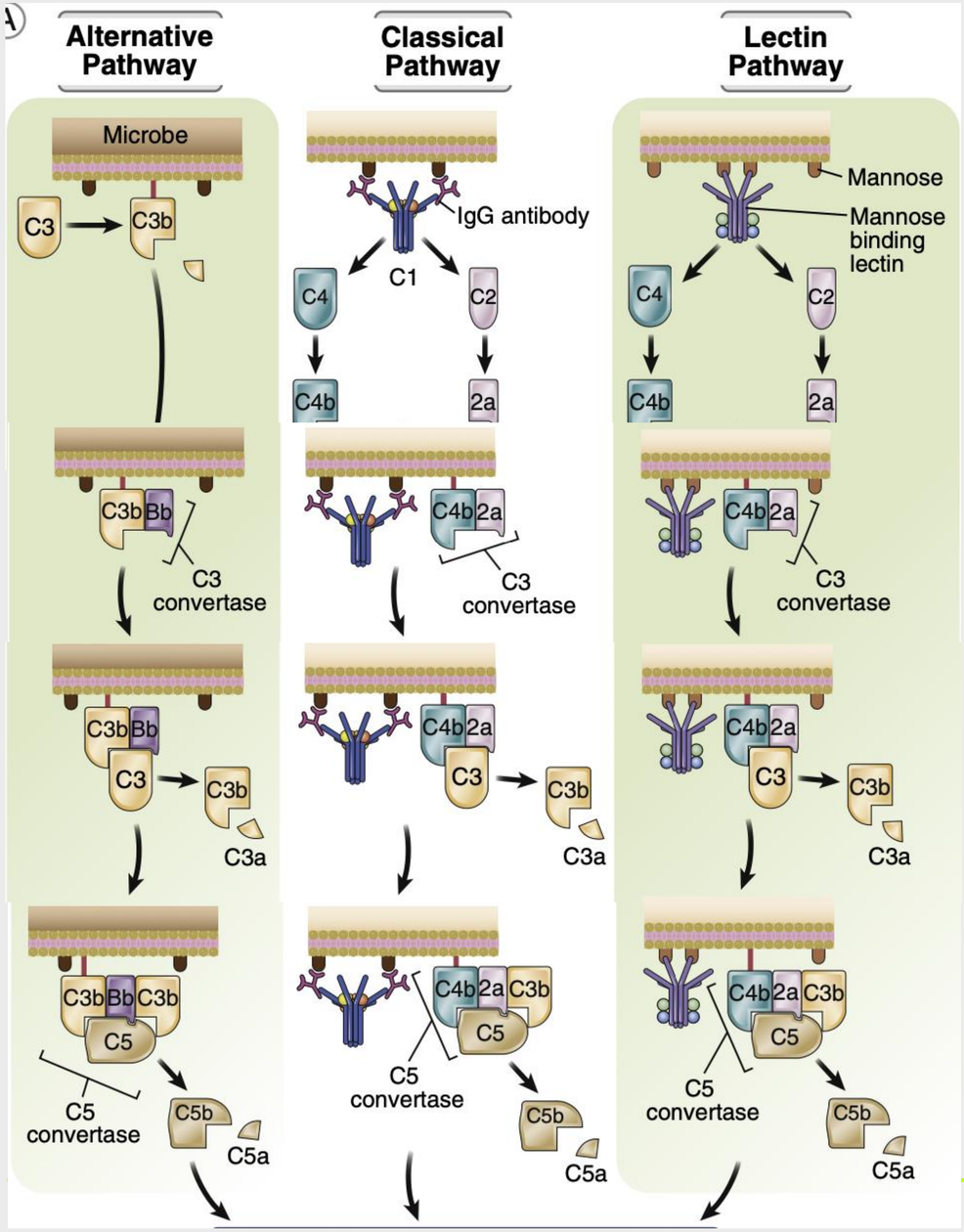
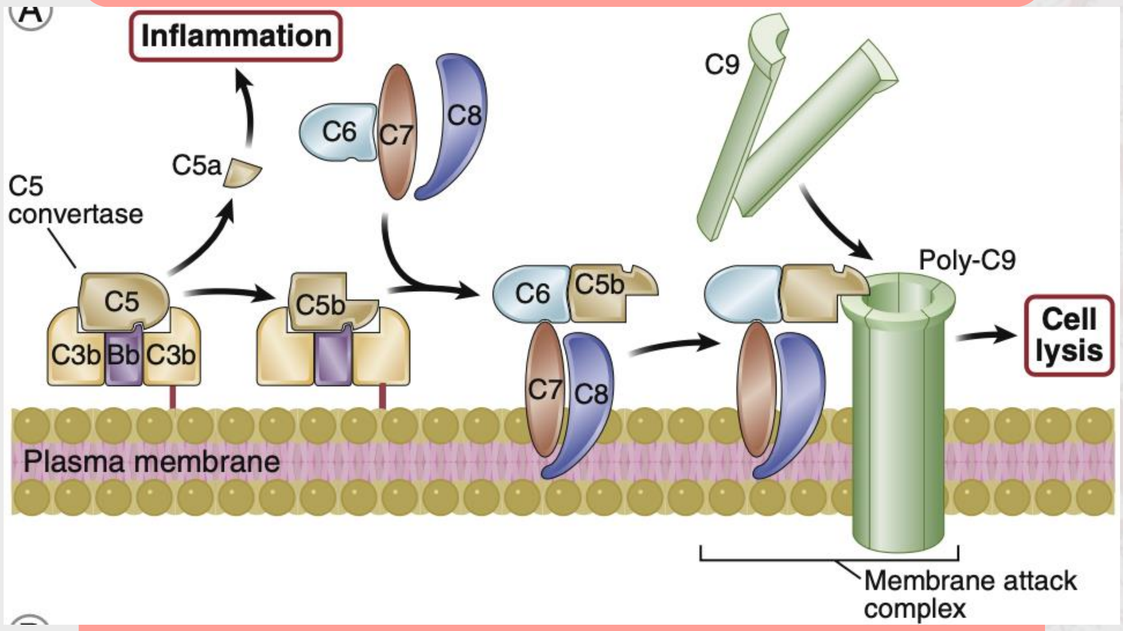
KOMPLEMAN İLİŞKİLİ HASTALIKLARA GENEL BAKIŞ VE BÖBREK NAKLİ

Dr. Gizem Kumru
ANKARA ÜNİVERSİTESİ TIP FAKÜLTESİ, NEFROLOJİ BİLİM DALI

Kompleman Sistemi



Kompleman proteinlerinin mikrobiyal hücrelere (alternatif/lektin yolağı) veya antikorlara (klasik yolak) bağlanması

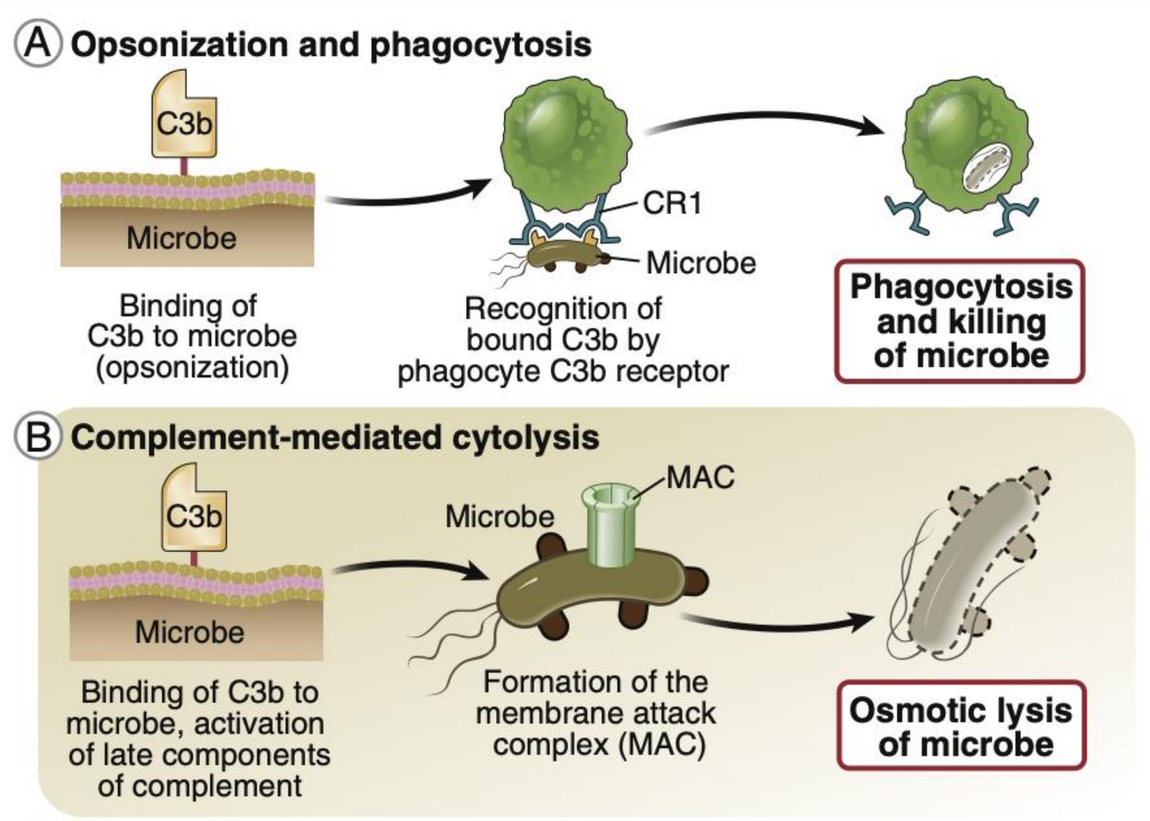


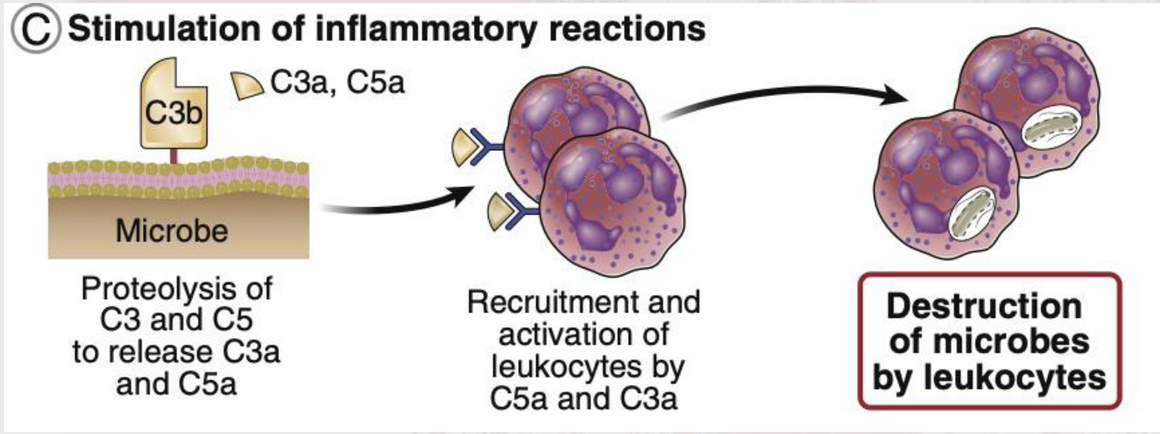
C3b kovalent bağlanması

C5 konvertaz oluşumu

Abbas AK, et al. Basic Immunology. 5th ed.

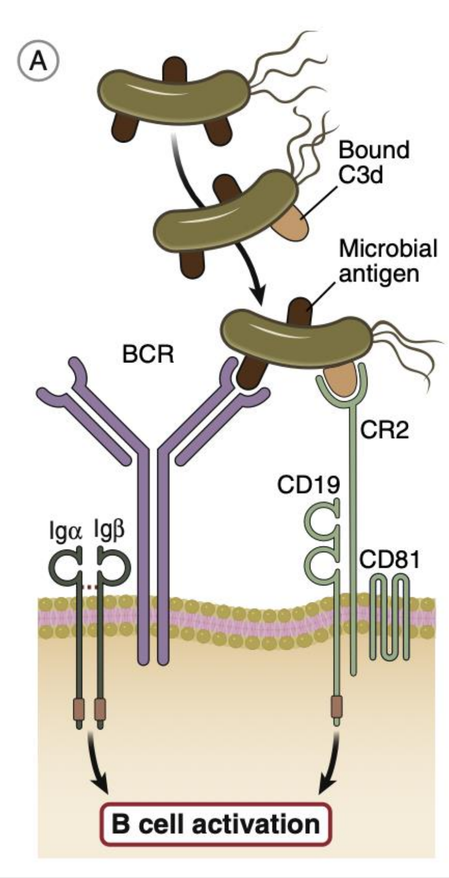
Kompleman sisteminin, doğal immünitede önemli antimikrobiyal efektör fonksiyonları vardır.

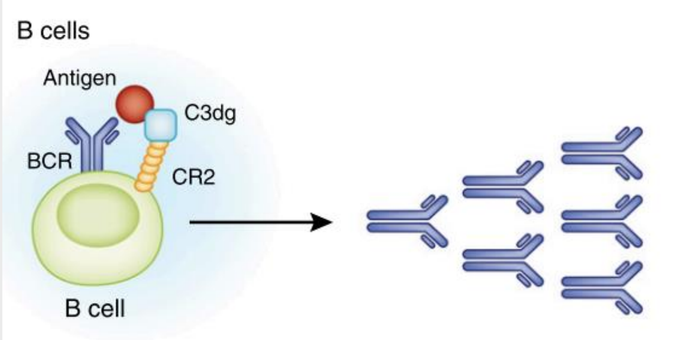




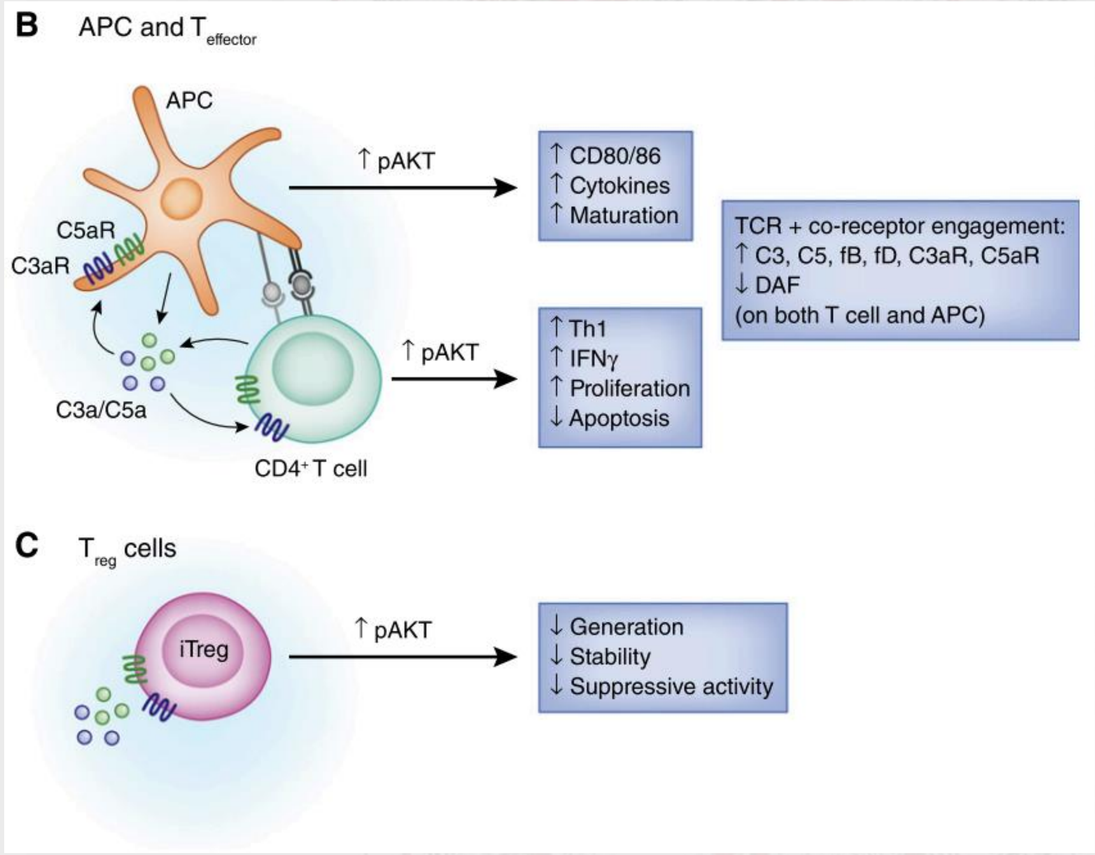
Abbas AK, et al. Basic Immunology. 5th ed.

Doğal immünitedeki rolünün yanı sıra, B hücre yanıtını ve antikor üretimini de uyarır.





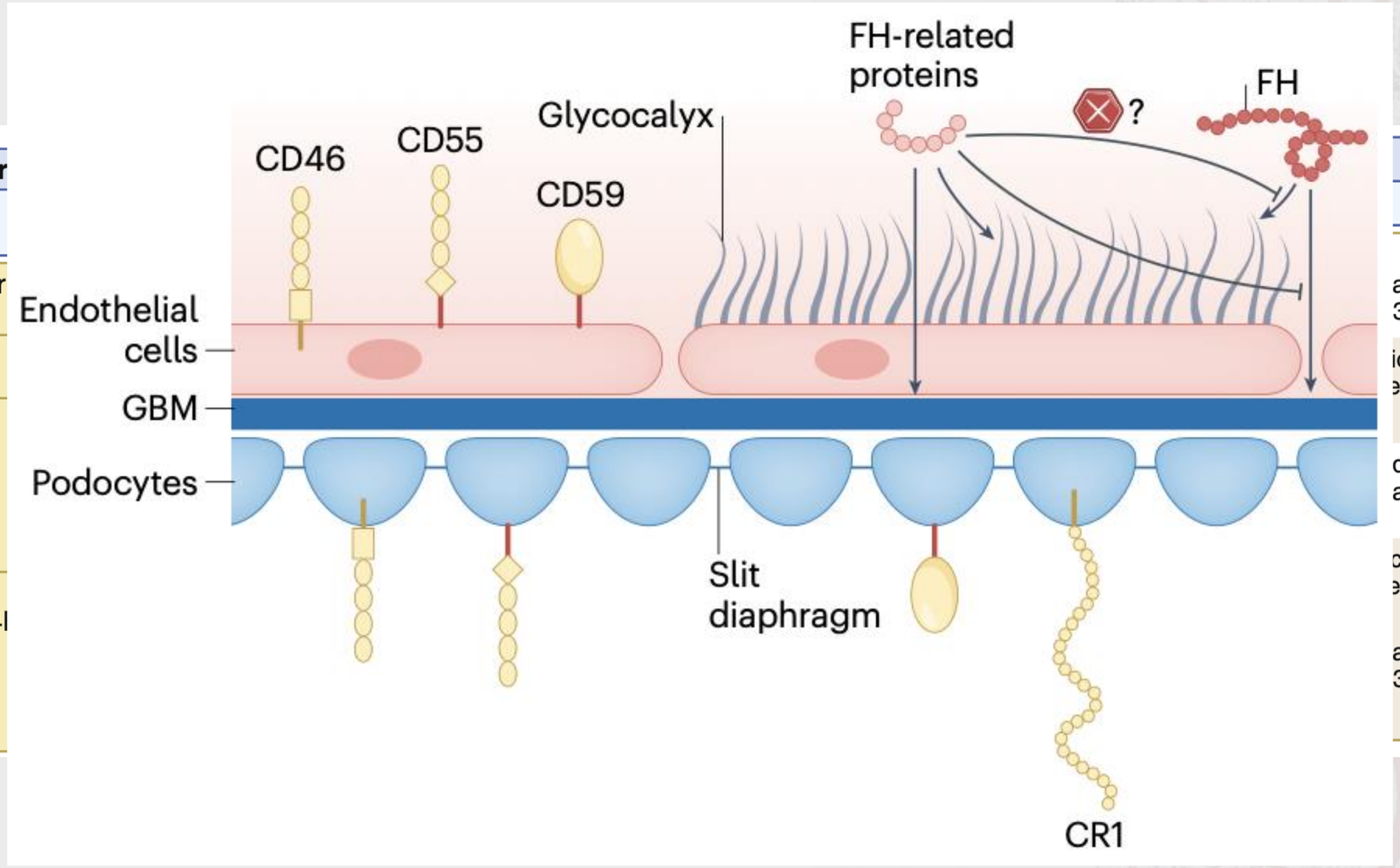
T hücre ve APC aktivasyon, proliferasyon ve sağkalımına katkıda bulunur.



Abbas AK, et al. Basic Immunology. 5th ed.

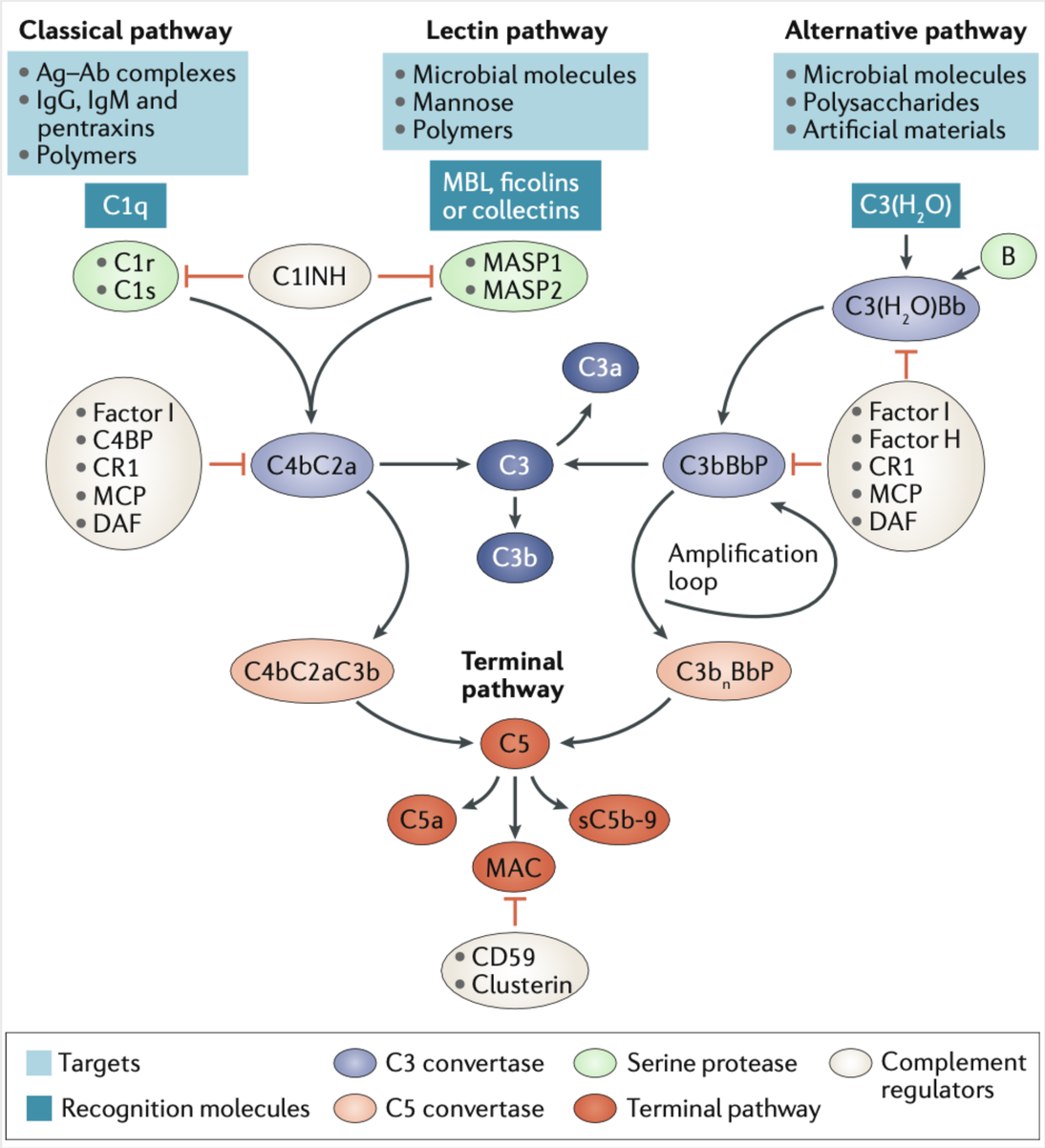
Mathern DR, Heeger PS. Clin J Am

Kompleman Aktivasyonu Regülasyonu



Abbas AK, et al. Basic Immunology. 5th ed.

