Convertases
C4bC2b
C3bBb
Various
Mirocept
TT10
sCR1
Mini FH etc.
C3a
C3
Amplification
C3b
Compstatin
Cp20
ABM2-cp20
C5 Convertases
C3bC4bC2b
C3bC3bBb
Terminal Complement Pathway
C5
Eculizumab
C5a
C5aR [CD88] antagonist
CCX168
C5b-9