Society for Heart Failure and Transplantation

SOCIETY FOR HEART FAILURE AND TRANSPLANTATION'S

THE REVIVAL

Promoting Academics to Improve Clinical Outcomes.

ISSUE: 34 | November 2023

EDITOR'S NOTE

Dr Manoj Durairaj

Heart Transplant Surgeon, MS, MCh. (AIIMS, New Delhi), FACC.

President of the Indian Association of Cardiovascular-Thoracic Surgeons.

Director, Marian Cardiac Centre and Research Foundation.

Program Director, Department of Heart and Lung Transplantation, Sahyadri Hospitals, Pune.

Dear Readers,

Greetings from the Editor's Desk!

We present to you the second article of the 4 article series by Dr. Chintan Sheth. This article focuses on the intricate landscape of transplant immunology in heart transplantation, detailing acute cellular and humoral responses and their clinical implications. Through a comprehensive examination, Dr. Sheth elucidates the role of various immune cells, including CD4+ T cells, CD8+ T cells, B cells, and regulatory T cells, in graft rejection mechanisms. The article highlights the interplay of cytokines, chemokines, and immunoglobulins in acute rejection processes, providing clinicians with valuable insights into managing post-transplant complications. Furthermore, Dr. Sheth's discussion on diagnostic hallmarks and non-HLA-mediated factors contributing to rejection offers critical guidance for improving patient outcomes. Overall, this insightful analysis offers a holistic understanding of transplant immunology in heart transplantation, paving the way for enhanced clinical management strategies and improved patient care.

Wishing our dear readers a Happy Reading as always!

Dr Manoj Durairaj
Editor "The Revival"

SUB EDITOR

Dr Talha Meeran

MBBS, MD, FACC,
Consultant Cardiologist,
Dept of Advanced Cardiac Sciences and Cardiac Transplant,
Sir HN Reliance Foundation Hospital, Mumbai

Dear Colleagues,

This edition of REVIVAL is the second in a series of four review articles by Dr Chintan Seth focusing on transplant immunology. In the current issue of REVIVAL, Dr Chintan Seth delves into the cellular and immunological mechanisms involved in cellular rejection and antibody mediated rejection with descriptive and detailed graphics to further our understanding of this complex topic. The parts explaining the cellular basis of the endomyocardial biopsy findings are particularly noteworthy. Lastly, the graphic on coronary allograft vasculopathy (CAV) elegantly depicts the immunopathological nature of CAV.

Sincerely,
Dr Talha Meeran
Sub Editor "The Revival"

Society Reg.No.: EKM/TC/186/2013,

Society secretariat: Address 36/117, 2nd Floor, Lisie Hospital Road, Kottecanal Junction, Kochi 682018. **Ph.:** 025750048, **Email:** infoshft@gmail.com, www.sfhft.org

Please call or write to us: Call: 9822322072, 9167048815, manojdurairaj@hotmail.com, talha.meeran@gmail.com

Link for membership, http://www.sfhft.org/application.html

Special thanks to Dr Chintan Sheth for authoring this month's article.

Designed by Maithili Kulkarni

PRESIDENTIAL MESSAGE

Dr Julius Punnen

Sr. Consultant Cardiothoracic Surgeon, Narayana Health, Bangalore

Dear Members and Colleagues,

In this edition of the Revival, we have an expert, Cardiac and Heart Transplant Anesthesiologist, Dr Chintan Sheth, continuing a review of transplant immunology. In the first part of the review, Dr. Sheth discussed the basics of immunology and immune responses. In the second part, he discusses clinical implications of these immunological responses. Heart transplantation offers a beacon of hope for many patients battling end-stage heart disease, offering the promise of extended and improved life. However, the interplay between the recipient's immune system and the graft can lead to complications, with acute cellular and antibody-mediated rejection emerging as significant challenges. The orchestration of immune responses during rejection involves a complex interplay of cells and cytokines, and treatment of rejection requires thorough understanding of these mechanisms, as detailed in this article.

Naïve alloreactive CD4+ T cells, activated by dendritic cells (DCs), differentiate into T helper cells, particularly Th1 and Th17 cells. Th1 cells, producing IFN-γ and IL-2, play a pivotal role in cytotoxic T lymphocyte (CTL) priming and humoral response stimulation. Meanwhile, Th17 cells induce the recruitment of inflammatory cells, causing damage to the graft. Activated CD4+ T cells can activate B cells and can activate antibody-mediated rejection. This dual assault of cellular and antibody-mediated rejection underscores the challenges in transplantation.