Petr V, Thurman JM. Nat

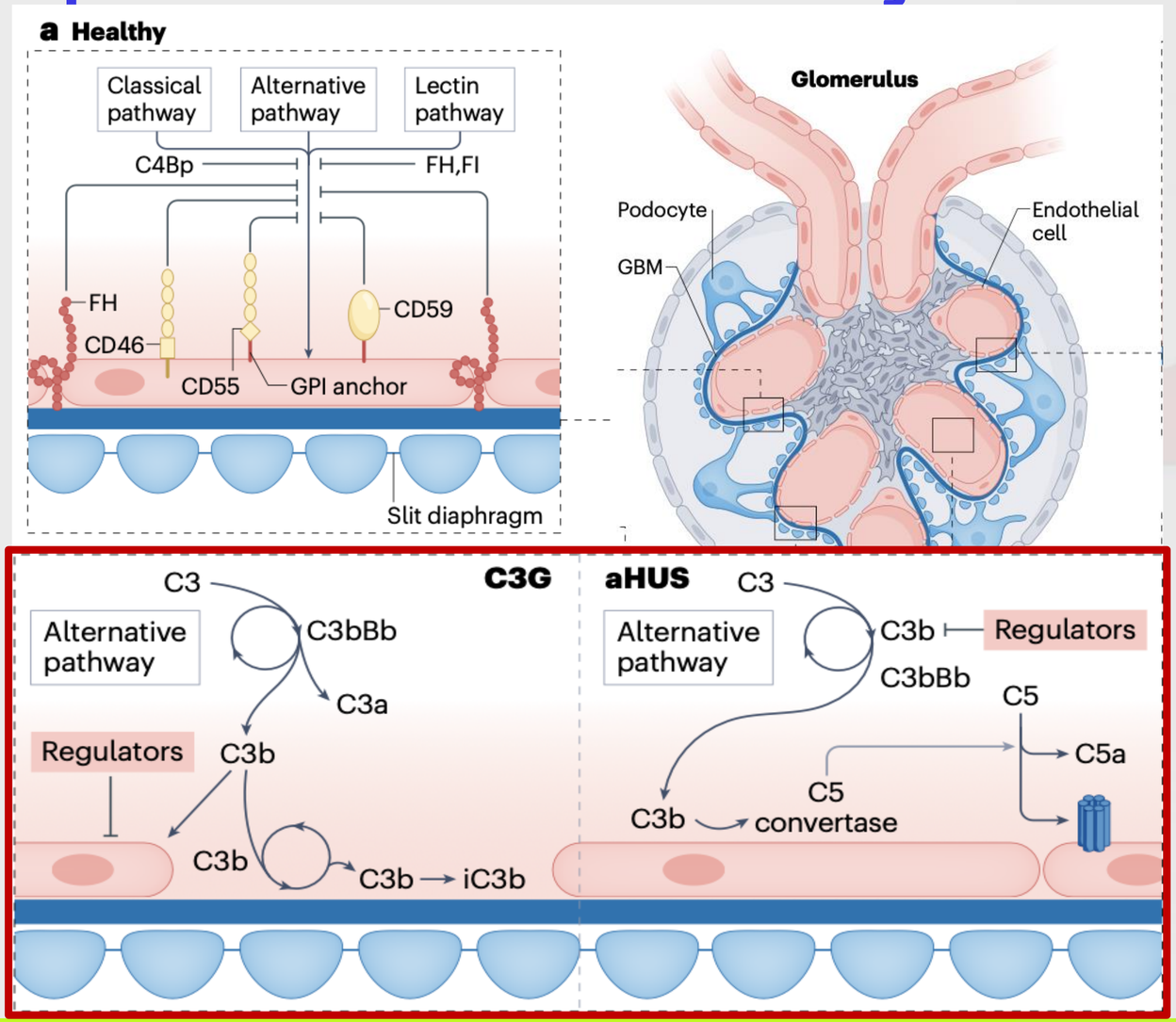


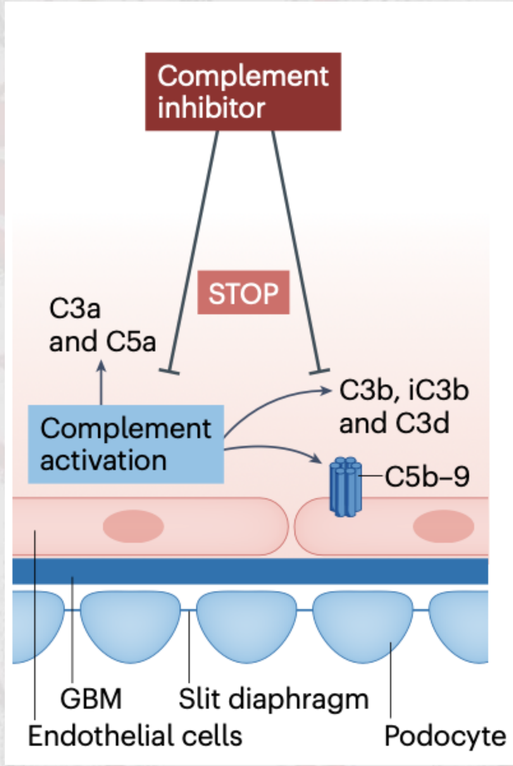
Kompleman sistemi,

konak savunması ve homeostazis için çok önemli olmasına rağmen, uygunsuz veya kontrolsüz aktivasyonu aynı zamanda doku hasarına da neden olabilir.

Biglarnia AR , et al. Nat Rev. 2018

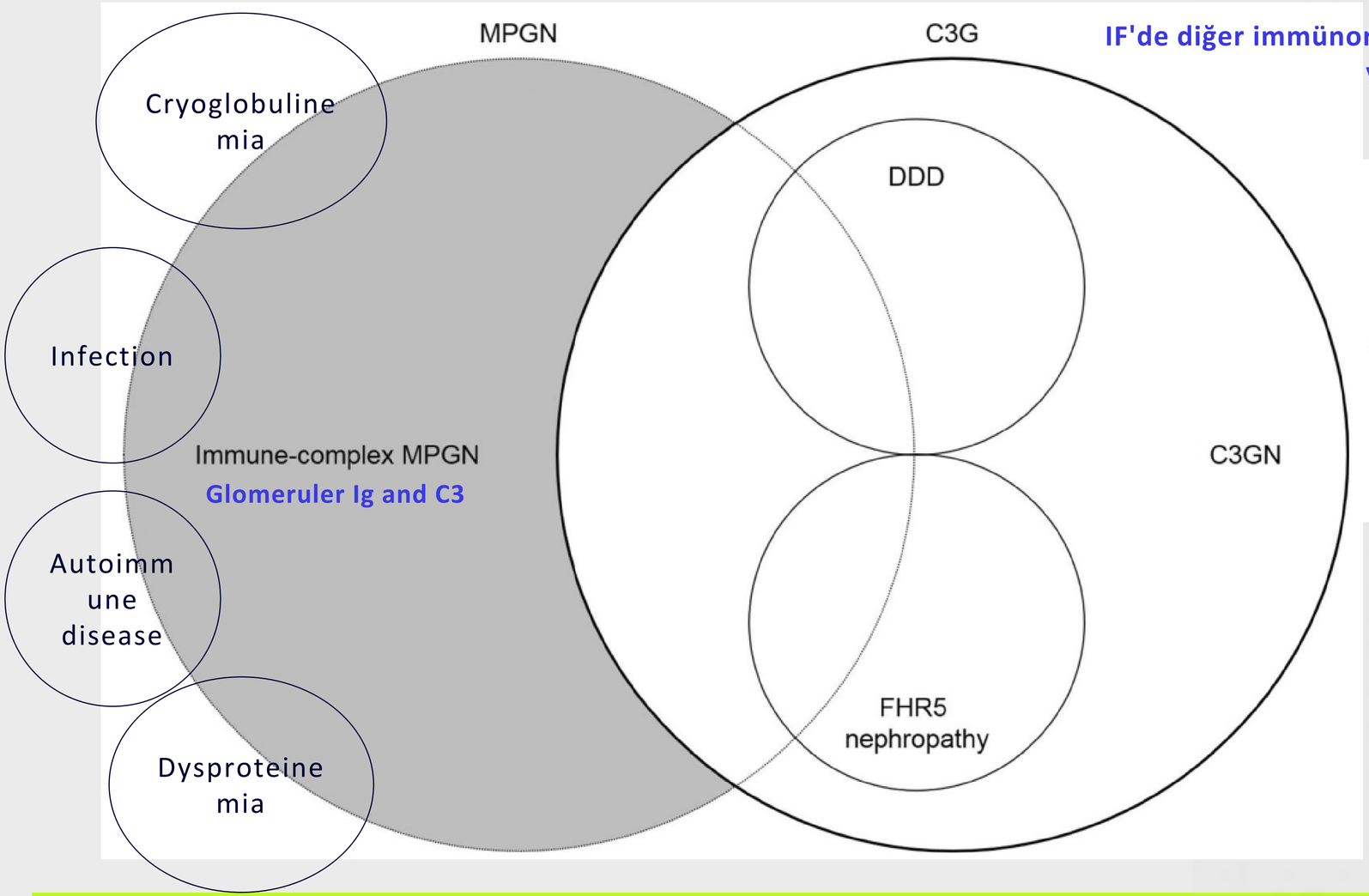
Kompleman Sistemi İlişkili Böbrek Hastalıkları



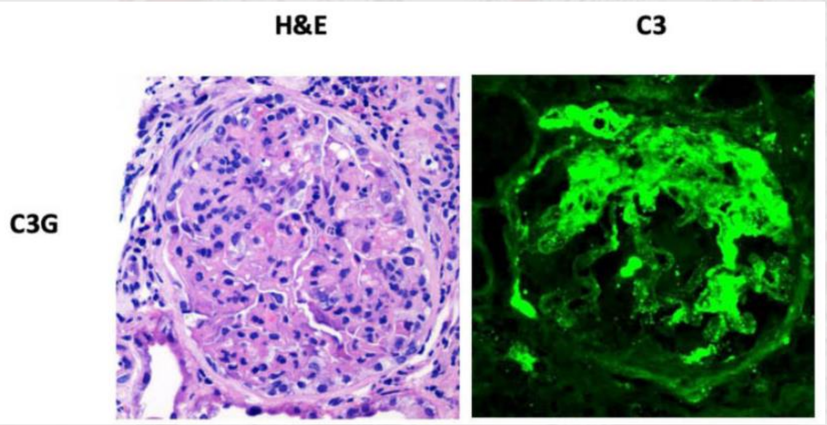


Petr V, Thurman JM. Nat Rev Nephrol. 2023.

MPGN ve C3 Glomerülopati Çakışması



IF'de diğer immünoreaktanlardan (IgG, IgM, IgA ve C1q) en az iki kat daha fazla yoğunlukta C3 baskın boyamanın varlığı



Gale DP, Maxwell PH. Nephrol Dial Transplant. 2013.

Wong EKS, Kavanagh D. Semin

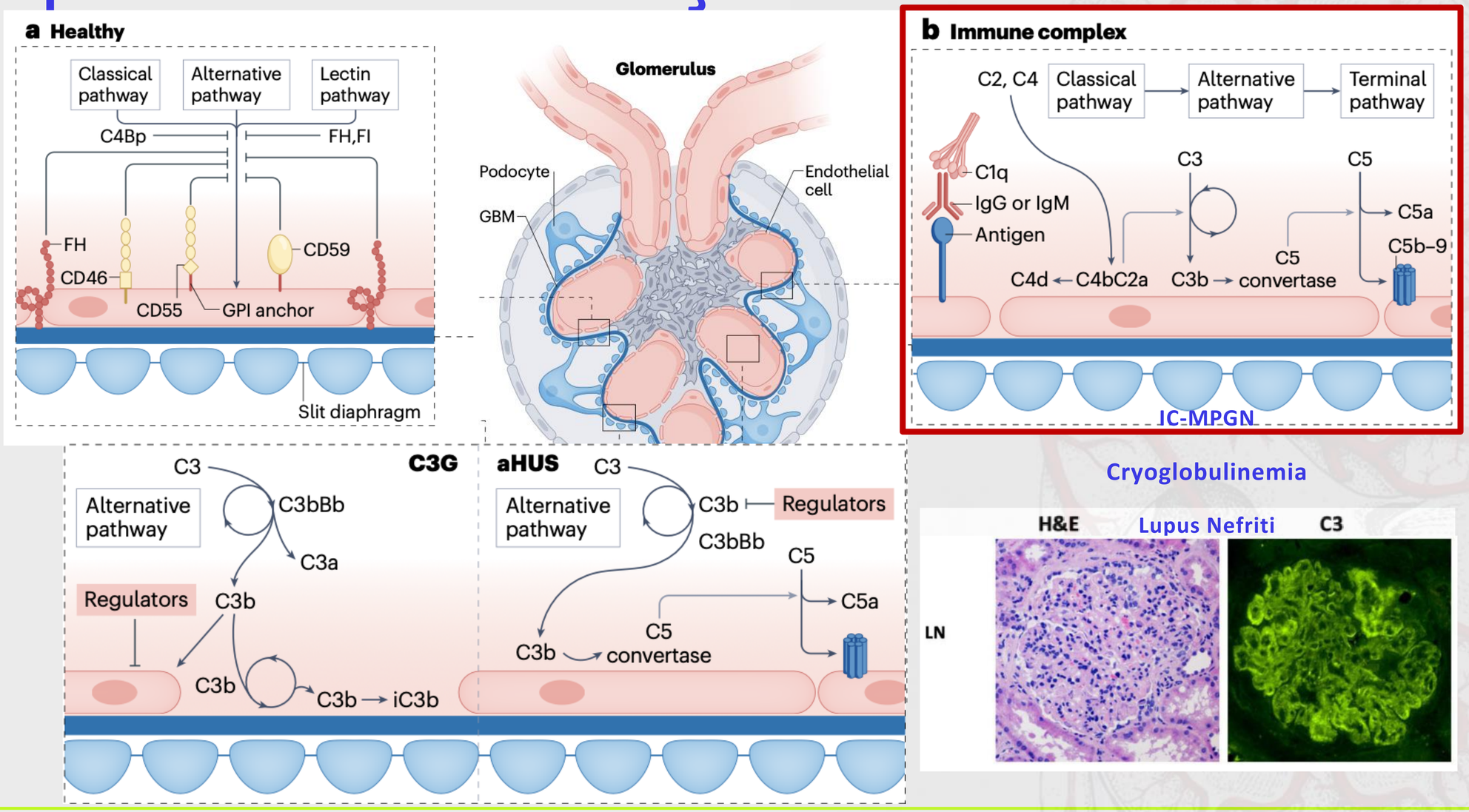
Parameter	aHUS[203]	C3G[204]
Clinical course	Acute	Chronic
Incidence	0.2–1.9/million/year[205]	1–3/million/year[206]
Associated infectious disease	Shiga toxin-producing *Escherichia coli* infection associated with haemolytic–uraemic syndrome	Post-infectious glomerulonephritis
Complement activation phase	Endothelial cell and/or glycocalyx	Fluid phase and/or glomerular basement membrane
Triggers	Autoimmunity, transplantation, pregnancy, infections, drugs and metabolic disease[207]	Infection[65,208]
Kidney failure	60–70% without complement inhibition; 10–15% with complement inhibition[203,209]	50% at 10 years[67]
Post-transplant recurrence	Variable; depends on genetic risk factors[210]	Very high[204]
Extrarenal manifestations	Systemic thrombotic microangiopathy; retinal drusen are rare	Partial lipodystrophy[211], retinal drusen[212]
C3 levels	Low in 30–50% of patients[213]	Low in up to 75% of patients[67,214]
Acquired drivers	Anti-factor H autoantibodies[215]	Nephritic factors[216], anti-factor H autoantibodies[215], monoclonal immunoglobulin[53,217]
Mutation	CFH, MCP, CFI, CFB, C3, THBD	CFH, C3, CFI, MCP, CFHR5
Type of mutation	Heterozyg > Homozyg	DDD: Homozyg > Homozyg C3GN: Heterozyg > Homozyg

Anti-C5 yanıtı?

Iptacopan ve pegcetacoplan ile proteinüride azalma ve böbrek fonk. stabilizasyonu

Petr V, Thurman JM. Nat Rev Nephrol. 2023.

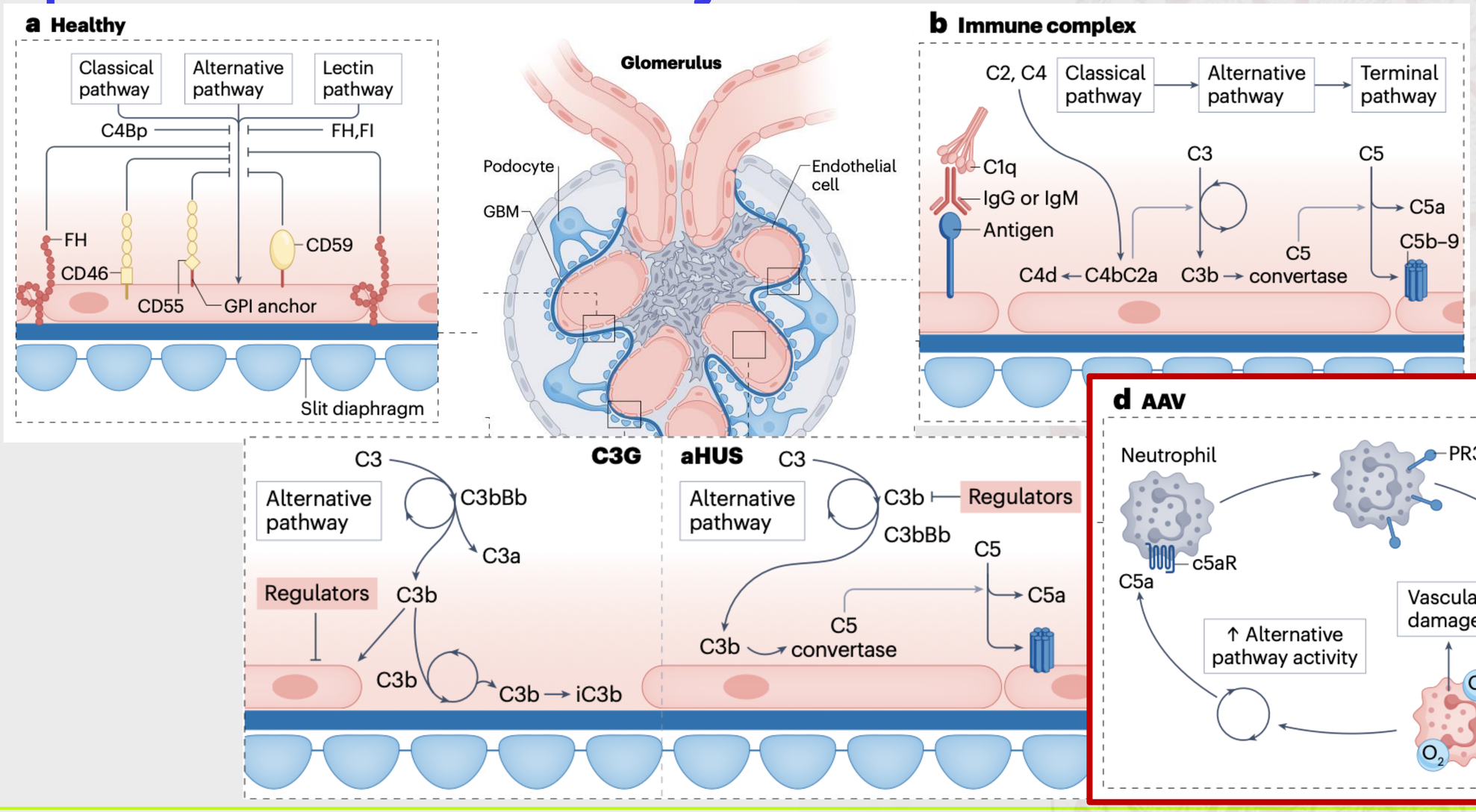
Kompleman Sistemi İlişkili Böbrek Hastalıkları



Cheung CK, et al. Nephrol Dial Tranplant. 2023.

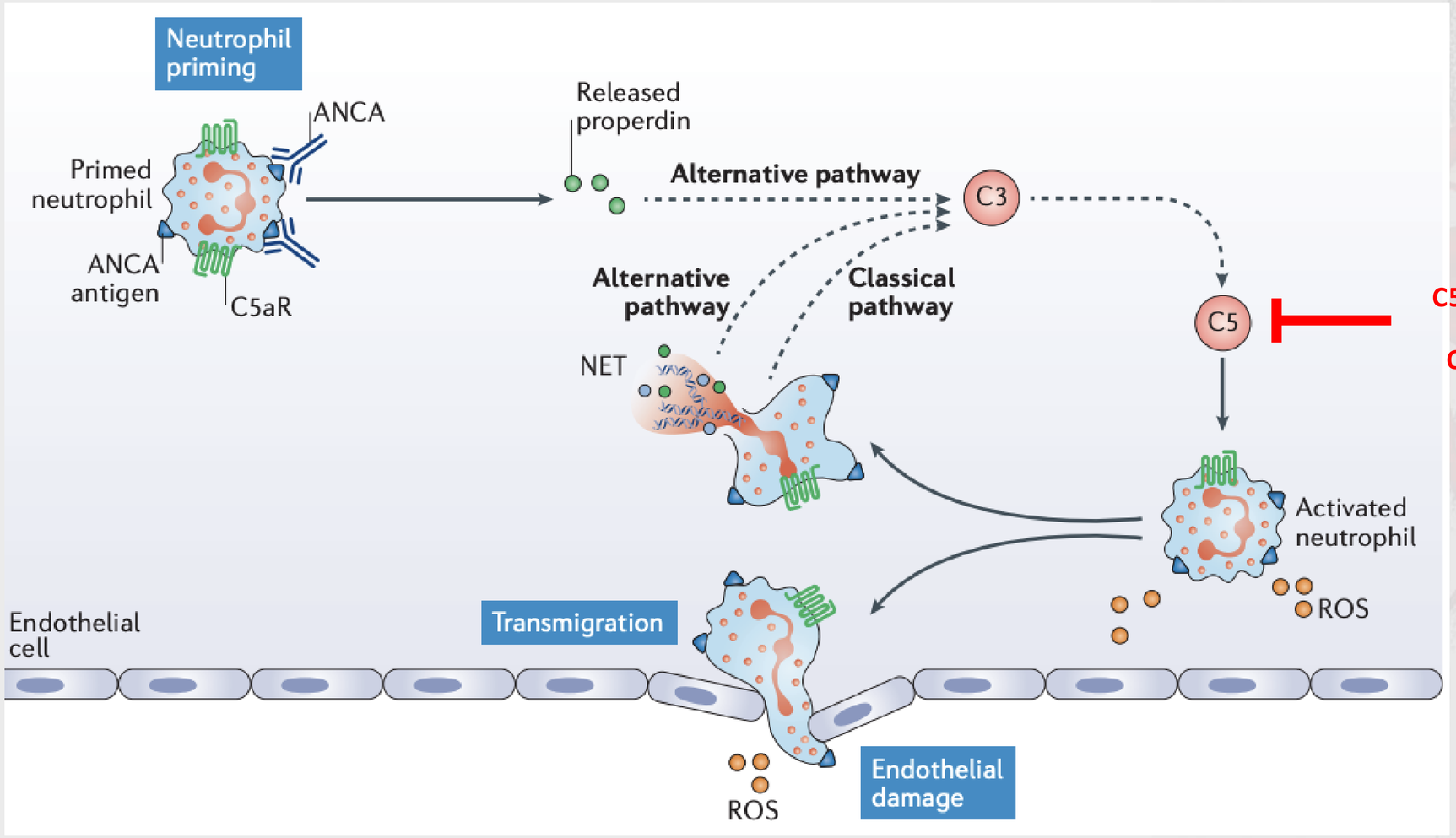
Petr V, Thurman JM. Nat

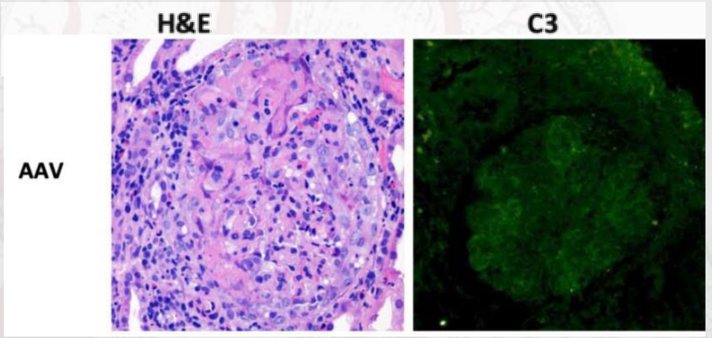
Kompleman Sistemi İlişkili Böbrek Hastalıkları



Petr V, Thurman JM. Nat Rev Nephrol. 2023.

ANCA İlişkili Vaskülitler ve Kompleman Sistemi





C5aR antagonisti

Oral Avacopan

Trouw LA, et al. Nat Rev Rheum. 2017.

Cheung CK, et al. Nephrol

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 18, 2021 VOL. 384 NO. 7

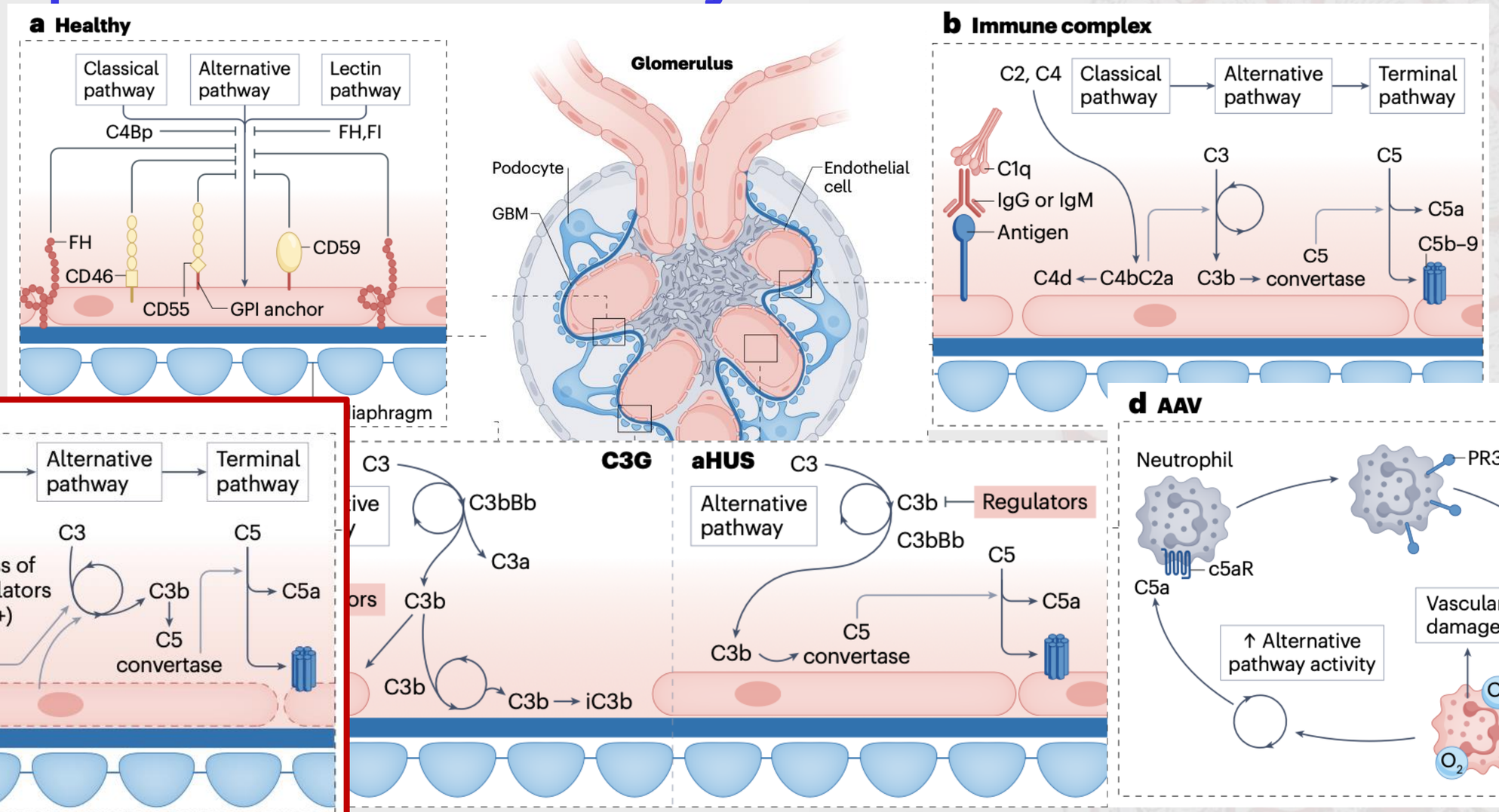
Avacopan for the Treatment of ANCA-Associated Vasculitis

David R.W. Jayne, M.D., Peter A. Merkel, M.D., M.P.H., Thomas J. Schall, Ph.D., and Pirow Bekker, M.D, Ph.D., for the ADVOCATE Study Group*

CONCLUSIONS

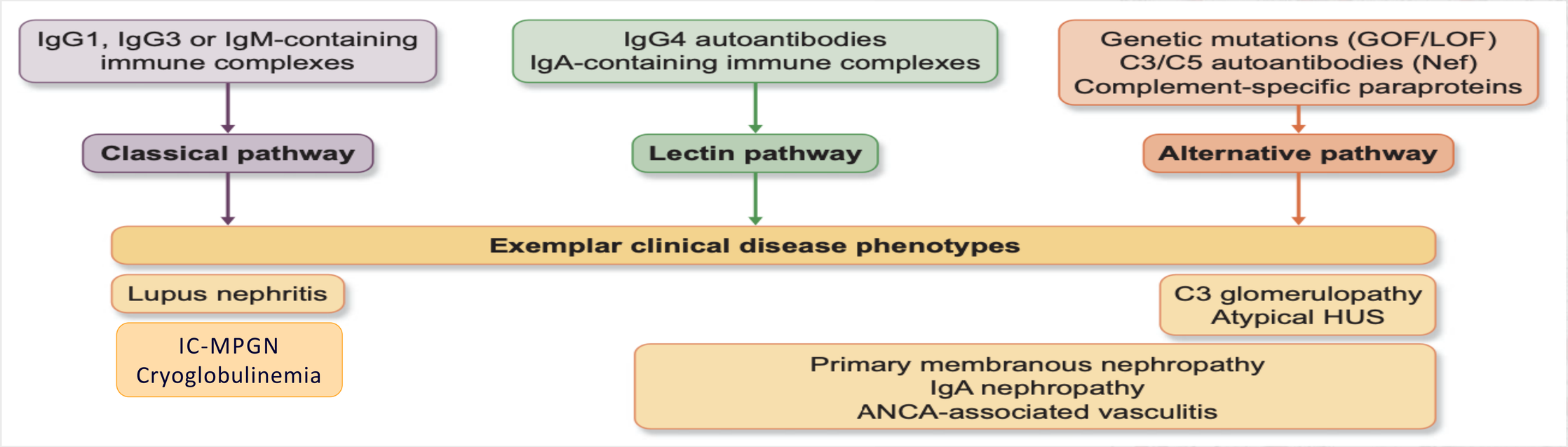
Among patients with ANCA-associated vasculitis, avacopan was noninferior to prednisone with respect to remission at 26 weeks and was superior with respect to sustained remission at 52 weeks.

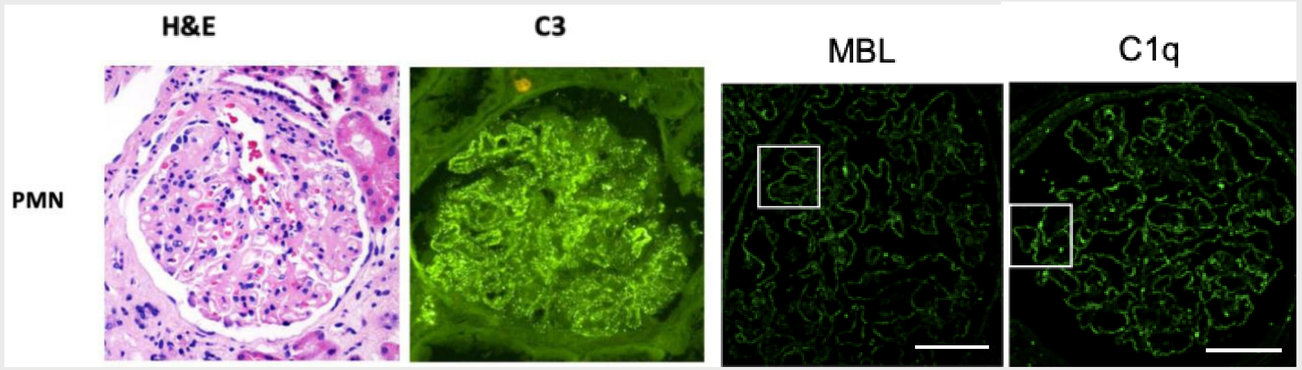
Kompleman Sistemi İlişkili Böbrek Hastalıkları



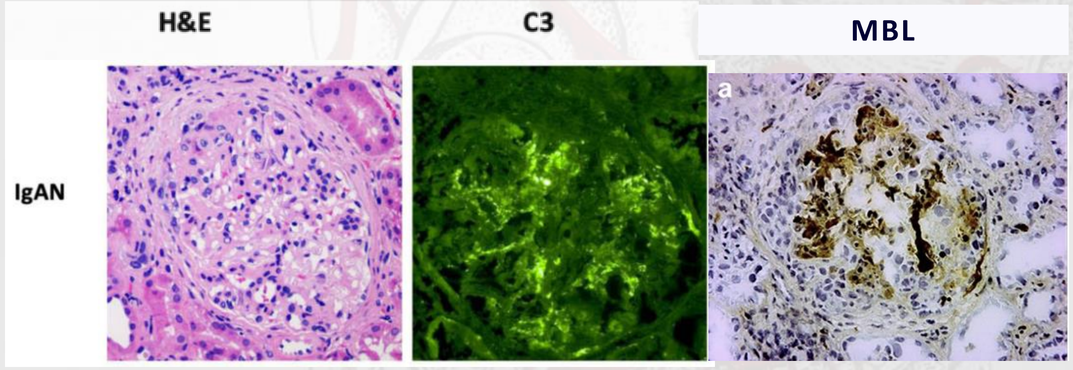
Petr V, Thurman JM. Nat Rev Nephrol. 2023.

Kompleman Sistemi İlişkili Böbrek Hastalıkları





Cheung CK, et al. Nephrol Dial Tranplant. 2023.

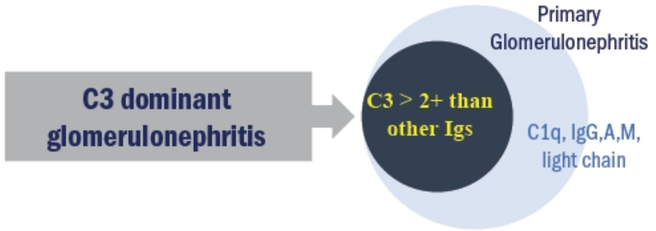


Seifert L, et al. Nat Commun. 2023.

Barratt J, et al.

Comparison of dominant and nondominant C3 deposition in primary glomerulonephritis

METHODS



21,697 patients

↓

Primary Glomerulonephritis (9,720 patients)

OUTCOME

- C3D-GN in primary GN

MPGN 19 (61.3%) > IgAN 8 (25.8%) > MN 4 (12.9%)

Cr 0.97 mg/dl ↑

CRP 0.95 mg/dl ↑

19.4% (vs 11.2%)

- Mesangial hypercellularity ↑
- Interstitial fibrosis ↑
- Sub-endothelial deposition ↑

CONCLUSION:

Greater progression of renal injury and higher mortality occurred in patients with C3D-GN than with C3ND-GN, along with pathologic difference in interstitium and tubular change.

KIDNEY RESEARCH AND CLINICAL PRACTICE
Jiwon Ryu, 2023
DOI: 10.23876/j.krcp.22.042

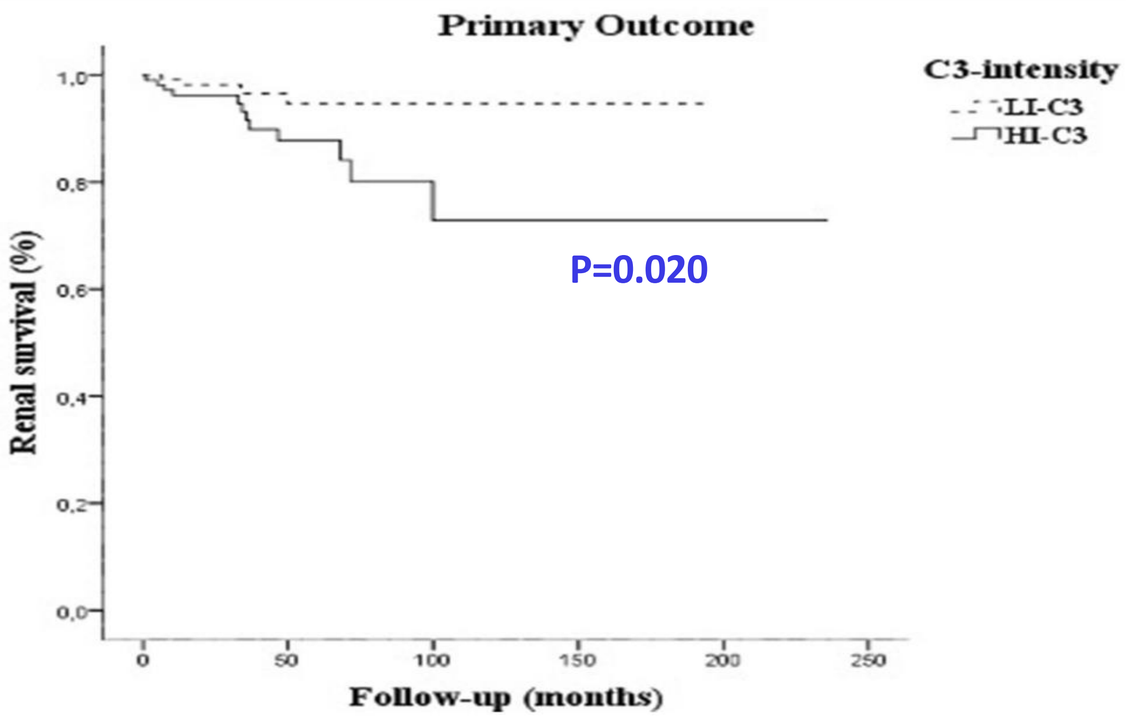
Journal of Nephrology (2021) 34:581–587
https://doi.org/10.1007/s40620-020-00915-w

ORIGINAL ARTICLE

Clinical significance of glomerular C3 deposition in primary membranous nephropathy

Ozgur Akin Oto[1] · Erol Demir[1] · Safak Mirioglu[1] · Ahmet Burak Dirim[1] · Yasemin Ozluk[2] · Egemen Cebeci[3] · Taner Basturk[4] · Ali Riza Ucar[1] · Lala Soltanova[1] · Kanan Nuriyev[1] · Isin Kilicaslan[2] · Halil Yazici[1] · Yasar Caliskan[1,5]

Received: 21 August 2020 / Accepted: 11 November 2020 / Published online: 2 January 2021



261 biyopsi tanılı MN

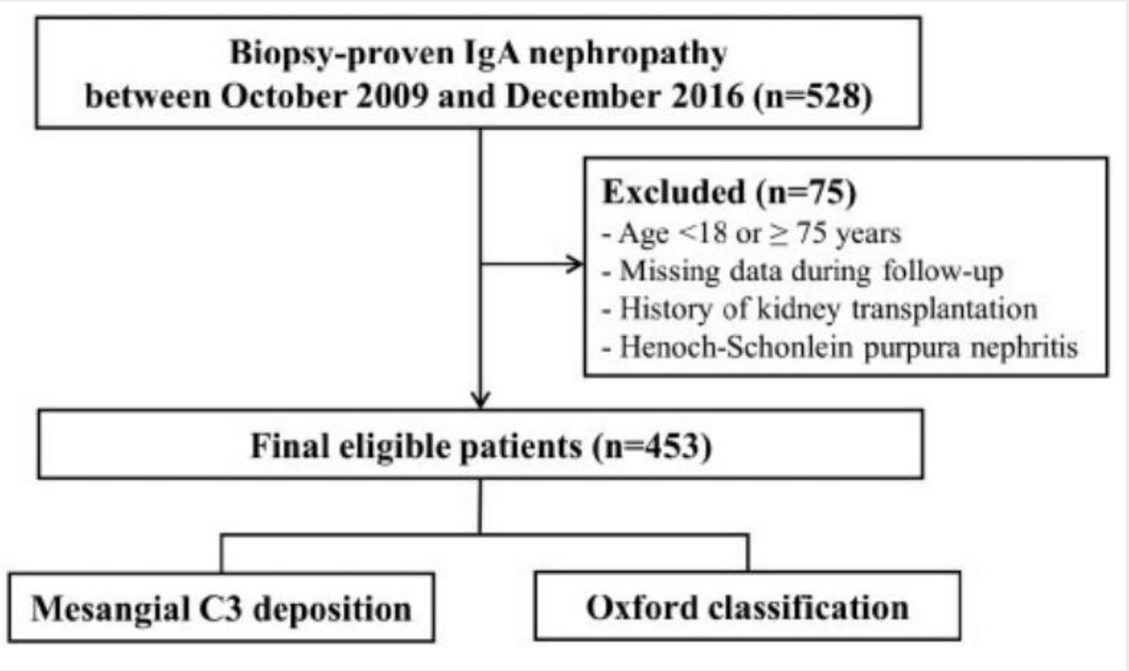
142 hasta LI; C3 1+

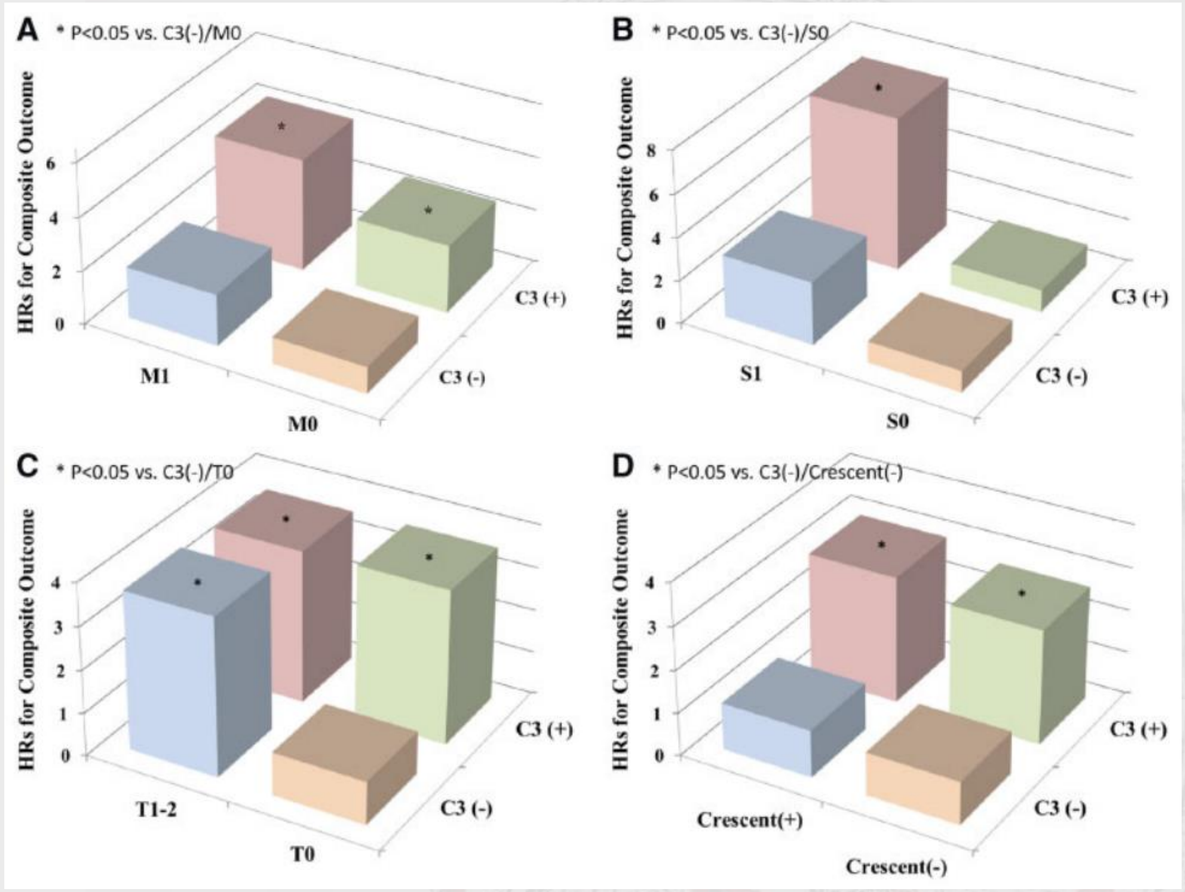
119 hasta HI; C3 2+, 3+

Nephrol Dial Transplant (2020) 35: 2130–2137
doi: 10.1093/ndt/gfz161
Advance Access publication 3 August 2019

Relationship between complement deposition and the Oxford classification score and their combined effects on renal outcome in immunoglobulin A nephropathy

Seohyun Park[1,*], Hyung Woo Kim[1,*], Jung Tak Park[1], Tae Ik Chang[2], Ea Wha Kang[2], Dong-Ryeol Ryu[3], Tae-Hyun Yoo[1], Ho Jun Chin[4], Hyeon Joo Jeong[5], Shin-Wook Kang[1], Beom Jin Lim[5] and Seung Hyeok Han [1] on behalf of the Korean Glomerulo Nephritis Study (KoGNET) Group





Conclusions. Complement deposition can strengthen the significance of the Oxford classification, and the presence of both components portends a poorer prognosis in IgA nephropathy.