The article sheds light on the intricate mechanisms of cellular rejection, where activated CD8+ T cells differentiate into cytotoxic lymphocytes (CTLs) that induce target cell apoptosis. Conversely, regulatory T cells (Tregs) play a crucial role in tolerance processes, suppressing effector T cells and limiting antigen presentation. The delicate balance between pro-rejection and tolerance mechanisms underscores the complexity of immune responses in graft acceptance or rejection.

The revelation that acute humoral response plays a predominant role in graft rejection challenges the traditional focus on T cells. Antibody-mediated rejection (AMR), accounting for a significant percentage of graft loss, occurs when recipient antibodies target donor HLA antigens. This leads to a cascade of events, including B cell activation, class-switching to IgG, and the production of long-lived plasma cells. Macrophages and natural killer cells further amplify the response, releasing proinflammatory cytokines and activating the complement cascade, resulting in tissue injury.

The presence of C3d and C4d on endomyocardial biopsies serves as indicative markers of AMR. Importantly, the article highlights that AMR can occur even in the absence of detectable antibodies against MHC/HLA antigens, emphasizing the need for comprehensive antibody testing to capture non-HLA antibodies responsible for rejection.

The intricate interplay of activated T cells, cytokines, and the complement cascade culminates in allograft dysfunction, evident in the manifestation of cardiac allograft vasculopathy (CAV). IFN-γ produced by activated T cells contributes to intimal expansion and diffuse stenosis, further emphasizing the systemic nature of rejection processes.

In conclusion, the article provides a comprehensive overview of the cellular and molecular intricacies involved in acute cellular and antibody-mediated rejection. Recognizing the multifaceted nature of immune responses in transplantation is crucial for advancing therapeutic strategies to enhance graft survival and improve long-term outcomes for transplant recipients. As research in immunology and transplantation continues to evolve, these insights pave the way for more targeted and effective interventions in the delicate dance between donor graft and recipient immune system. This evolving landscape challenges the transplantation community to rethink immunosuppressive strategies and move towards a personalized approach, considering the unique immunological profiles of each patient.

With warm regards,

Dr Julius Punnen

President, Society for Heart Failure and Transplantation

TRANSPLANT IMMUNOLOGY-
CLINICAL IMPLICATIONS (PART - II)

ABOUT THE AUTHOR

Dr. Chintan Sheth

DA, DNB, FICA, FTEE

Consultant Cardiac and Heart Transplant Anesthesiologist, Marengo CIMS Hospital, Ahmedabad, Gujarat

Working as a Consultant Cardiac and Heart & Lung Transplant Anesthesiologist And Cardiac Critical Specialist at Marengo CIMS Hospital for 12 years.

Successfully managed 45 Heart transplant recipients over 6 years.

Completed structured observer ship for heart and Lung Transplant and MCS for 1 month at UPMC under Dr. Robert Kormos, Pittsburgh and Allegheny general Hospital, Pittsburgh in 2016.

Had Topped the FTEE (Fellowship in Transesophageal Echocardiography) exams in 2016 with Prof. Dr. Kumar Belani award.

Did DA (Diploma Anesthesia) from Stanley Medical College, Chennai in 2008 and DNB anesthesia from Narayana Hrudayala, Bangalore in 2010.

Fellowship in Cardiac Anesthesia (FICA) from Narayana Hrudayalaya, Banglore under Dr. Muralidhar Kanchi in 2011.

Continued from Part I

Acute Cellular Response and acute cellular rejection

On activation by DCs, naïve alloreactive $CD4^+$ T cells can differentiate into T helper cells, mainly into Th1 and Th17 cells. Th1 cells produce IFN-γ and IL-2 **(Basiliximab used as an induction agent to inhibit IL-2)**. This activated $CD4^+$T cells and produced cytokines (IFN-γ and IL-2) are involved in cytotoxic T lymphocyte (CTL: CD8) priming, stimulation of the humoral response, and activation of other cell types such as NK cells. IL-17 produced by Th17 cells, stimulates the production of inflammatory cytokines and chemokines leading to the recruitment of neutrophils and macrophages to the graft which ultimately damages graft by secreting various chemokines and further activating T cells. Activated $CD4^+$ T cells can activate B cells and can activate Antibody mediate rejection, that is why **in many patients both cellular and antibody mediated rejection coexist. (Figure: 4)**

Naïve $CD8^+$ cells can be activated by DCs and also by $CD4^+$ T cells and this activated $CD8^+$ T cells can differentiate into CTLs (cytotoxic lymphocytes) which secretes TNF-α and induce target cell apoptosis. Memory $CD8^+$ T cells act as CTLs as they are able to directly kill target cells, mainly via the granzyme/perforin pathway.