Could Mesangial C3 Deposition Be an Independent Prognostic Marker in Immunoglobulin A Nephropathy?

Biopsy-proven IgA Nephropathy (n=1655)
January 2000-January 2022
Retrospective, Multicentre
The Turkish Nephrology Association Glomerular Diseases Working Group (TSN-GOLD) database

Türk Nefroloji Derneği
Turkish Society of Nephrology

Excluded (n=520)
- Age <18 or ≥ 75 years
- Follow-up period of less than 6 months
- Missing data during follow-up

Eligible patients (n=1135)
The primary endpoints were the development of end-stage renal disease, a decrease of 30% in glomerular filtration rate (GFR) compared to the basal value or an elevation in proteinuria to a nephrotic level (3.5 gr/day).

Mesangial C3 deposition with Oxford Classification (n=896)

Mesangial C3 deposition with Oxford Classification in nephroKc syndrome patients are excluded (n=884)

Mesangial C3 deposition with Steroid therapy (n=1135)

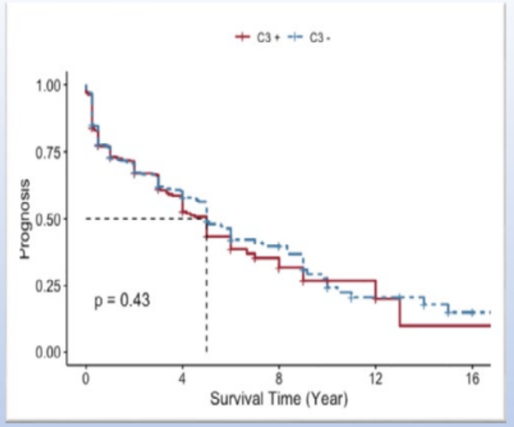


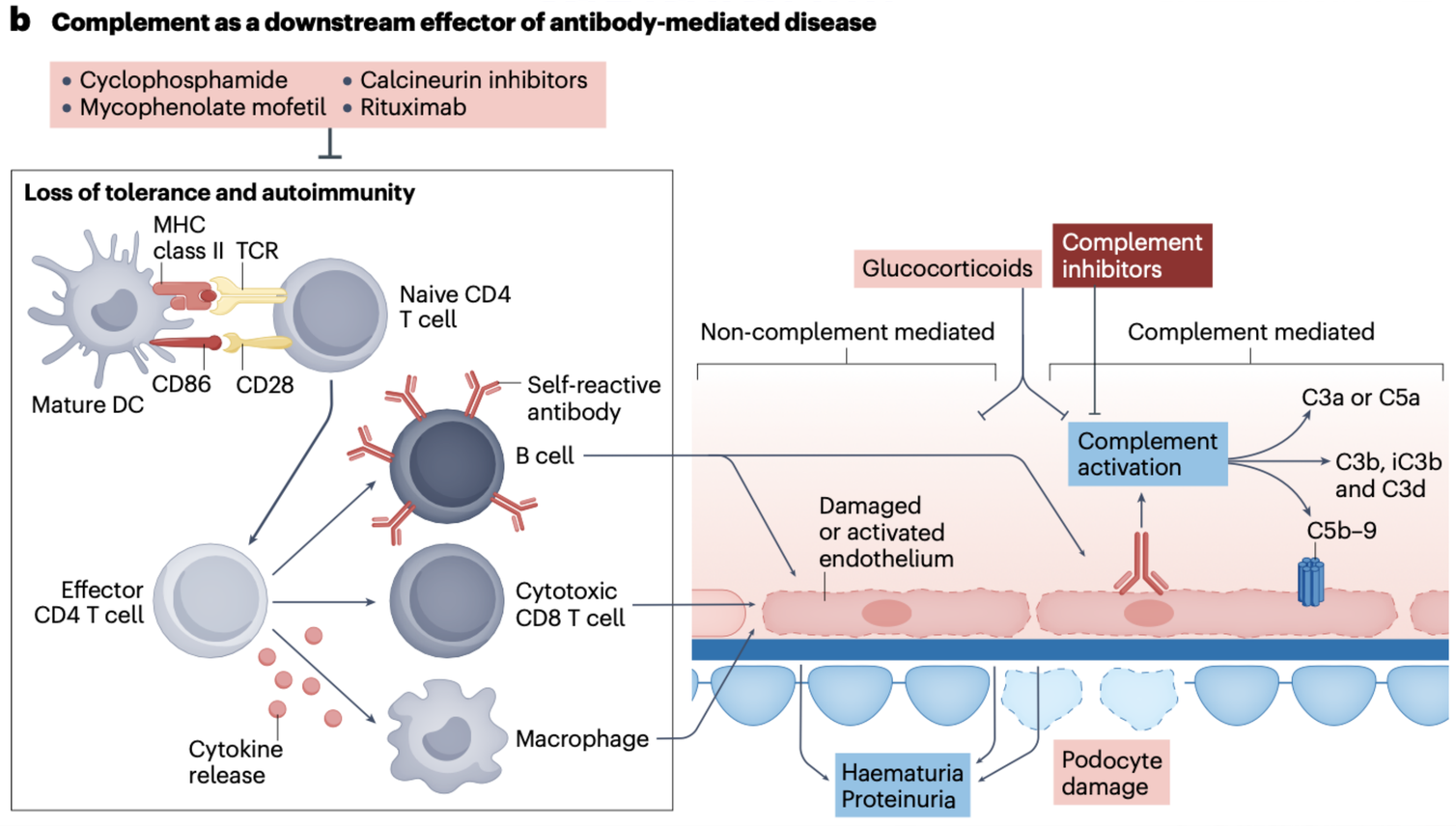
Figure: Renal survival of patients with IgA nephropathy according to mesangial C3 deposition

Results: Mesangial C3 deposition was observed in 603 (53.1%) patients. It was not possible to conclude that C3 deposition alone or together with the Oxford classification parameters could be used as a prognostic marker for negative renal outcomes.

Journal of NEPHROLOGY
official journal of the Italian Society of Nephrology

Conclusions: Although a correlation was observed between mesangial C3 deposition and the S1 MEST-C classification, mesangial C3 deposition is not an appropriate prognostic factor in IgAN.

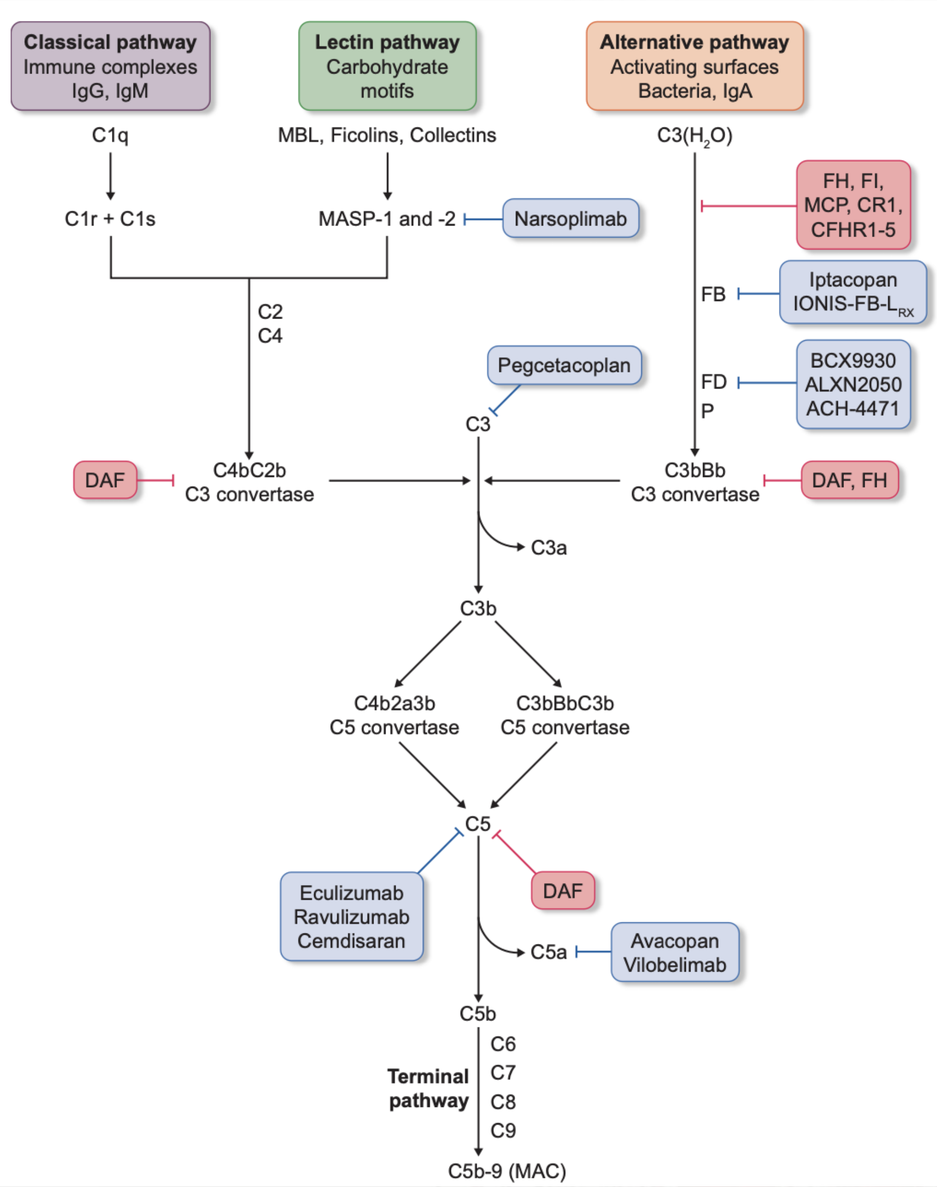
Kompleman inhibitörleri hasara yol açan yalnızca bir yolağı bloke edebilir ve birincil otoimmün mekanizmayı inhibe eden ilaçlarla **kombinasyonu** tedavi yanıtının daha etkin ve hızlı olmasını sağlayabilir



Petr V, Thurman JM. Nat Rev Nephrol. 2023.

Glomerülonefritlerde Yeni Kompleman Hedefli Tedaviler

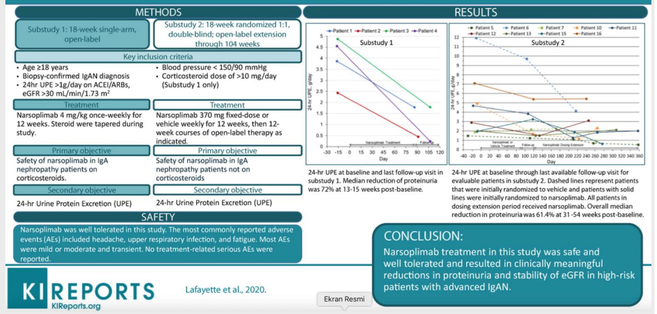
Agent	Company	Target	Type	Phase	Identifier	Status
C3 glomerulopathy						
Narsoplimab (OMS721)	Omeros	MASP-2	mAb	II	NCT02682407	Recruiting
Iptacopan (LNP023)	Novartis	Factor B	Small molecule	III (APPEAR-C3G)	NCT04817618	Recruiting
Danicopan (ACH-4471)	Achillion	Factor D	Small molecule	II	NCT03459443 NCT03124368	Completed—also IC-MPGN Completed—also IC-MPGN
BCX9930	Biocryst	Factor D	Small molecule	II (RENEW)	NCT05162066	Recruiting
Pegcetacoplan (APL-2)	Apellis	C3	Peptide	III (VALIANT)	NCT05067127	Recruiting—also IC-MPGN
Eculizumab	Alexion	C5	mAb	II	NCT01221181 NCT02093533	Completed Completed
IgAN						
Narsoplimab (OMS721)	Omeros	MASP-2	mAb	III (ARTEMIS-IgAN)	NCT03608033	Recruiting
Iptacopan (LNP023)	Novartis	Factor B	Small molecule	III (APPLAUSE-IgAN)	NCT04578834	Recruiting
IONIS-FB-L_{RX}	Ionis	Factor B	Anti-sense oligonucleotide	II	NCT04014335	Recruiting
BCX9930	Biocryst	Factor D	Small molecule	II (RENEW)	NCT05162066	Recruiting
ALXN2050	Alexion	Factor D	Small molecule	II	NCT05097989	Not yet recruiting
Pegcetacoplan (APL-2)	Apellis	C3	Peptide	II	NCT03453619	Active, not recruiting
Ravulizumab	Alexion	C5	mAb	II	NCT04564339	Recruiting
Cemdisaran	Alnylam	C5	siRNA	II	NCT03841448	Active, not recruiting
Avacopan (CCX168)	Chemocentryx	C5aR1	Small molecule	II	NCT02384317	Completed (ref) [31]
Membranous nephropathy						
Narsoplimab (OMS721)	Omeros	MASP-2	mAb	II	NCT02682407	Recruiting
Iptacopan (LNP023)	Novartis	Factor B	Small molecule	II	NCT04154787	Recruiting
BCX9930	Biocryst	Factor D	Small molecule	II (RENEW)	NCT05162066	Recruiting
Pegcetacoplan (APL-2)	Apellis	C3	Peptide	II	NCT03453619	Active, not recruiting
AAV						
Avacopan (CCX168)	Chemocentryx	C5aR1	Small molecule	Licensed	NCT02994927	Completed (ref) [47]
Vilobelimab (IFX-1)	InflaRx	C5a	mAb	II	NCT03712345	Completed
LN						
Narsoplimab (OMS721)	Omeros	MASP-2	mAb	II	NCT02682407	Recruiting
BCX9930	Biocryst	Factor D	Small molecule	II (RENEW)	NCT05162066	Recruiting
ALXN2050	Alexion	Factor D	Small molecule	II	NCT05097989	Not yet recruiting
Pegcetacoplan (APL-2)	Apellis	C3	Peptide	II	NCT03453619	Active, not recruiting
Ravulizumab	Alexion	C5	mAb	II	NCT04564339	Recruiting



Cheung CK, et al. Nephrol Dial Tranplant. 2023.

IgA- N Tedavisinde Kompleman Hedefli Tedaviler

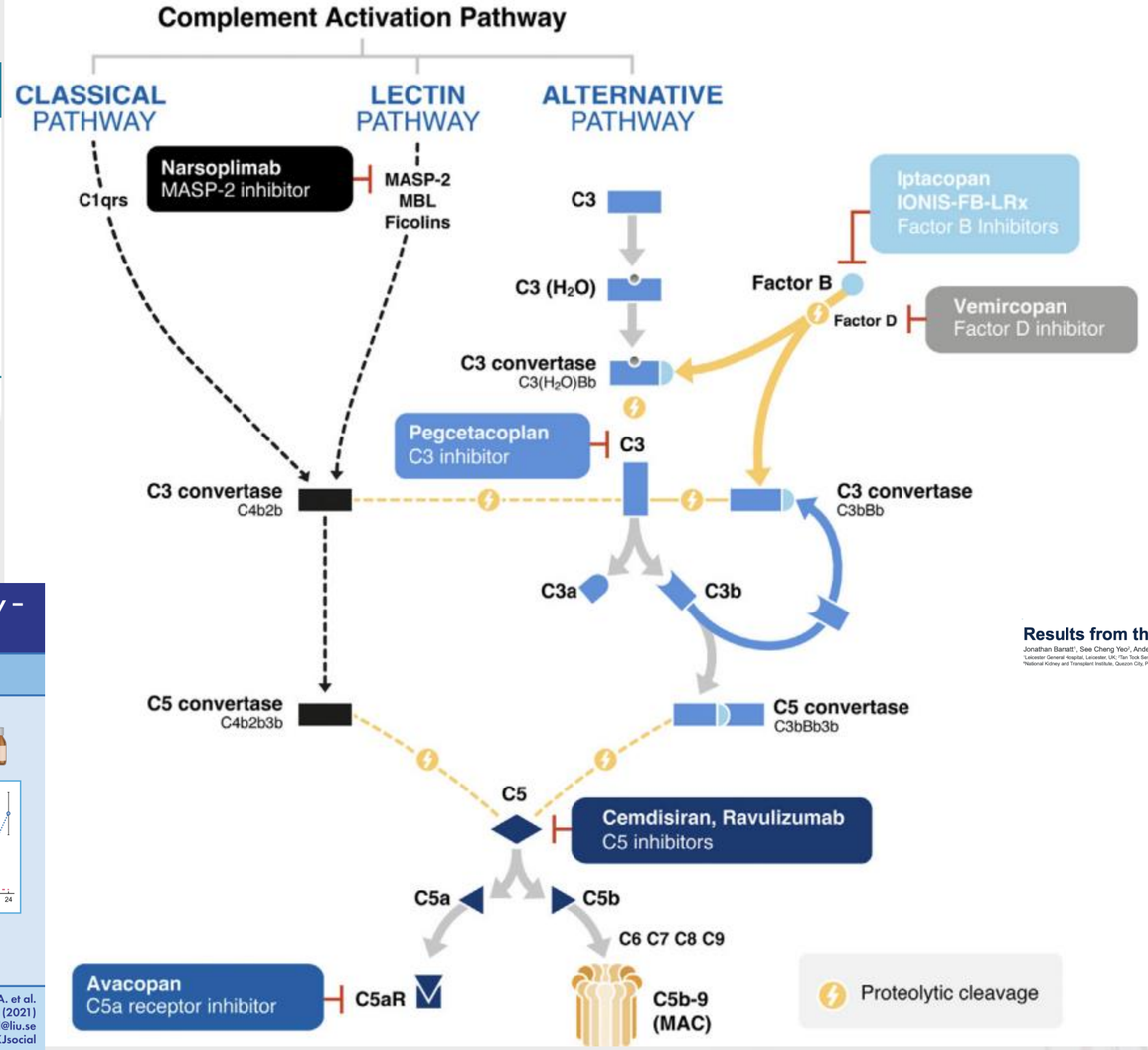
Safety, Tolerability and Efficacy of Narsoplimab, a Novel MASP-2 Inhibitor for the Treatment of IgA Nephropathy



KI REPORTS KiReports.org Lafayette et al., 2020.

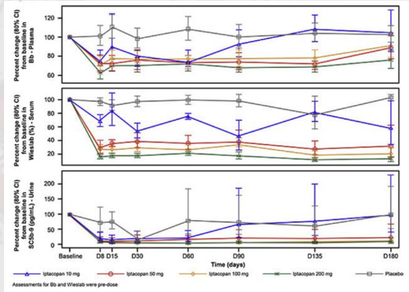
Ekran Resmi

Complement Activation Pathway



EFFICACY AND SAFETY OF IPTACOPAN IN IGA NEPHROPATHY: RESULTS OF A RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED PHASE 2 STUDY AT 6 MONTHS

Barratt, J[1], Rovin, B[2], Zhang, H[3], Kashihara, N[4], Maes, B[5], Rizk, D*[6], Trimarchi, H[7], Sprangers, B[8], Meier, M[9], Kollins, D[9], Wang, W[10], Magirr, A[9], Perkovic, V[11]

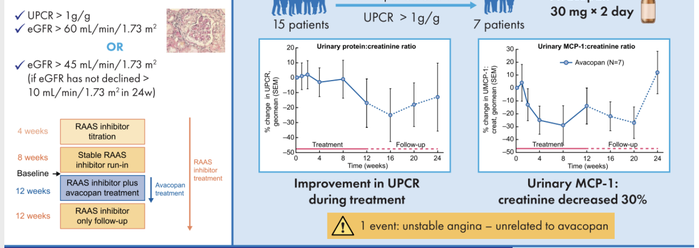


Conclusions: Iptacopan was well tolerated and led to continuous reduction in proteinuria and strong inhibition of AP activity through 6 months in patients with IgAN. These data are consistent with previous findings from the interim analysis at 3 months and support further evaluation of iptacopan in the ongoing Phase 3 APPLAUSE-IgAN trial (NCT04578834).

C5a receptor inhibitor avacopan in IgA nephropathy – an open-label pilot study

Clinical Kidney Journal

This study evaluates the safety and efficacy of avacopan in patients with IgAN with persistent proteinuria despite RASi blockage



Conclusion: This short-term trial showed an improvement in the slope of UPCR in 6 out of 7 patients, with ~ 50% improvement in 3 out of 7 patients with IgAN. Longer avacopan treatment duration may be indicated for maximal benefit.

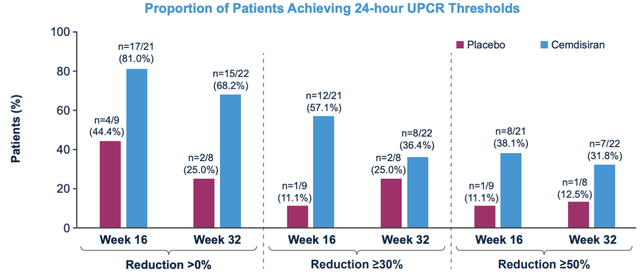
Bruchfeld, A. et al.
Clinical Kidney Journal (2021)
annette.bruchfeld@liu.se
@CKJsocial

Results from the Phase 2 Study of Cemdisiran in Adult Patients with IgA Nephropathy

Jonathan Barratt[1], See Cheng Yeo[2], Anders Fernström[3], Sean J. Barbour[4], C. John Sperati[5], Russell Villanueva[6], Ming-Ju Wu[7], Dazhe Wang[6], Anna Borodovsky[6], Prajakta Badri[6], Elena Yuryeva[6], Ishir Bhan[6], Daniel Cattran[8]
[1]Leicester General Hospital, Leicester, UK; [2]Tan Tock Seng Hospital, Renal Medicine Clinic, Singapore, Singapore; [3]Department of Nephrology and Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden; [4]University of British Columbia, Division of Nephrology, British Columbia, Canada; [5]Johns Hopkins University, Baltimore, MD, USA; [6]Alnylam Pharmaceuticals, Cambridge, MA, USA; [7]National Kidney and Transplant Institute, Quezon City, Philippines; [8]Toronto General Hospital, Toronto, Ontario, Canada; [9]Taichung Veterans General Hospital, Taichung, Taiwan

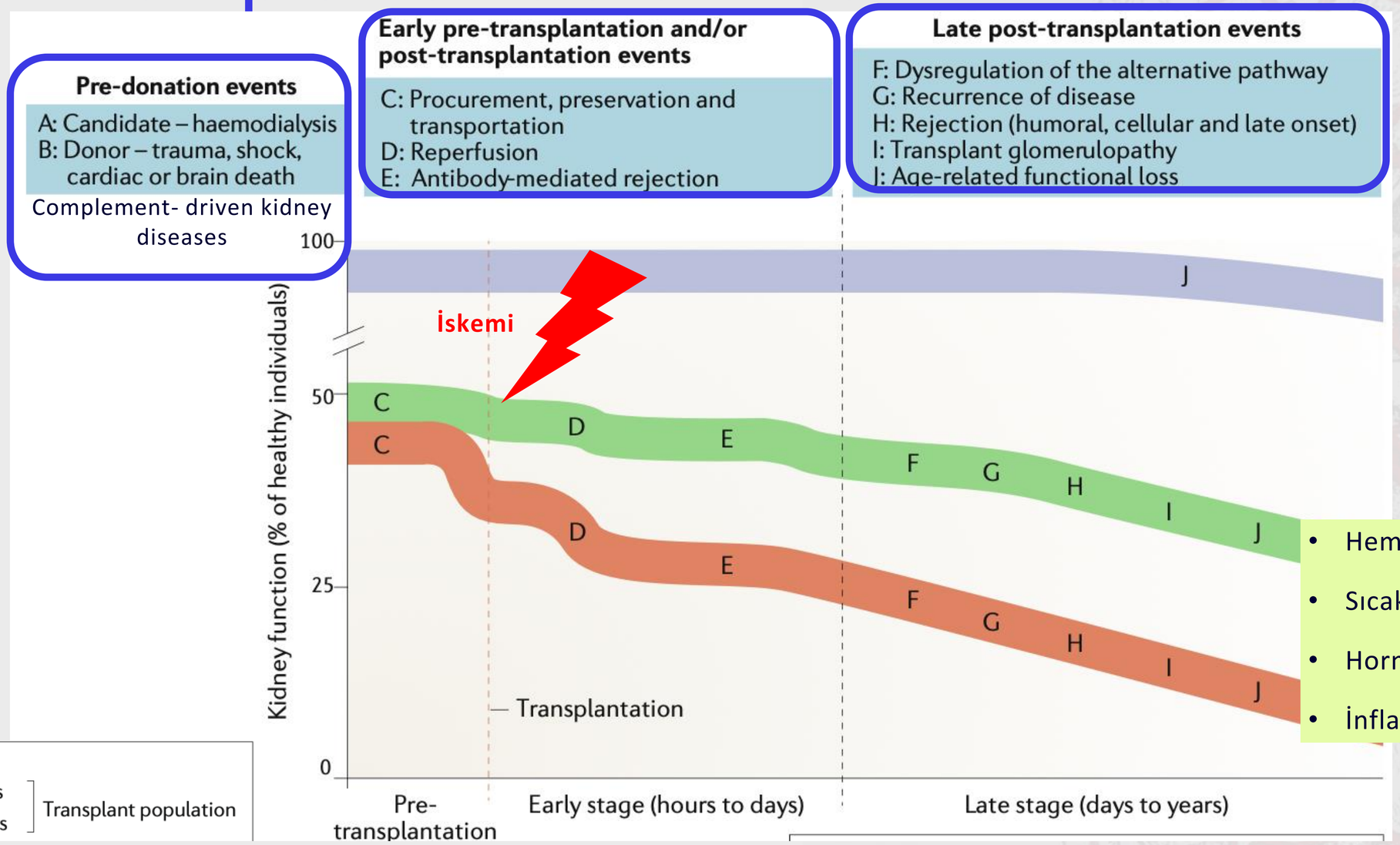
Higher Proportion of Patients Demonstrated Meaningful Reductions in 24-hour UPCR with Cemdisiran Compared with Placebo at Week 32

- **31.8%** of patients treated with cemdisiran achieved ≥50% reduction in 24-hour UPCR at Week 32, compared with 12.5% of placebo-treated patients[a]



Tesar V, et al. KI Reports. 2023.

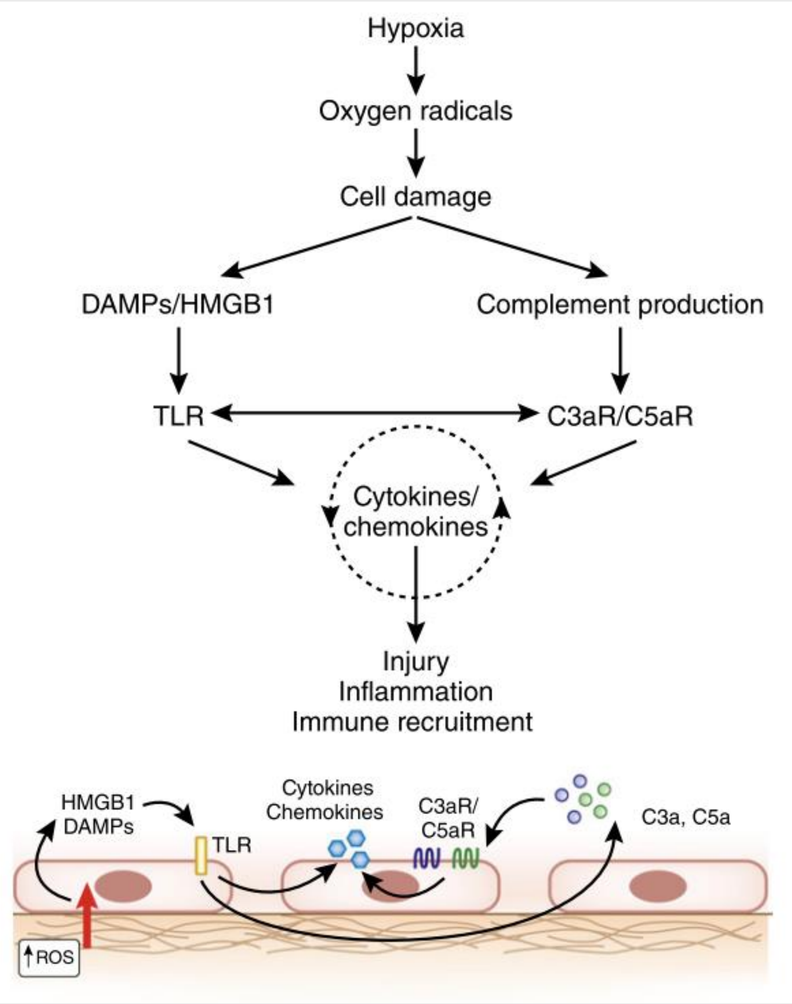
Kompleman Sistemi ve Böbrek Nakli

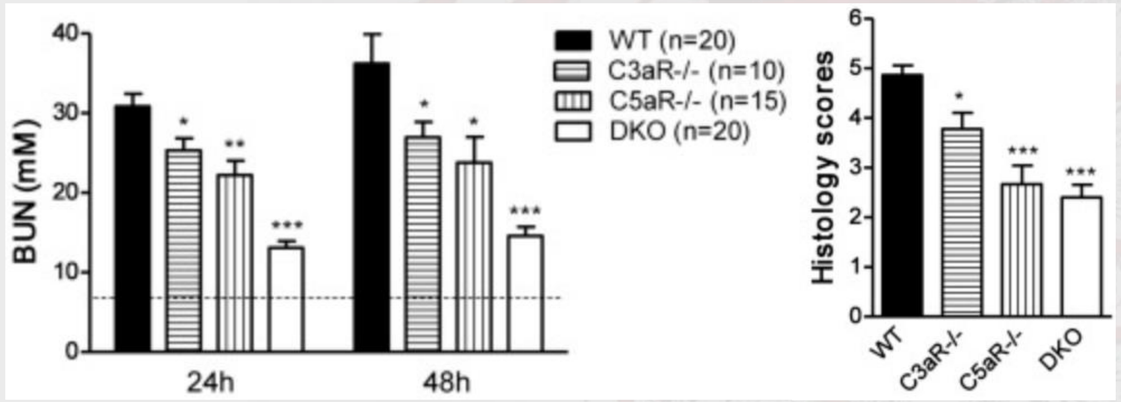


- Hemodinamik instabilite
- Sıcak iskemi
- Hormon disregülasyonu
- İnflamatuar yanıt

Biglarnia AR, et al. Nat Rev Nephrol. 2018

İskemi-Reperfüzyon Hasarı ve Kompleman Sistemi



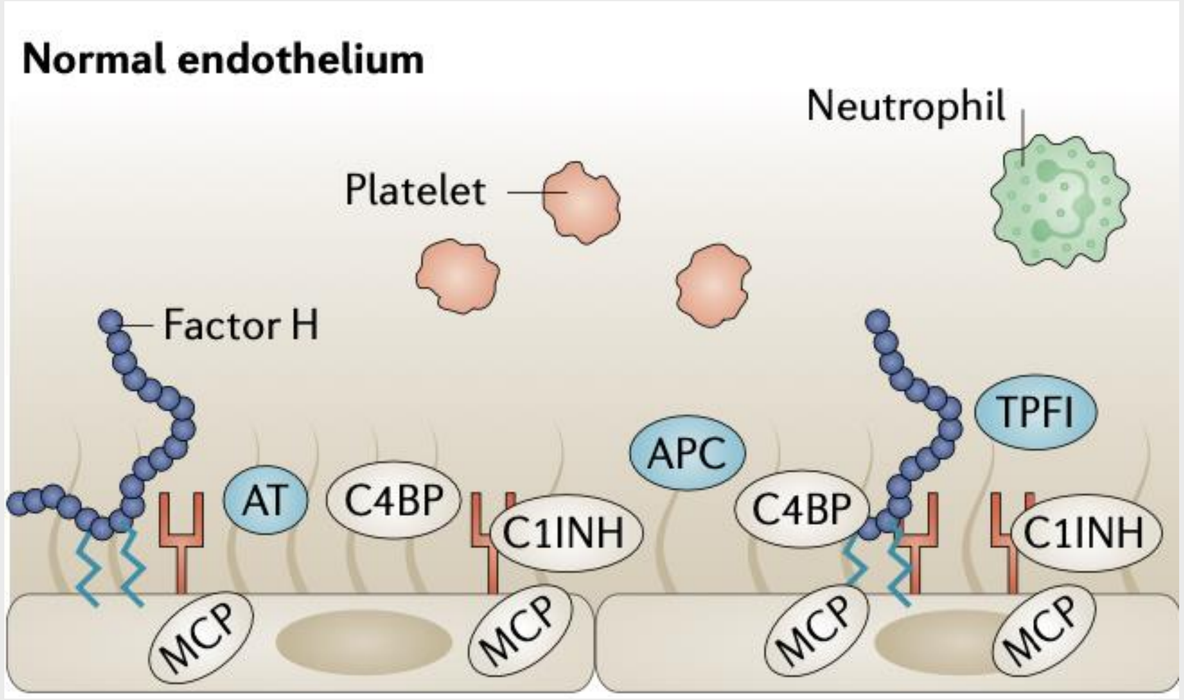


C3aR / C5aR negatif fareler böbrek IR hasarından korunmuştur.

Mathern DR, Heeger PS. Clin J Am Soc Nephrol. 2015.

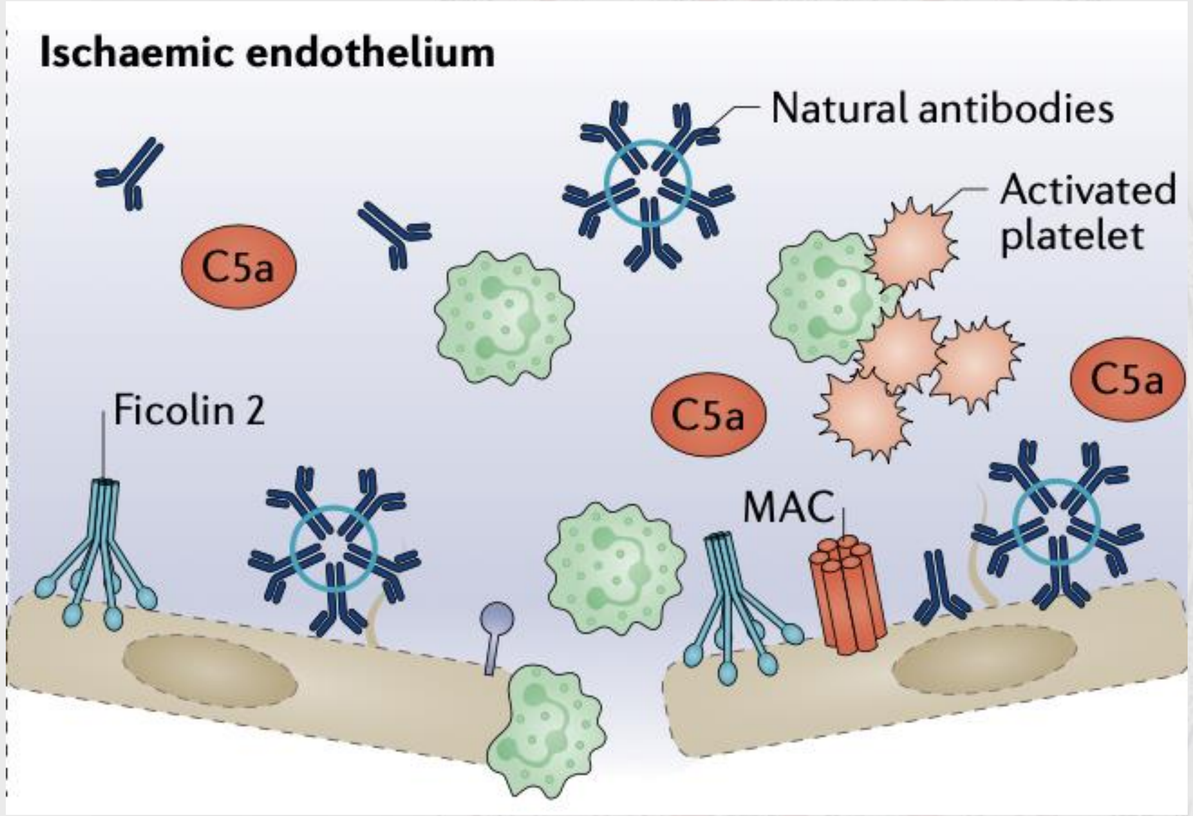
Peng Q, et al. J Am

İskemi-Reperfüzyon Hasarı ve Kompleman Sistemi



Antiinflamatuar

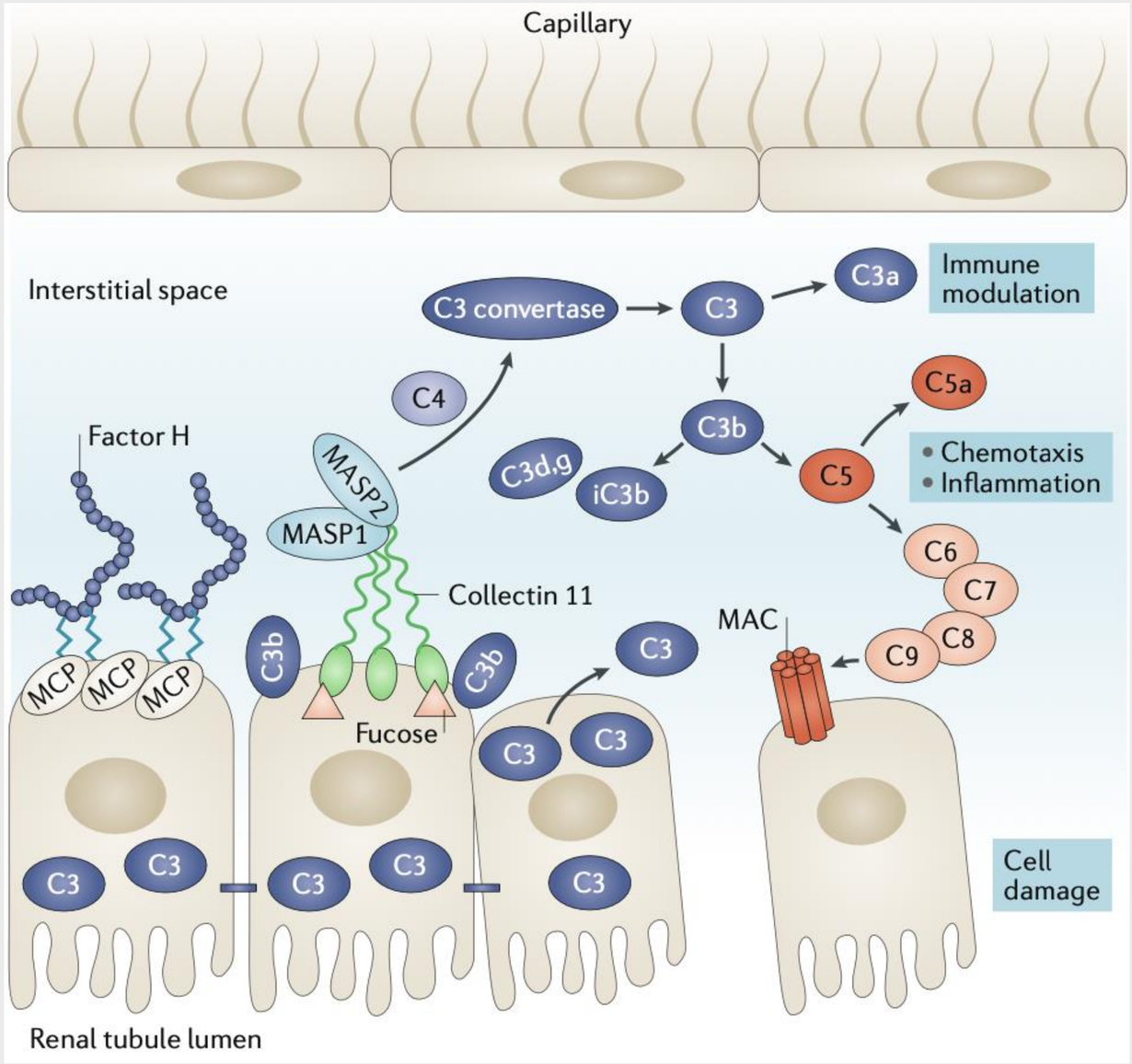
Antitrombotik



Kompleman ve koagülasyon regülatörleri kaybı

İnflamatuar yanıtta artış

Biglarnia AR, et al. Nat Rev Nephrol. 2018

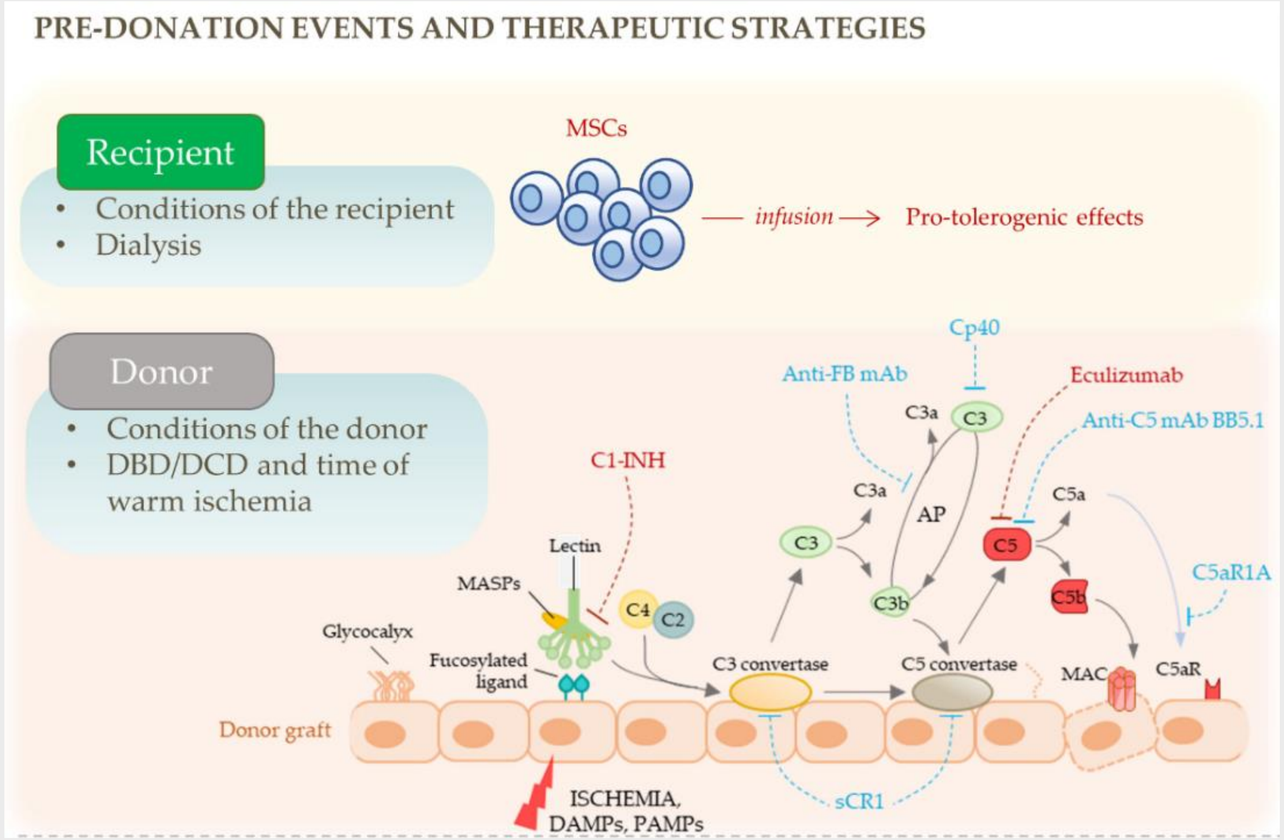


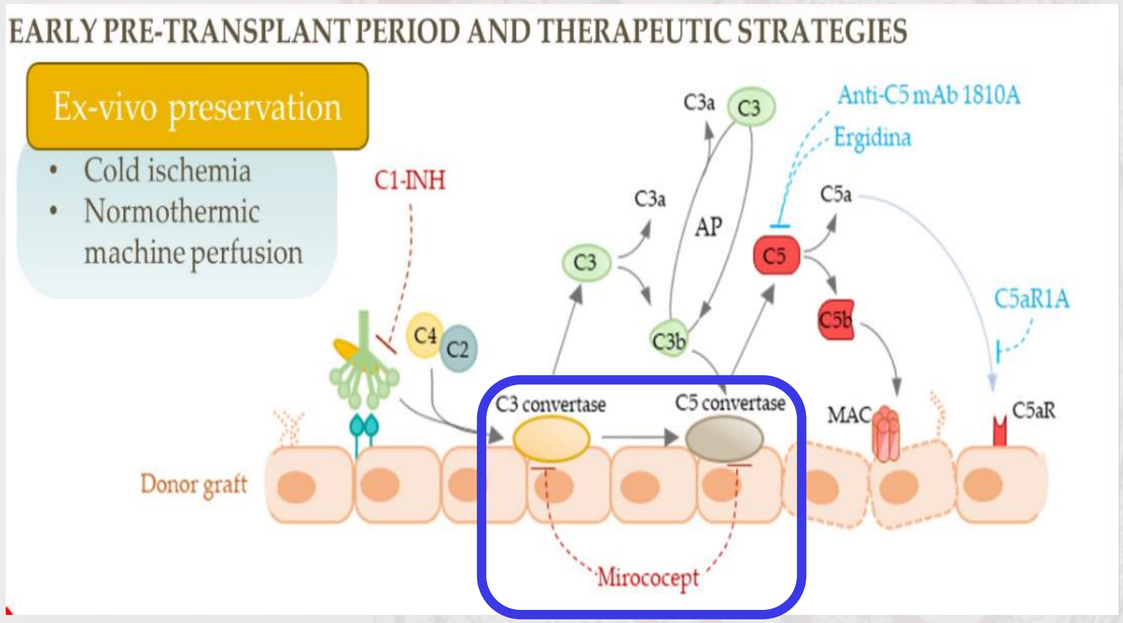
Böbrek iskemi-reperfüzyon hasarında **lektin yolağı** kompleman aktivasyonunun ana tetikleyicisidir, **alternatif yolak** ise takiben yanıtı güçlendirir.