$CD4^+$ $CD25^+$ $FoxP3^+$ Tregs (T regulatory cells) have been shown to be involved in the tolerance process and to prevent graft rejection. These cells are able to suppress $CD4^+$ and $CD8^+$ effector T cells and can also target APCs, decreasing their capacity for antigen-presentation and costimulation.

CLINICAL PEARL

In sensitized patients, the presence of memory T cells specific for alloantigens are due to prior blood transfusion, pregnancy, or transplant rejection that can induce hyperacute/ acute rejection.

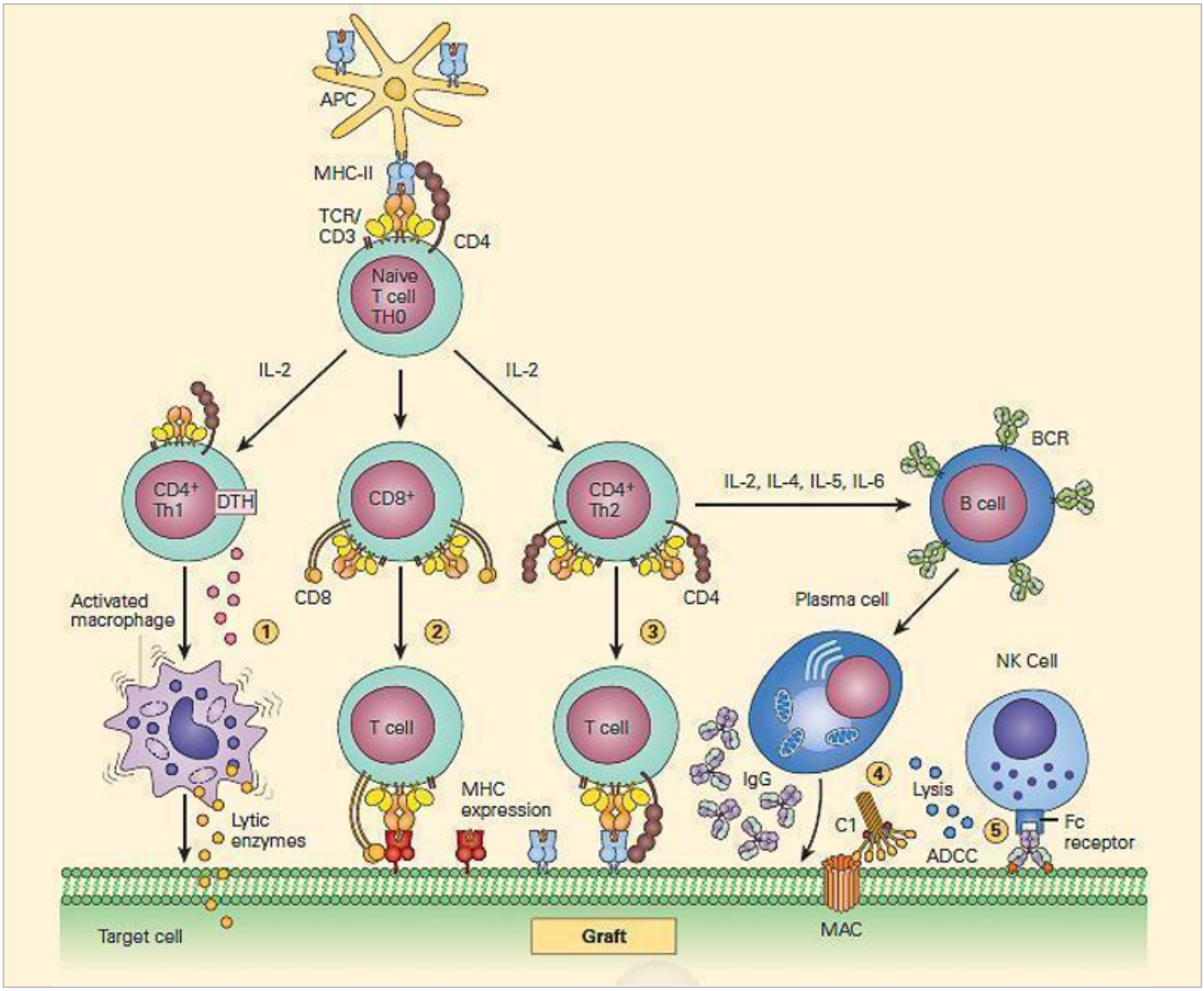

Figure 4: Mechanism of Acute Cellular Rejection

Figure 4 Courtesy: Bellanti, JA (Ed). Immunology IV: Clinical Applications in Health and Disease. I Care Press, Bethesda, MD, 2012Acute Humoral Response and Antibody mediated rejection.

Acute Humoral Response and Antibody mediated rejection

Although, T cells have been considered for many years as playing a predominant role in graft rejection, it is now known that the acute humoral response is the main cause of acute graft loss. In fact, acute humoral rejection accounts for 15% to 20% of graft rejection within the first posttransplant year, despite immunosuppressive therapies. AMR develops when recipient antibody is directed against donor HLA antigens on Naïve-B cell recognises donor-specific HLA antigen and present the antigen peptides from MHC-II to T cell receptor and activate T cells. The activated T cells regulate the growth and survival of B cells through the production of IL-4, 6, 7, 10, 21, TNF-α, IFN-γ, etc.

Activated B cell migrates to secondary lymphoid tissue, class-switches to IgG with high affinity for donor-specific HLA antigen. These cells migrate into the bone marrow and differentiate into long-lived plasma cells, and keep producing IgG DSAs for a long term.

Macrophages and natural killer cells function as antigen-presenting cells and induce B cells and T cells activation. IgG-type DSA binds to Fcγ on the macrophages and natural killer cells' surface and activates. These activated cells produce proinflammatory cytokines such as IFN-γ, Tumor Necrosis Factor (TNF), and granzyme B, which induce coagulation, inflammation, vascular permeability, and leukocyte trafficking on the vascular endothelium. (Figure: 5). **Presence of CD68 – marker of macrophage in capillaries is suggestive of AMR on EMB.**

Antibodies induce fixation and activation of the complement cascade, resulting in tissue injury. **Complement activation,** a key contributor to the

pathogenesis of AMR, results in activation of the innate and adaptive immune responses. Complement and immunoglobulin are deposited within the allograft microvasculature, which results in an inflammatory process that is characterized by endothelial cell activation, upregulation of cytokines, infiltration of macrophages, increased vascular permeability, and microvascular thrombosis (Figure: 5). This process ultimately manifests as allograft dysfunction. **Presence of C3d and C4d on EMB is suggestive of AMR.** AMR can also occur with alloantibodies other than HLA/MHC class 1 and class 2 antigens like MICA and MICB antigens (MHC class I-related molecules, minor histocompatibility antigens and non-HLA antigens including the angiotensin II type 1 receptor, vimentin, myosin, the ABO blood group antigens, perlecan, type IV and VI collagen, agrin, unknown endothelial antigens, and ICAM-1 and **these can produce DSA negative AMR as DSA test can check only MHC/HLA antibodies and not the non HLA antibodies responsible for AMR.**

CLINICAL PEARL

- Presence of intracapillary Macrophages and activation of complement cascade which can be confirmed on immunohistochemistry by positive for CD 68 and C4d respectively is diagnostic hallmark of AMR
- Non HLA mediated AMR (e.g. antibodies against MICA antigen) can be associated with DSA negative as DSA can recognize only HLA antibodies