Klasik yolağın önemli bir rolü yoktur.

Biglarnia AR, et al. Nat Rev Nephrol. 2018

Böbrek IR ve Kompleman Hedefli Tedaviler



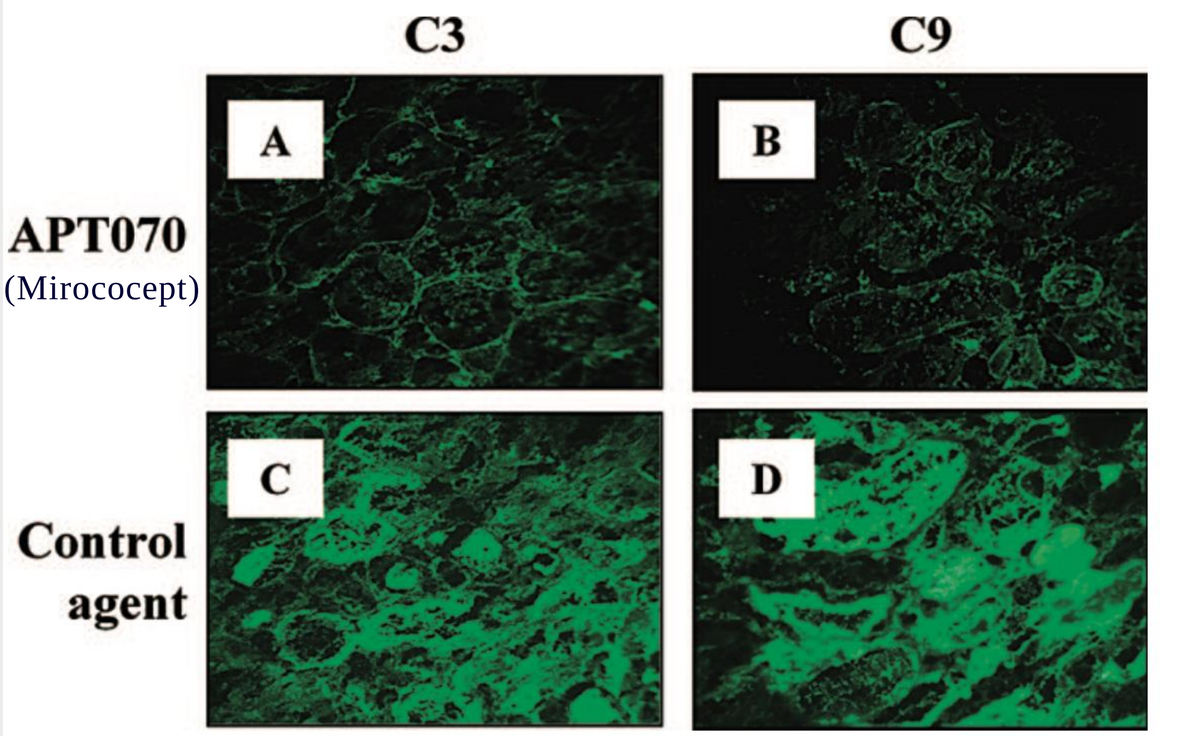


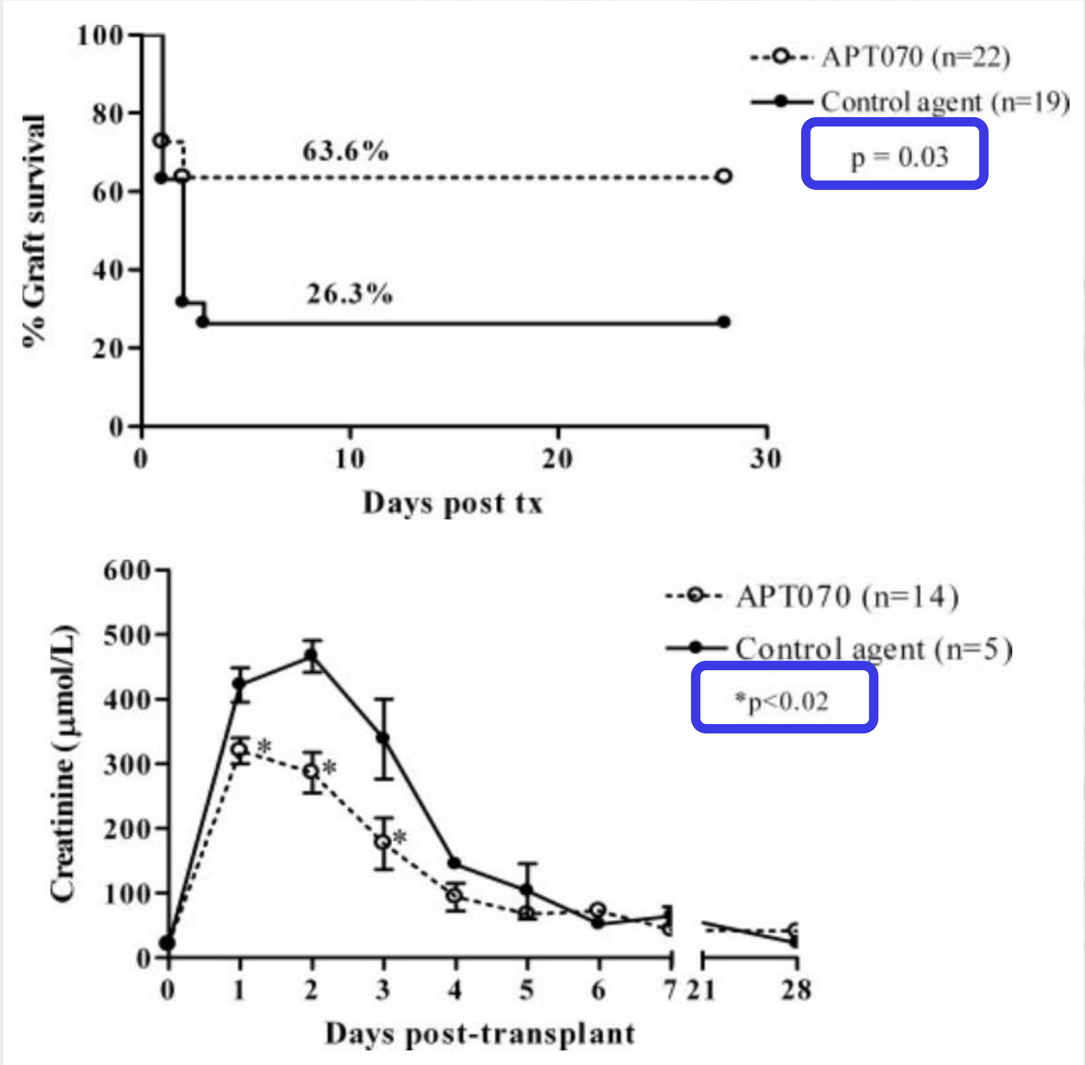
Santarsiero D, Aiello S. Cells. 2023.

Therapeutic Strategy with a Membrane-Localizing Complement Regulator to Increase the Number of Usable Donor Organs after Prolonged Cold Storage

Hetal Patel,* Richard A.G. Smith,† Steven H. Sacks,* and Wuding Zhou*

**King's College London School of Medicine at Guy's, King's College and St. Thomas' Hospitals, Department of Nephrology and Transplantation, Guy's Hospital, London, United Kingdom; and †Inflazyme Pharmaceuticals Ltd., Richmond, British Columbia, Canada*

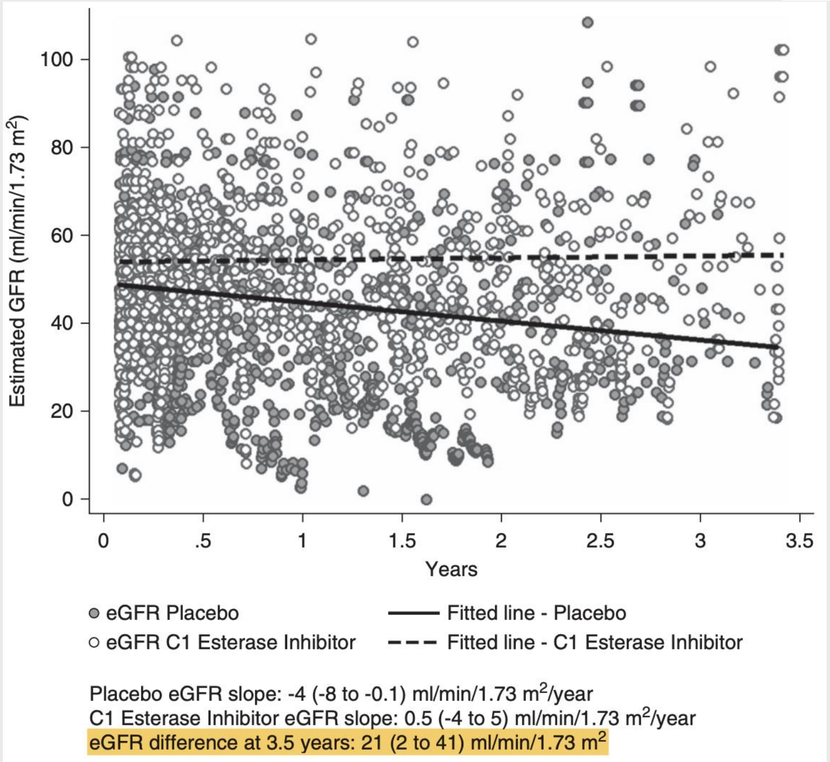




Three-Year Outcomes of a Randomized, Double-Blind, Placebo-Controlled Study Assessing Safety and Efficacy of C1 Esterase Inhibitor for Prevention of Delayed Graft Function in Deceased Donor Kidney Transplant Recipients

Edmund Huang,[1] Ashley Vo,[1] Jua Choi,[1] Noriko Ammerman,[1] Kathlyn Lim,[1] Supreet Sethi,[1] Irene Kim,[2] Sanjeev Kumar,[1] Reiad Najjar,[1] Alice Peng,[1] and Stanley C. Jordan[1]

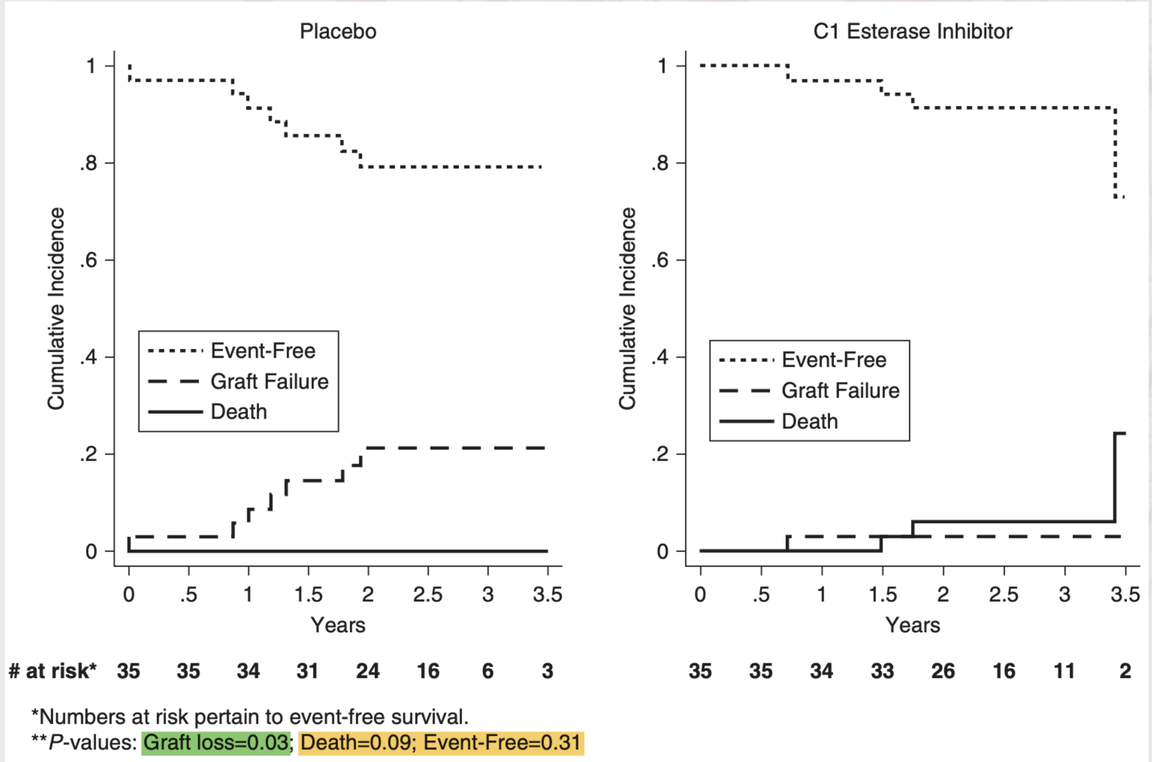
CJASN 15: 109–116, 2020.



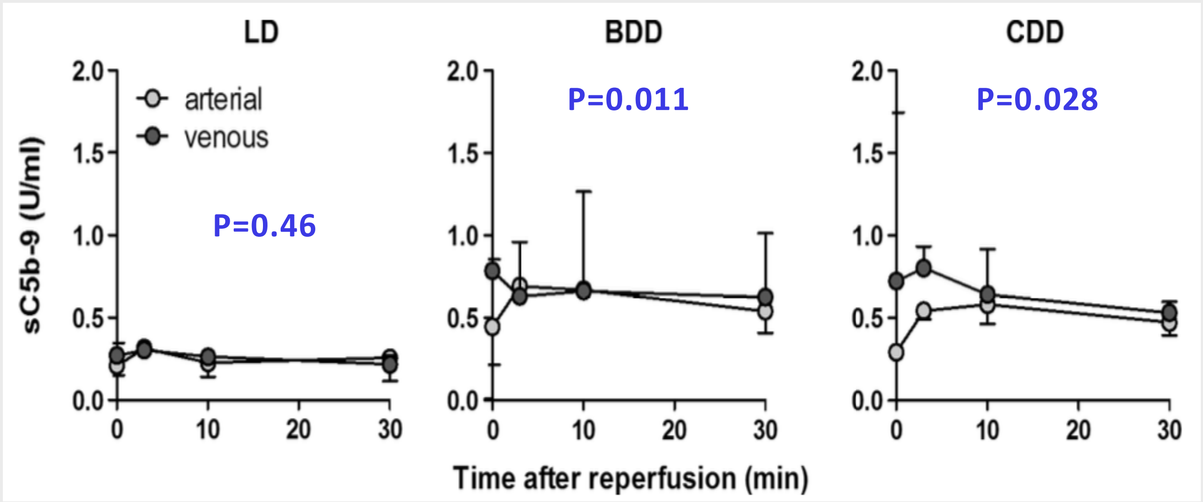
DGF riski yüksek 70 kadavra böbrek nakli alıcısı

İntraoperatif ve 24.saatte

- C1 esteraz inhibitor 50 U/kg (n=35)
- Plasebo (n=35)

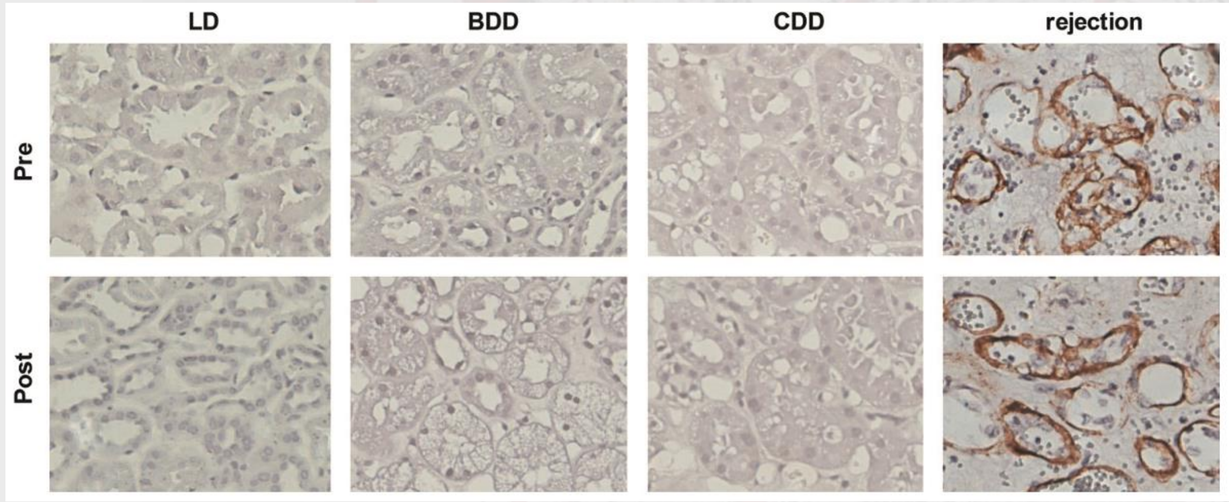


Daha kısa iskemi süresi, daha az kompleman aktivasyonu ile ilişkilidir.



Kadavra böbrek greftlerinde reperfüzyondan sonra saniyeler içinde önemli bir sC5b-9 salınımı varken, canlı böbrek greftlerinde bu artış görülmemiştir.

Takip eden zamanlarda fark kalmamıştır.

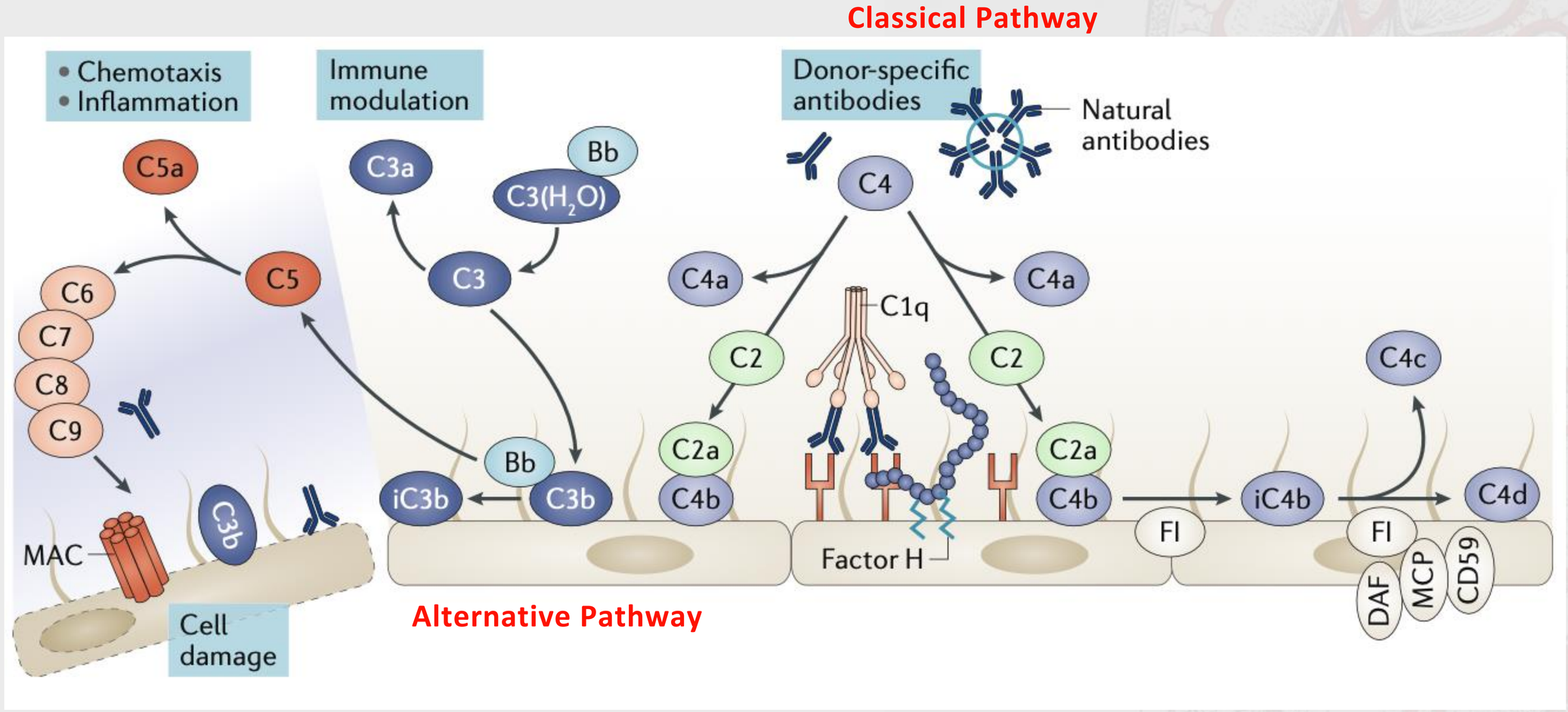


Canlı ve kadavra nakil greftlerin nakil öncesi sonrası biyopsilerinin hiçbirinde C5b-9 birikimi saptanmamıştır.

Buna karşılık, akut rejeksiyonda masif peritübüler ve tübüler C5b-9 birikimlerini gösterilmiştir.

De Vries DK, et al. Transplantation. 2013.

Antikor-Aracılı Rejeksiyon ve Kompleman Sistemi



Biglarnia AR, et al. Nat Rev Nephrol. 2018

Category 2: Antibody-mediated changes

Active ABMR; all 3 criteria must be met for diagnosis

1. Histologic evidence of acute tissue injury, including 1 or more of the following:
- Microvascular inflammation (g > 0 and/or ptc > 0), in the absence of recurrent or de novo glomerulonephritis, although in the presence of acute TCMR, borderline infiltrate, or infection, ptc ≥ 1 alone is not sufficient and g must be ≥ 1
- Intimal or transmural arteritis (v > 0)[b]
- Acute thrombotic microangiopathy, in the absence of any other cause
- Acute tubular injury, in the absence of any other apparent cause

2. Evidence of current/recent antibody interaction with vascular endothelium, including 1 or more of the following:
- Linear C4d staining in peritubular capillaries or medullary vasa recta (C4d2 or C4d3 by IF on frozen sections, or C4d > 0 by IHC on paraffin sections)
- At least moderate microvascular inflammation ([g + ptc] ≥2) in the absence of recurrent or de novo glomerulonephritis, although in the presence of acute TCMR, borderline infiltrate, or infection, ptc ≥ 2 alone is not sufficient and g must be ≥1
- Increased expression of gene transcripts/classifiers in the biopsy tissue strongly associated with ABMR, if thoroughly validated

3. Serologic evidence of circulating donor-specific antibodies (DSA to HLA or other antigens). C4d staining or expression of validated transcripts/classifiers as noted above in criterion 2 may substitute for DSA; however thorough DSA testing, including testing for non-HLA antibodies if HLA antibody testing is negative, is strongly advised whenever criteria 1 and 2 are met

Loupy A, et al. Am J Transplant. 2020.