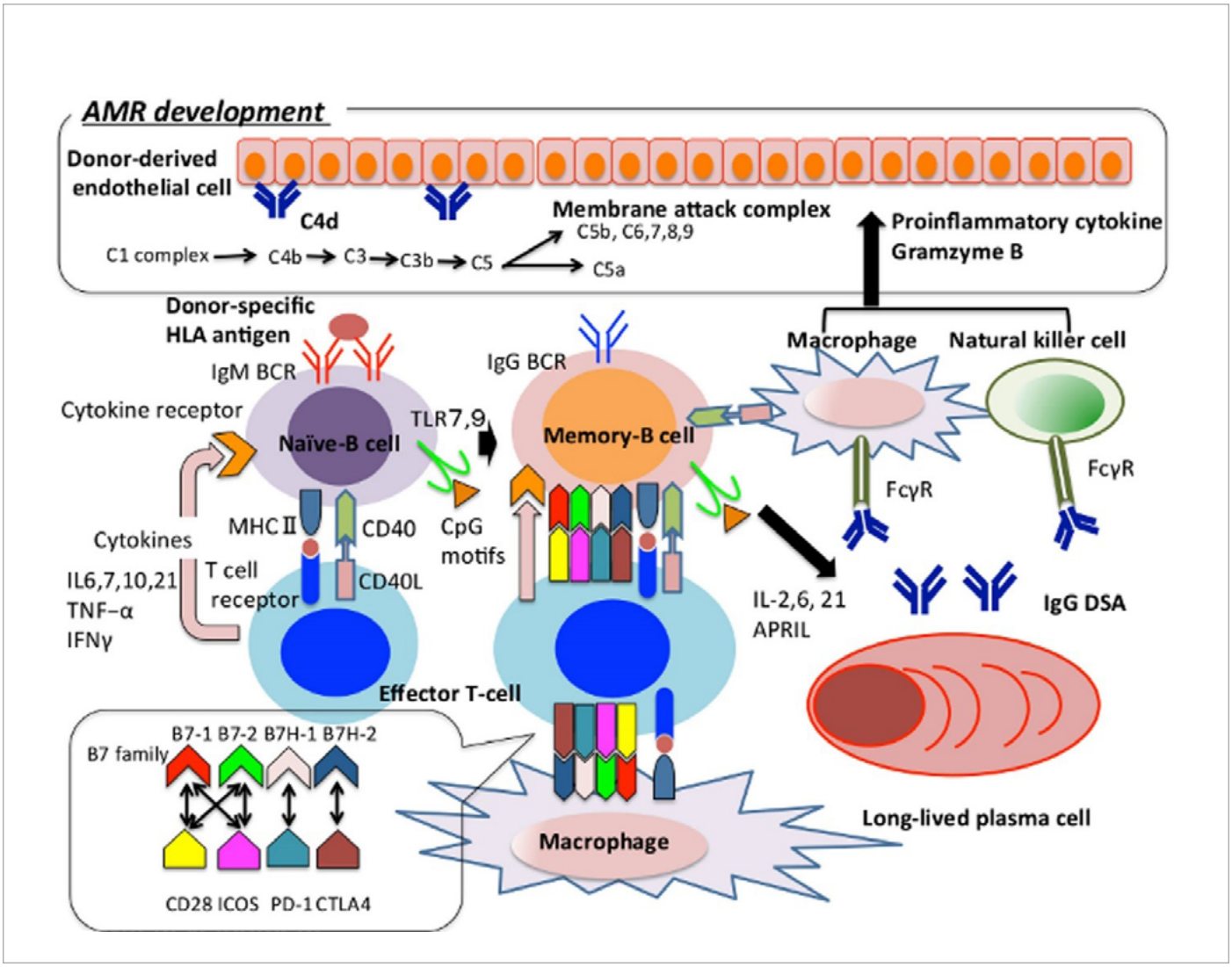

Figure 5: Mechanism of Antibody Mediated Rejection

Figure 5 courtesy: Matsuda Yoshiko, Watanabe Takeshi, Li Xiao-Kang, Approaches for Controlling Antibody-Mediated Allograft Rejection Through Targeting B Cells, Frontiers in Immunology, VOLUME=12, YEAR=2021

Interacting Mechanisms in the Pathogenesis of Cardiac Allograft Vasculopathy

The activated T cells elaborate cytokines, notably IFN-γ, which acts on the EC to promote further recruitment of T cells that acts upon smooth muscle cells (SMC) to cause proliferation, resulting in intimal expansion and diffuse stenosis characteristic of CAV[8].

CLINICAL PEARL

Ischemia/reperfusion (I/R) injury, innate immune signals and donor-specific antibody (DSA), CMV infection can enhance the ability of EC (endothelial cells) to recruit and activate T cells and ultimately signal for smooth muscle cells hyperplasia and proliferation causing CAV. (Figure: 6)

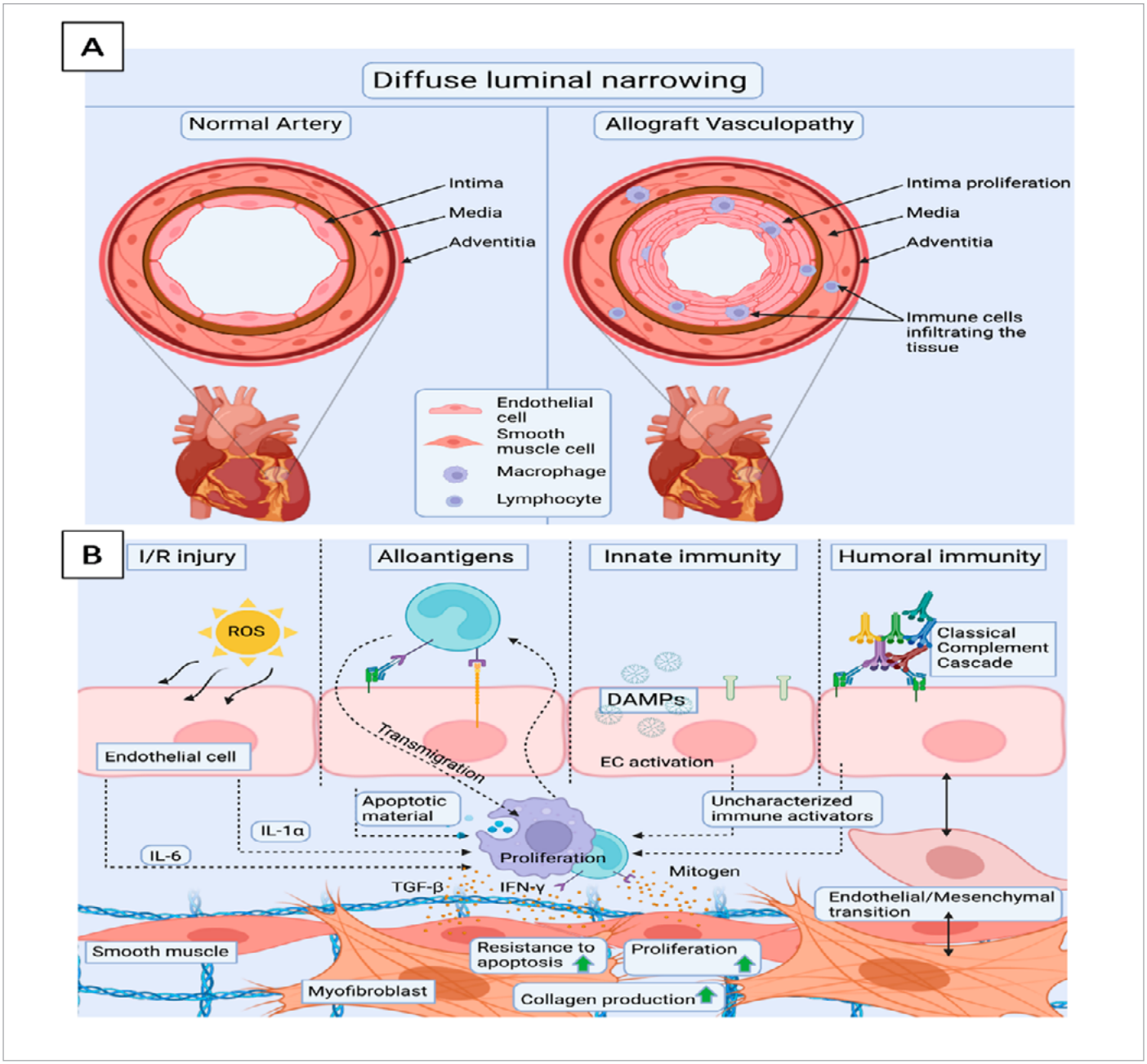

Figure 6: Mechanism of Cardiac Allograft Vasculopathy

Figure 6 Courtesy: Hurskainen, M.; Ainasoja, O.; Lemström, K.B. Failing Heart Transplants and Rejection—A Cellular Perspective. J. Cardiovasc. Dev. Dis. **2021**, 8, 180.

To Be continued...