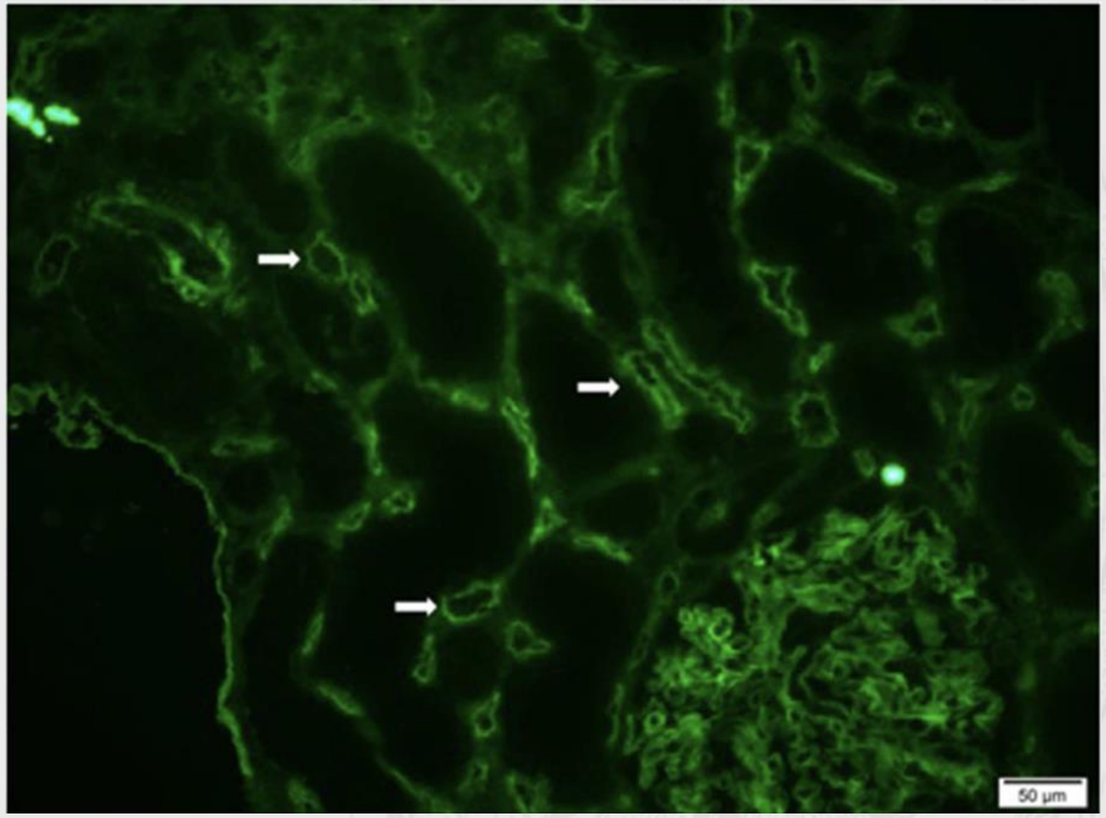


FIGURE 3 | Immunofluorescence microscopy demonstrating diffuse and prominent deposition of C4d on the endothelium of peritubular capillaries (white arrows) in a renal allograft undergoing acute antibody mediated rejection (AMR).

Tatapudi VS, Montgomery RA.

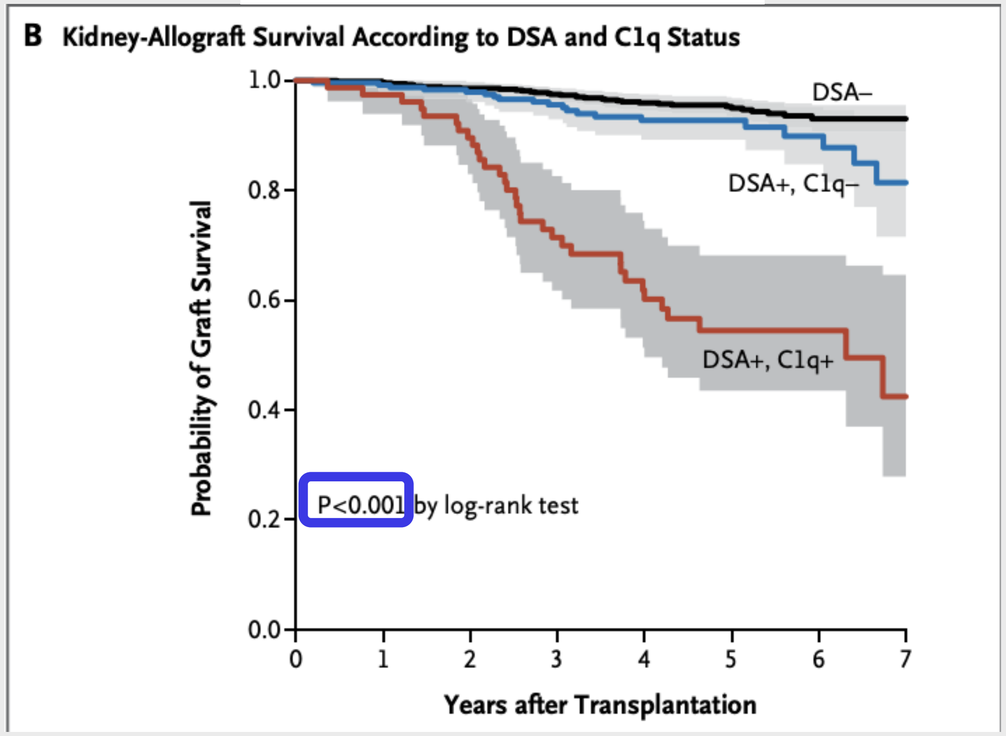
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Complement-Binding Anti-HLA Antibodies and Kidney-Allograft Survival

Alexandre Loupy, M.D., Ph.D., Carmen Lefaucheur, M.D., Ph.D., Dewi Vernerey, M.P.H., Christof Prugger, M.D., Jean-Paul Duong van Huyen, M.D., Ph.D., Nuala Mooney, Ph.D., Caroline Suberbielle, M.D., Ph.D., Véronique Frémeaux-Bacchi, M.D., Ph.D., Arnaud Méjean, M.D., François Desgrandchamps, M.D., Dany Anglicheau, M.D., Ph.D., Dominique Nochy, M.D., Dominique Charron, M.D., Ph.D., Jean-Philippe Empana, M.D., Ph.D., Michel Delahousse, M.D., Christophe Legendre, M.D., Denis Glotz, M.D., Ph.D., Gary S. Hill, M.D.,* Adriana Zeevi, Ph.D., and Xavier Jouven, M.D., Ph.D.

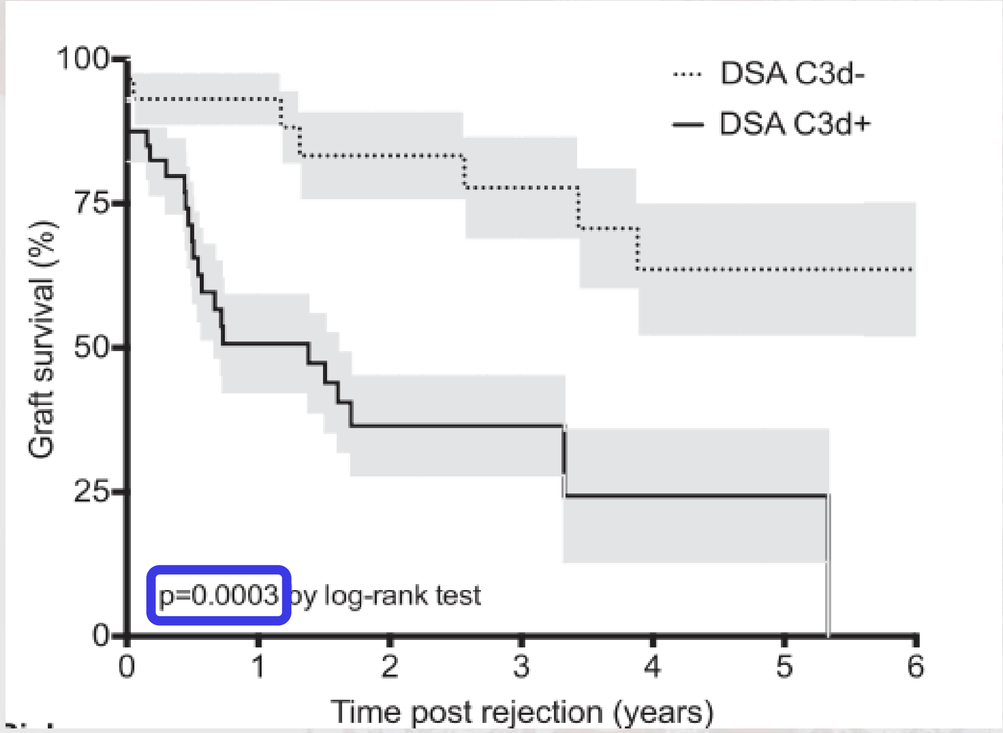
N ENGL J MED 369;13 NEJM.ORG SEPTEMBER 26, 2013



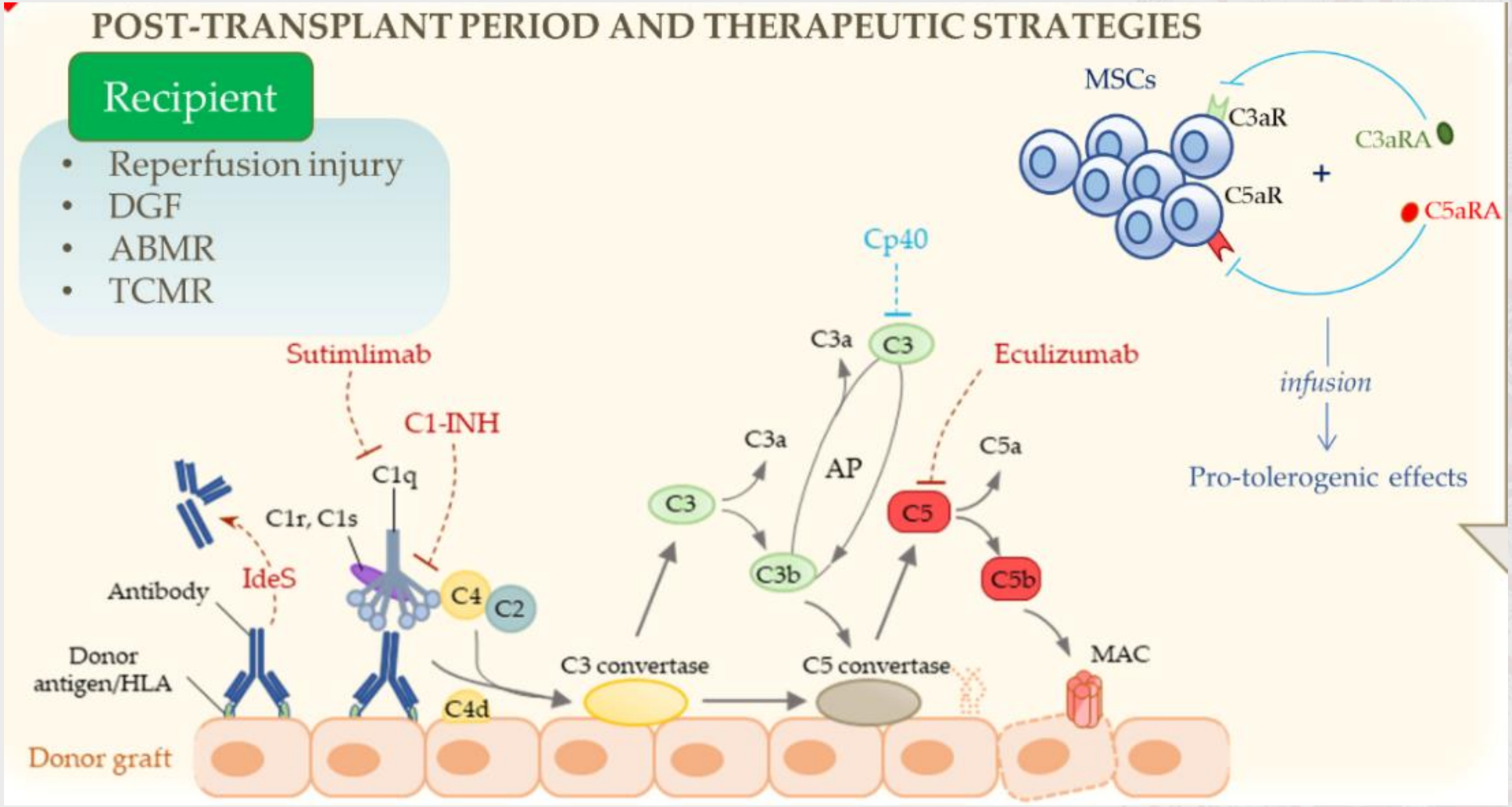
Detection of C3d-Binding Donor-Specific Anti-HLA Antibodies at Diagnosis of Humoral Rejection Predicts Renal Graft Loss

Antoine Sicard,*†‡ Stéphanie Ducreux,§ Maud Rabeyrin,‖ Lionel Couzi,¶** Brigitte McGregor,‖ Lionel Badet,‡†† Jean Yves Scoazec,‡‖ Thomas Bachelet,¶** Sébastien Lepreux,‡‡ Jonathan Visentin,§§ Pierre Merville,¶** Véronique Fremeaux-Bacchi,‖‖¶¶ Emmanuel Morelon,*†‡ Jean-Luc Taupin,§§ Valérie Dubois,§ and Olivier Thaunat*†‡

J Am Soc Nephrol 26: 457–467, 2015.



ABMR ve Kompleman Hedefli Tedaviler



Santarsiero D, Aiello S. Cells. 2023.

ABMR ve Ekulizumab

Terminal Complement Inhibition Decreases Antibody-Mediated Rejection in Sensitized Renal Transplant Recipients

M. D. Stegall[a,*], T. Diwan[a], S. Raghavaiah[a], L. D. Cornell[b], J. Burns[a,c], P. G. Dean[a], F. G. Cosio[d], M. J. Gandhi[b], W. Kremers[e] and J. M. Gloor[d]

American Journal of Transplantation 2011; 11: 2405–2413
Wiley Periodicals Inc.

Table 2: Posttransplant outcomes in the eculizumab-treated and control groups

Category	Eculizumab group (n = 26)	Control group (n = 51)	p-Value
Follow-up (mean months ± SD, range)	11.8 ± 6.3 (3.0–27.5)	48.8 ± 14.1 (7.8–69.8)	
Graft survival at 1 year (n, %)	16/16 (100%)	49/51 (96%)	1.00
Antibody-mediated rejection ≤ 3months (n, %)	2 (7.7%)	21 (41%)	0.0031
Patients developing high DSA levels ≤ 3 months[1]	13 (50%)	22 (43%)	0.63
High DSA biopsies C4d+ (n, %)	13 (100%)	20 (91%)	0.52
High DSA and C4d+ biopsies showing AMR (n, %)	2 (15%)	20 (100%)	<0.0001
Cellular rejection ≤3 months (n, %)	1 (6.2%)	1 (2%)	0.42

Ekulizumab, kontrol grubuna göre ABMR insidansını azaltmaktadır.

Eculizumab for Prevention of Antibody-Mediated Rejection in Blood Group-Incompatible Renal Transplantation

P. West-Thielke[a,*], K. Progar[b], M. Campara[b], N. Jasiak[b], L. Gallon[c], I. Tang[d], M. Spaggiari[a], I. Tzvetanov[a], and E. Benedetti[a]

Transplantation Proceedings, 50, 66–69 (2018)

ABSTRACT

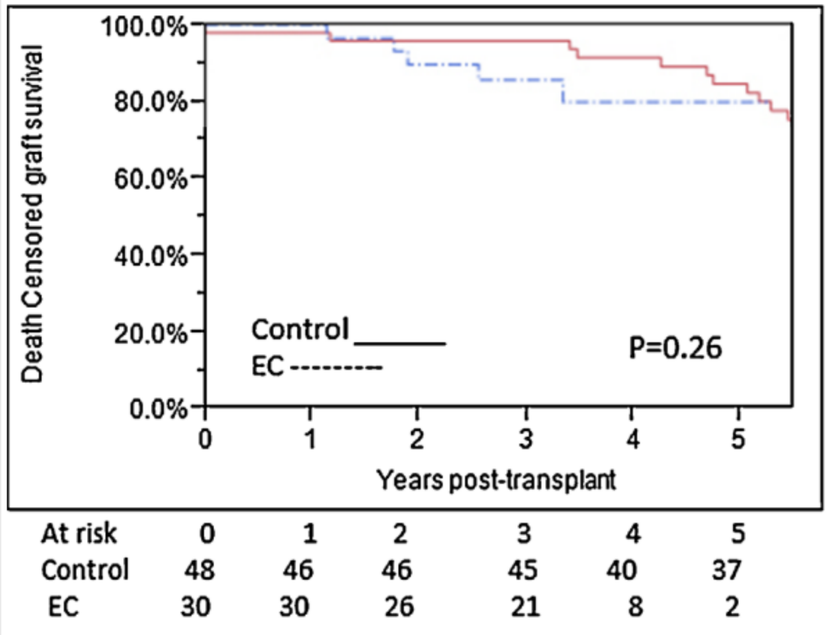
Antibody-mediated rejection (AMR) is one of the leading causes of allograft failure especially in patients undergoing ABO-incompatible (ABOi) renal transplantation. We hypothesized that complement inhibition with eculizumab, a C5 inhibitor, would protect against AMR and maintain graft function in ABOi renal transplant recipients. Four patients undergoing living donor kidney transplant from ABOi donors were treated with a 9-week eculizumab course without therapeutic plasma exchange, intravenous immunoglobulin, or splenectomy. All patients had successful transplants and have normal graft function at the time of last follow-up. There were no cases of AMR or acute cellular rejection. Of note, 2 patients were transplanted despite persistent ABO antibody titers of 1:32, conventionally considered a contraindication to proceed in standard protocols. Eculizumab is a promising option to prevent AMR with ABOi renal transplantation without the need for splenectomy, post-transplant therapeutic plasma exchange, and intravenous immunoglobulin. Future multicenter studies are needed to determine long-term efficacy and safety.

ABMR ve Ekulizumab

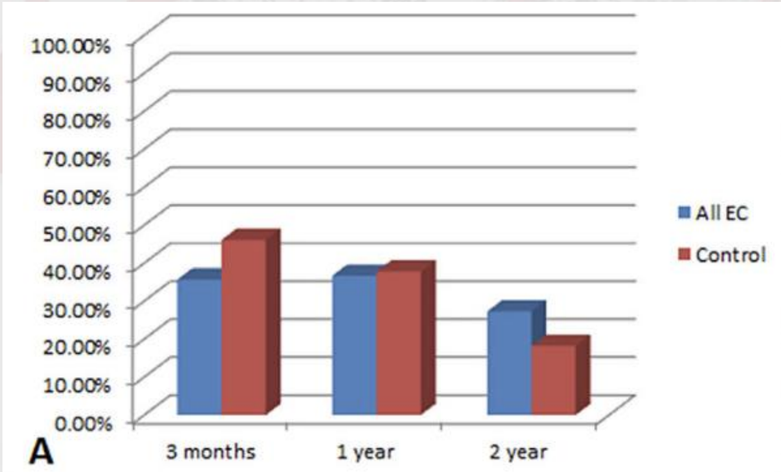
Positive Crossmatch Kidney Transplant Recipients Treated With Eculizumab: Outcomes Beyond 1 Year

L. D. Cornell[1], C. A. Schinstock[2], M. J. Gandhi[3], W. K. Kremers[2] and M. D. Stegall[2,*]

American Journal of Transplantation 2015; 15: 1293–1302
Wiley Periodicals Inc.



İki yıllık takipte subklinik ABMR ve greft sağ kalımında ekulizumabın üstünlüğü gösterilmemiştir.



Subclinical ABMR in Controls vs. Eculizumab			
	3-4 months	1 year	2 year
All EC	35.7% (10/28)	36.7% (11/30)	27.3% (6/22)
Control	46.2% (18/39)	36.8% (14/38)	15.1% (5/33)
p-value (EC vs. control)	P=0.46	P=1.0	P=0.32

ABMR ve Ekulizumab

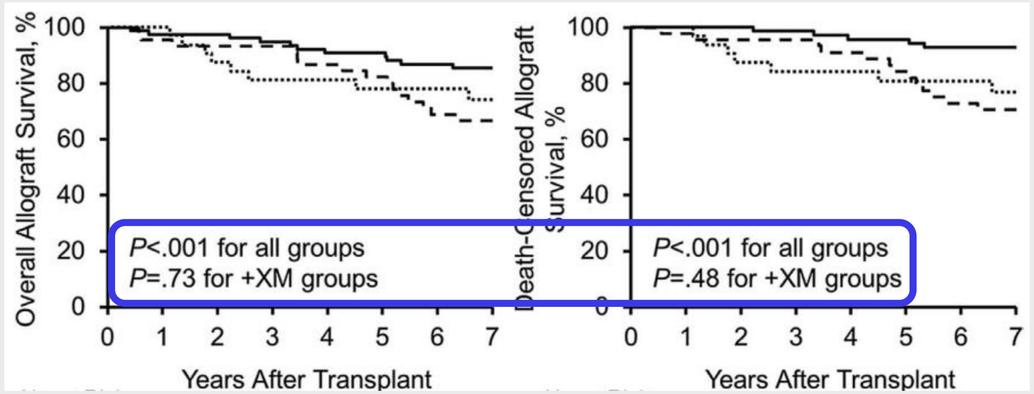
Received: 13 June 2018 | Revised: 30 October 2018 | Accepted: 1 November 2018

DOI: 10.1111/ajt.15175

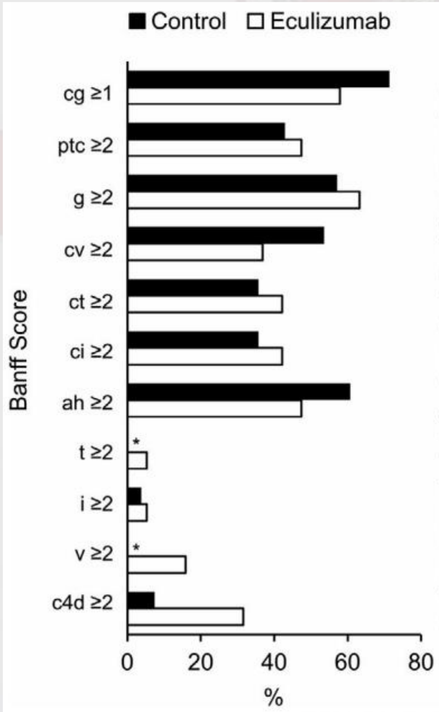
ORIGINAL ARTICLE

Long-term outcomes of eculizumab-treated positive crossmatch recipients: Allograft survival, histologic findings, and natural history of the donor-specific antibodies

Carrie A. Schinstock[1,2] | Andrew J. Bentall[1,2] | Byron H. Smith[3] | Lynn D. Cornell[4] | Matthew Everly[5] | Manish J. Gandhi[4] | Mark D. Stegall[2,6]



Greft sağ kalımı ekulizumab alan ve almayan XM pozitif gruplarda benzer iken, XM negatif gruba göre anlamlı olarak azalmıştır.



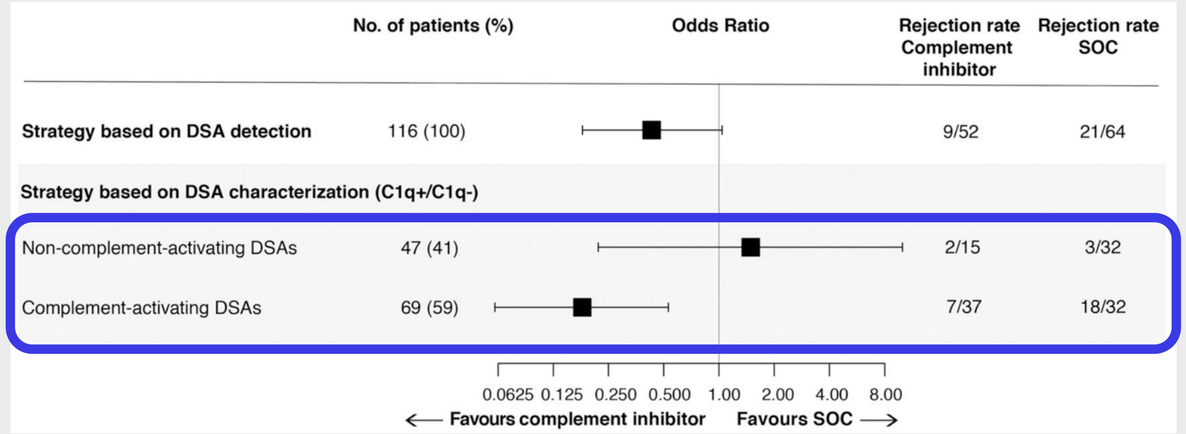
	Eculizumab +XM (%) (n=19)	Control +XM (%) (n=28)	*P Value*
Chronic ABMR cg score ≥0	57.9 (11)	71.4 (20)	.36
Peritubular capillaritis ptc score ≥2	47.4 (9)	42.9 (12)	.77
Glomerulitis g score ≥2	63.2 (12)	57.1 (16)	.77
Vascular intimal thickening cv score ≥2	36.8 (7)	53.6 (15)	.37
Tubular atrophy ct score ≥2	42.1 (8)	35.7 (10)	.76
Interstitial fibrosis ci score ≥2	42.1 (8)	35.7 (10)	.76
Arteriolar hyalinosis ah score ≥2	47.4 (9)	60.7 (17)	.39
Tubulitis t score ≥2	5.3 (1)	0.0 (0)	.40
Inflammation i score ≥2	5.3 (1)	3.7 (1)	1.0
Intimal arteritis v score ≥2	15.8 (3)	0.0 (0)	.06
C4d ≥2	31.6 (6)	7.4 (2)	.05

Ekulizumab alan ve almayan XM pozitif gruplar arasında 5.yıl protokol biyopsileri histopatolojik bulguları benzer bulunmuştur.

Complement-Activating Anti-HLA Antibodies in Kidney Transplantation: Allograft Gene Expression Profiling and Response to Treatment

Carmen Lefaucheur,[1,2] Denis Viglietti,[1,2] Luis G. Hidalgo,[3] Lloyd E. Ratner,[4] Serena M. Bagnasco,[5] Ibrahim Batal,[6] Olivier Aubert,[1] Babak J. Orandi,[7] Federico Oppenheimer,[8] Oriol Bestard,[9] Paolo Rigotti,[10] Anna V. Reisaeter,[11] Nassim Kamar,[12] Yvon Lebranchu,[13] Jean-Paul Duong Van Huyen,[1,14] Patrick Bruneval,[1,15] Denis Glotz,[1,2] Christophe Legendre,[1,16] Jean-Philippe Empana,[1] Xavier Jouven,[1] Dorry L. Segev,[17] Robert A. Montgomery,[18] Adriana Zeevi,[19] Philip F. Halloran,[3] and Alexandre Loupy[1,16]

J Am Soc Nephrol 29: 620–635, 2018.



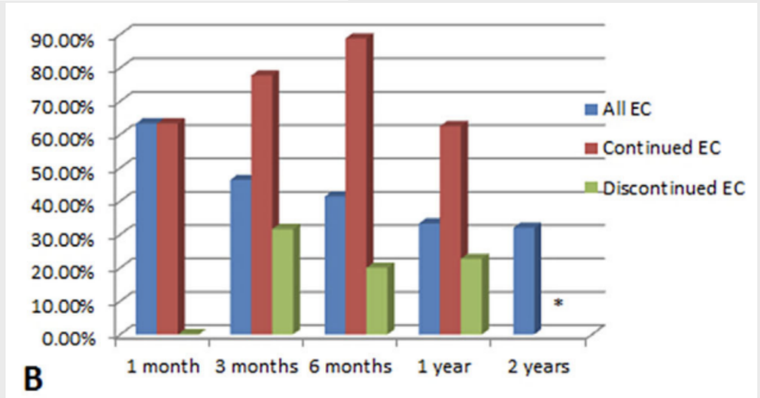
Ekulizumab, C1q-bağlayan HLA DSA'lı hastalarda ABMR insidansını azaltmaktadır.

Yalnızca **komplemana bağımlı efektör mekanizmaların neden olduğu ABMR**'nin kompleman karşıtı tedaviye duyarlı olabileceğini düşündürmektedir.

Positive Crossmatch Kidney Transplant Recipients Treated With Eculizumab: Outcomes Beyond 1 Year

L. D. Cornell[1], C. A. Schinstock[2], M. J. Gandhi[3], W. K. Kremers[2] and M. D. Stegall[2,*]

American Journal of Transplantation 2015; 15: 1293–1302
Wiley Periodicals Inc.



C4d over time in Eculizumab group					
	1 month	3-4 months	6 months	1 year	2 years
All EC	63.3% (19/30)	46.4% (13/28)	41.4% (12/29)	33.3% (10/30)	31.8% (7/22)

Ekulizumab alan HLA-DSA'lı böbrek nakli alıcılarında 1. ay (%63) ve 2. yılda (%32) böbrek C4d birikimi görülmektedir.

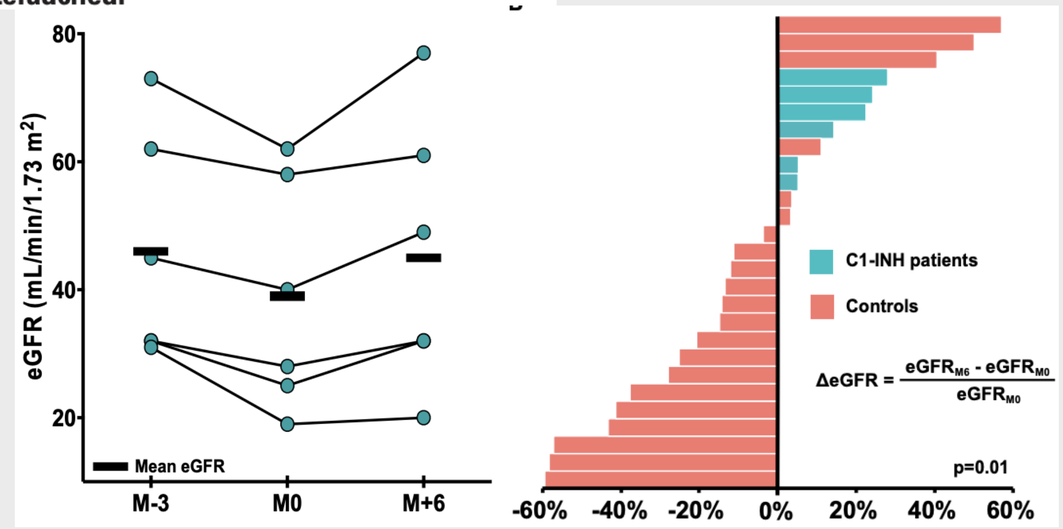
Kompleman sisteminin terminal yolağını hedefleyen ekulizumab, **daha önceki kompleman bileşenlerinin aktivitesini** ve buna bağlı ABMR'yi önlemez.

ABMR ve C1-INH

C1 Inhibitor in Acute Antibody-Mediated Rejection Nonresponsive to Conventional Therapy in Kidney Transplant Recipients: A Pilot Study

D. Viglietti[1,2,†], C. Gosset[1,†], A. Loupy[2,3], L. Deville[4], J. Verine[5], A. Zeevi[6], D. Glotz[1] and C. Lefaucheur[1,2,*]

American Journal of Transplantation 2016; 16: 1596–1603
Wiley Periodicals Inc.



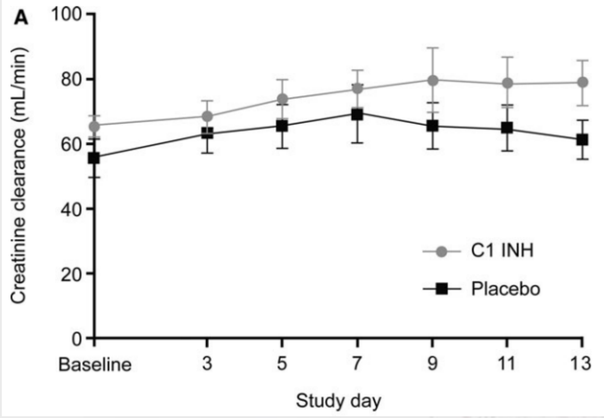
Standart tedaviye dirençli AMBR, 6 hasta

C1-INH ile 6. ayda eGFR'de iyileşme, anti-HLA DSA MFI ve anti-HLA DSA C1q düzeyinde azalma izlendi.

Plasma-Derived C1 Esterase Inhibitor for Acute Antibody-Mediated Rejection Following Kidney Transplantation: Results of a Randomized Double-Blind Placebo-Controlled Pilot Study

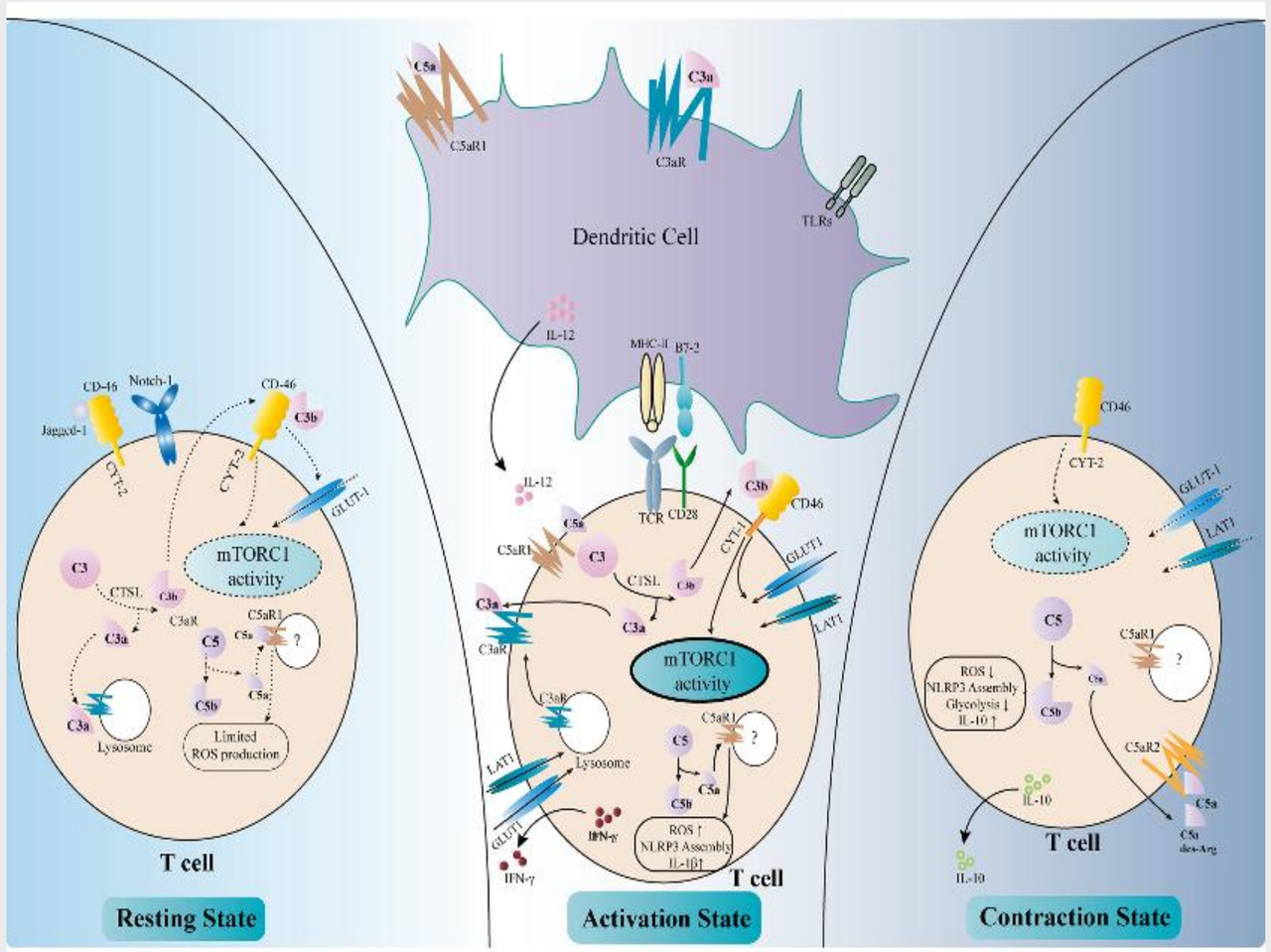
R. A. Montgomery[1,*], B. J. Orandi[1], L. Racusen[2], A. M. Jackson[3], J. M. Garonzik-Wang[1], T. Shah[4], E. S. Woodle[5], C. Sommerer[6], D. Fitts[7], K. Rockich[7], P. Zhang[7] and M. E. Uknis[7]

American Journal of Transplantation 2016; 16: 3468–3478
Wiley Periodicals Inc.



Standart tedaviye C1-INH eklenmesi, ABMR histopatolojisi (20.gün) ve böbrek fonksiyonunda anlamlı fark yaratmamıştır.

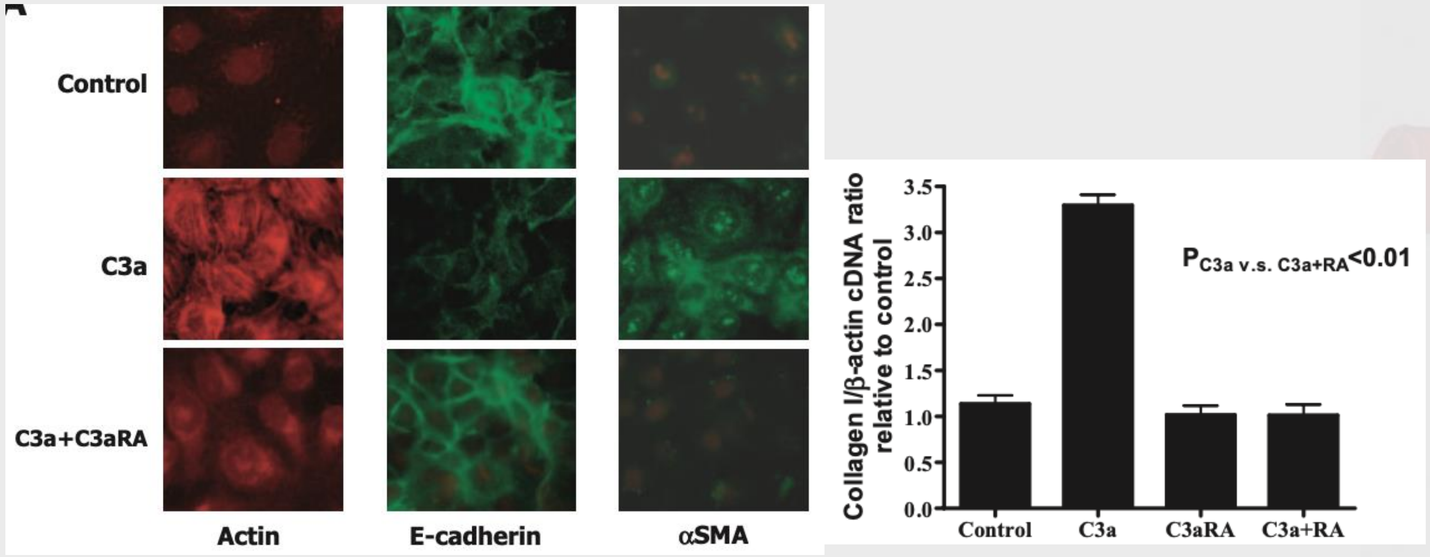
Ancak subgrup analizde C1-INH grubunda hiçbir hastanın 6.ay protokol biyopsisinde transplant glomerülopati görülmemiştir (plasebo grubunda %43).



Klinik transplantasyonda alloimmün yanıtı azaltmak için **kompleman sistemi ve T-hücre** immünitesi arasındaki etkileşim, geleneksel anti-T hücre immünsupresyonuna çekici bir alternatiftir.

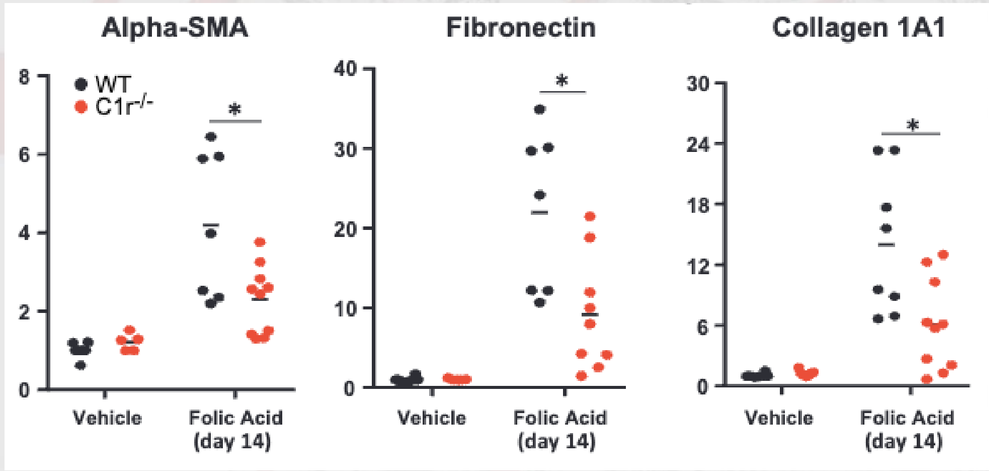
Qi R, Qin W. Front Immunol. 2022.

Kompleman sisteminin böbrek fibrozisindeki rolü, **kronik rejeksiyonda** alternatif bir tedavi yolağı olabileceğini düşündürmektedir.



C3a ile E-cadherin ekpresyonu azalmış, α- düz kas aktin proteini ve kollajen I mRNA ekspresyonu artmıştır. C3aR antagonisti ise bunu önler.

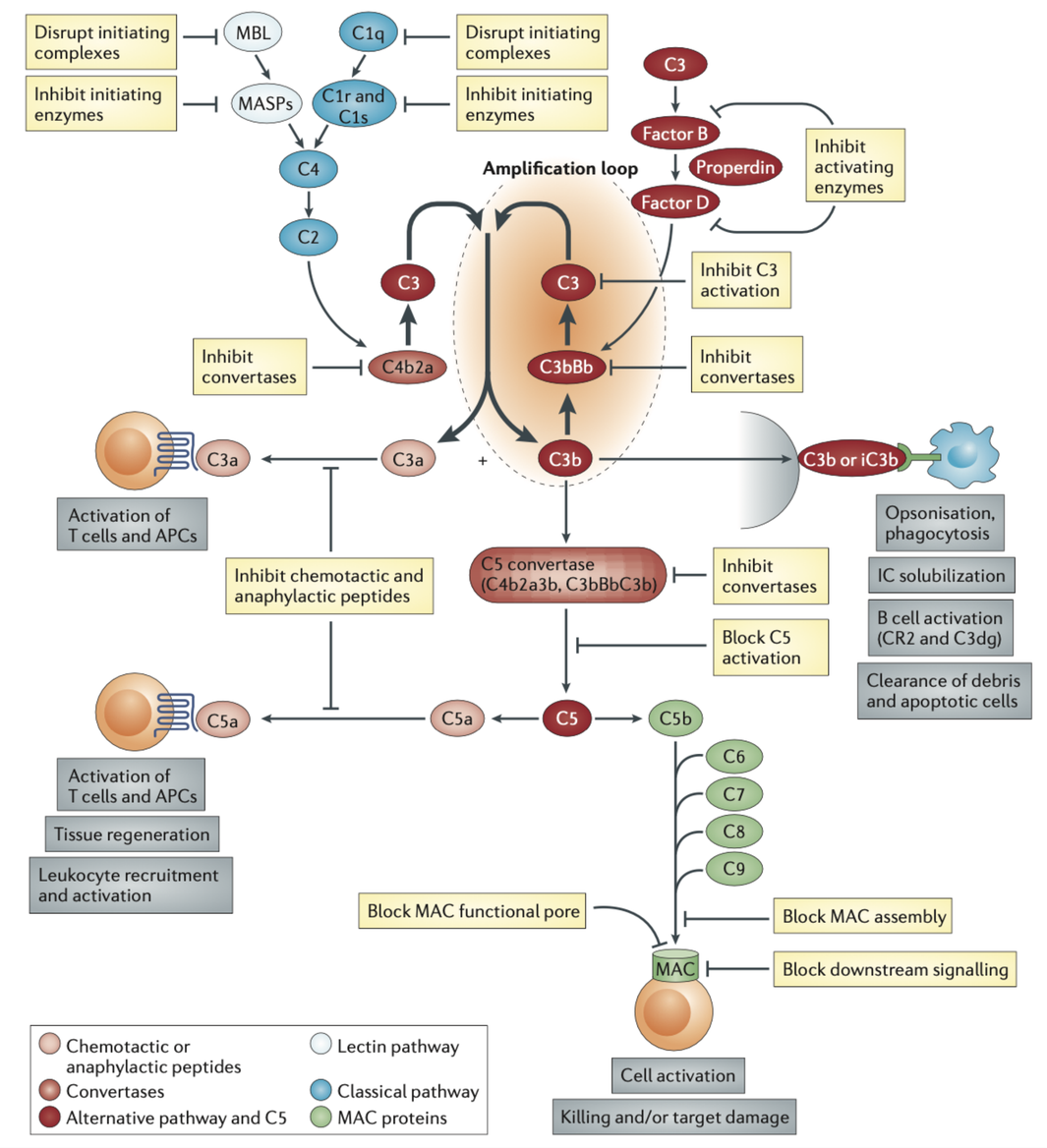
Bu C3a'nın epitelyal-mezenkimal dönüşümdeki önemli rolünü göstermektedir.



C1r -/- farelerde tüm fibrotik marker genlerin ekspresyonu azalmıştır.

Tang Z, et al. J Am Soc Nephrol. 2009.

Xavier S, et al. Am J Physiol



Kompleman Sistemi ve Potansiyel Tedavi Hedefleri

Morgan BP, Harris CL. Nat. Rev Drug Discov. 2015.

KOMPLEMAN SİSTEMİ, PEK ÇOK BÖBREK HASTALIĞININ PATOFİZYOGENEZİNDE FARKLI BASAMAKLARDA ROL OYNAMAKTADIR.

NAKİL ÖNCESİNDE, SIRASINDA VE SONRASINDA DONÖRDE, ALICIDA VE GREFTTE KOMPLEMAN AKTİVASYONU, BÖBREK NAKLİNDE HASARIN ÖNEMLİ BİR NEDENİDİR.

- İSKEMİ-REPERFÜZYON HASARI
- GECİKMİŞ GREFT DİSFONKSİYONU
- AKUT ANTİKOR-ARACILI VE T-HÜCRE ARACILI REJEKSİYON
- KRONİK REJEKSİYON
- PRİMER HASTALIK REKÜRRENSİ

KOMPLEMAN HEDEFLİ TEDAVİ STRATEJİLERİ, BU HASARIN ÖNLENMESİ VE TEDAVİSİ İLE GREFT FONKSİYONUNUN OPTİMİZE EDİLMESİNDE ROL OYNAYARAK, BÖBREK NAKLİ STANDART TAKİBİNİN BİR PARÇASI OLMA POTANSİYELİNE SAHİPTİR.

Teşekkürler...