Disclaimer:

The Revival newsletter, published by the Society for Heart Failure and Transplantation, is committed to upholding the highest standards of integrity and ethical conduct. While every effort is made to ensure the accuracy and originality of the content published in The Revival, it is important to note the following:

1. Plagiarism: The Society for Heart Failure and Transplantation and the editorial board of The Revival unequivocally condemn plagiarism in any form. All authors are responsible for ensuring that their submissions are original and properly attributed. The Society and editorial board do not accept any liability for any instances of plagiarism committed by authors.

2. Copyright Infringement: The Society for Heart Failure and Transplantation respects the intellectual property rights of others and endeavors to obtain proper permissions for the use of copyrighted material in The Revival. However, in the event that copyright infringement issues arise, the Society and editorial board shall not be held liable for any unauthorized use of copyrighted material by contributors.

3. Author Responsibility: Authors submitting content to The Revival are solely responsible for obtaining permissions and licenses for any third-party content used in their submissions. The Society and editorial board do not assume any responsibility for any copyright violations or legal disputes arising from the content submitted by authors.

4. Editorial Oversight: The editorial board of The Revival exercises due diligence in reviewing submissions for originality and adherence to ethical guidelines. However, the Society and editorial board cannot guarantee the absence of unintentional errors or instances of plagiarism in published content.

By accessing and reading The Revival newsletter, readers acknowledge and accept the terms of this disclaimer. Any concerns regarding plagiarism or copyright infringement should be promptly reported to the editorial board for investigation and appropriate action.

The Society for Heart Failure and Transplantation and the editorial board of The Revival reserve the right to modify or update this disclaimer as needed without prior notice.

PRESIDENT

DR JULIUS PUNNEN

Mob: 9980072785

Email: jpunnen@hotmail.com

VICE PRESIDENTS

DR AJITKUMAR V K

Mob: 9895153684

Email: ajitkumarvk@yahoo.com

DR P CHANDRASEKHAR

Mob: 9443047152

Email: chanpad@gmail.com

SECRETARY

DR S RAJAN

Mob: 98412 71353

Email: dr_rajan_icvd@hotmail.com

JOINT SECRETARY

DR RAJAGOPAL S

Mob: 9747606600

Email: srajagovindam@gmail.com

TREASURER

DR JACOB ABRAHAM

Mob: 9847128123

Email: jacabraham1@gmail.com

IMMEDIATE PAST PRESIDENT:

DR V NANDAKUMAR (2019-2023)

Mob: 9843015888

Email: drvnandakumar@gmail.com

PAST PRESIDENTS PERMANENT:

DR JOSE CHACKO PERIAPURAM

Mob: 9847043224

Email: joseperiapuram@hotmail.com

DR K VENUGOPAL

Mob: 9847005444

Email: venugopalknair@gmail.com

PAST PRESIDENTS

DR GEEVAR ZACHARIAH
(2013-2014 and 2014-2015)

Mob: 9846066816

Email: geevarzachariah@gmail.com

DR SHIV K NAIR (2015-2016)

Mob: 9846010220

Email: Shivnairmd@gmail.com

DR K VENUGOPAL (2016-2017)

Mob: 9847005444

Email: venugopalknair@gmail.com

DR JOSE CHACKO PERIAPURAM (2017-2018)

Mob: 9847043224

Email: joseperiapuram@hotmail.com

DR P P MOHANAN (2018-2019)

Mob: 9846076006

Email: drppmohanan@yahoo.com

MEMBERS

DR BASHA KHAN

Mob: 8296825550

Email: bashajalal@gmail.com

DR ADITI SIGHVI

Mob: 9999445511

Email: aditisinghvi4@gmail.com

DR K U NATARAJAN

Mob: 9895057660

Email: kunatarajan@aims.amrita.edu

DR JAMES THOMAS

Mob: 9892797060

Email: thomasdrjames@yahoo.in

DR MANOJ DURAIRAJ

Mob: 9822322072

Email: manojdurairaj@hotmail.com

DR NAGAMALLESH

Mob: 9880135258

Email: nmalesh@yahoo.co.in

DR JAYAGOPAL P B

Mob: 9847023777

Email: jaigopallakshmi@gmail.com

DR PRADEEP KUMAR

Mob:

Email:

DR BAGIRATH

Mob: 9845144830

Email: drbagirath@gmail.com

DR JO JOSEPH

Mob:

Email:

DR TALHA MEERAN

Mob: 9167048815

Email: talha.meeran@gmail.com

DR JABIR ABDULLAKUTTY

Mob: 9447011773

Email: drjabi@yahoo.co.in