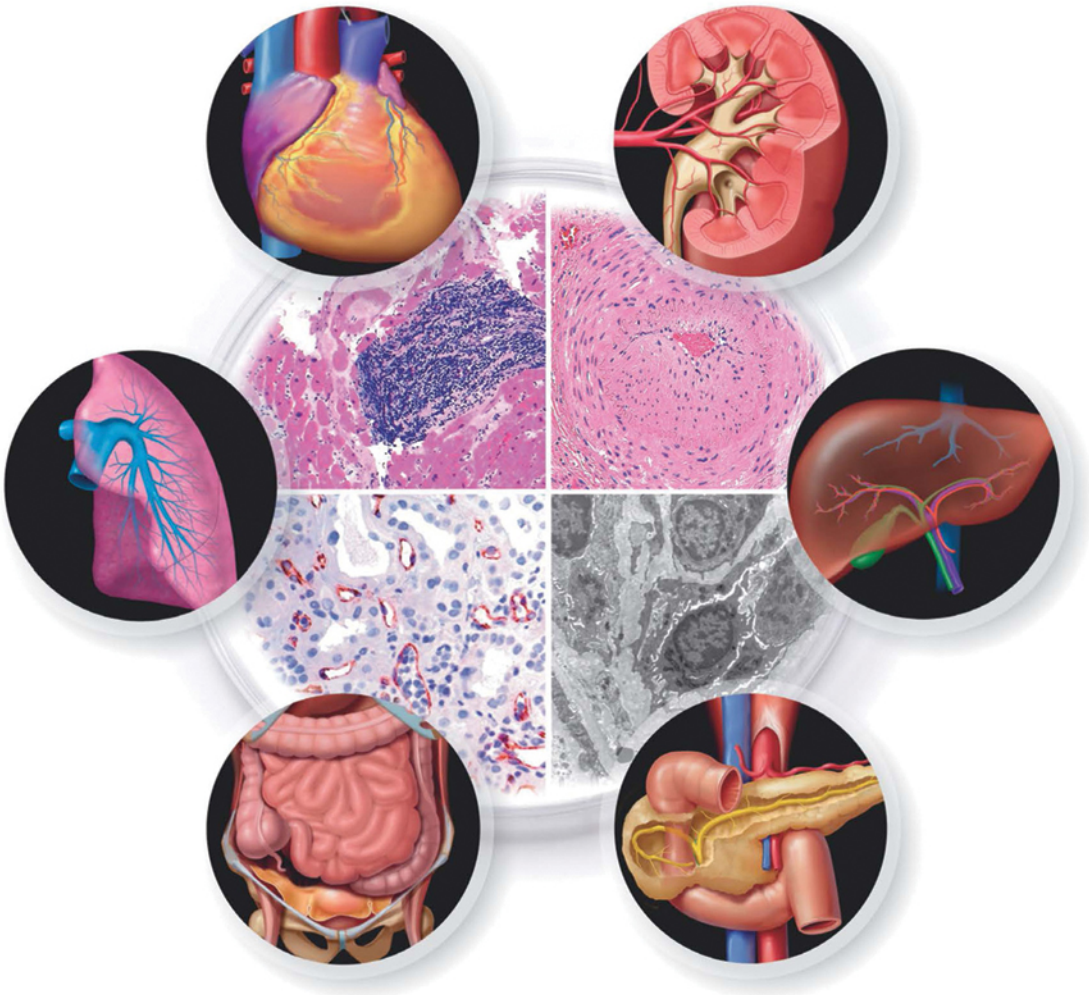
DIAGNOSTIC PATHOLOGY

Transplant Pathology

SECOND EDITION

CHANG | COLVIN

Abraham | Ahn | Alpert | Ananthanarayanan | Bracamonte | Cendales | Cornell
Farris | Gandhi | Gordon | Hart | Husain | Kambham | Langman | Masia | Meehan | Pai
Pogoriler | Ranganathan | Rosales | Seshan | Sharma | Wang | Westerhoff | Yeh | Yerian



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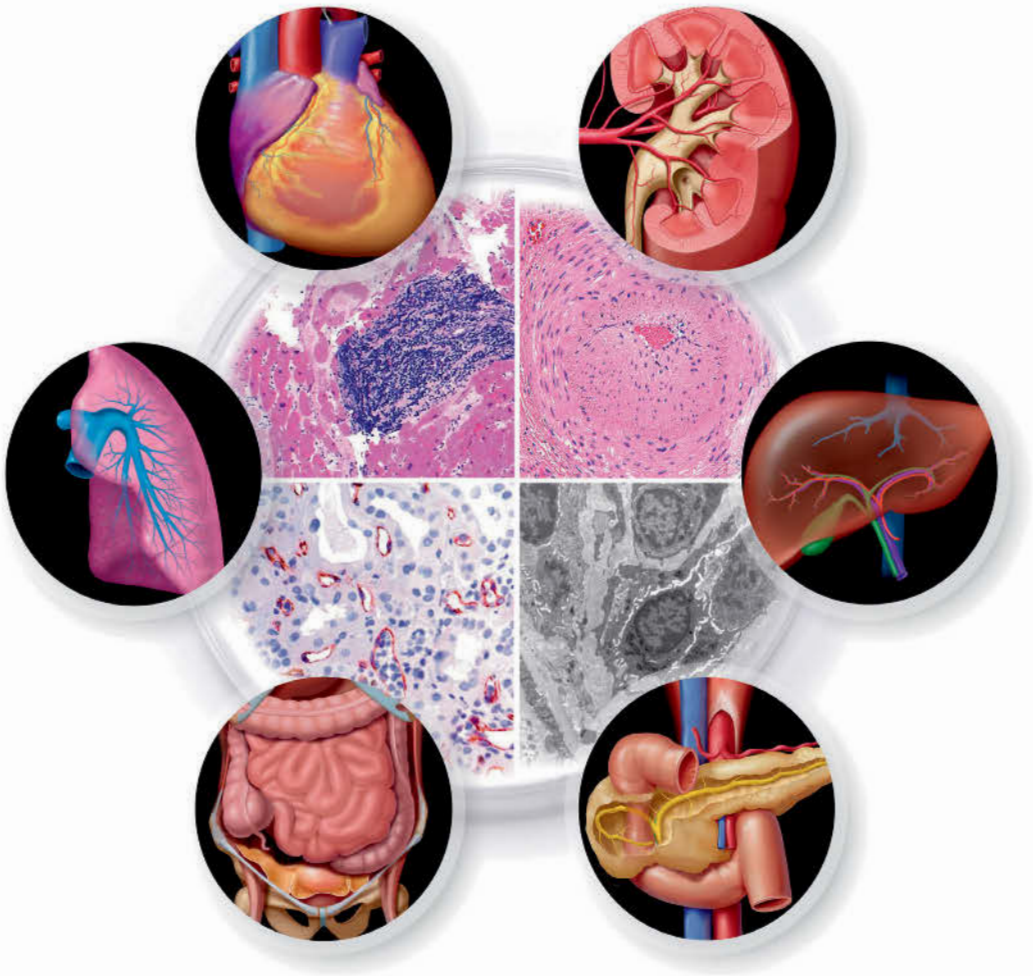

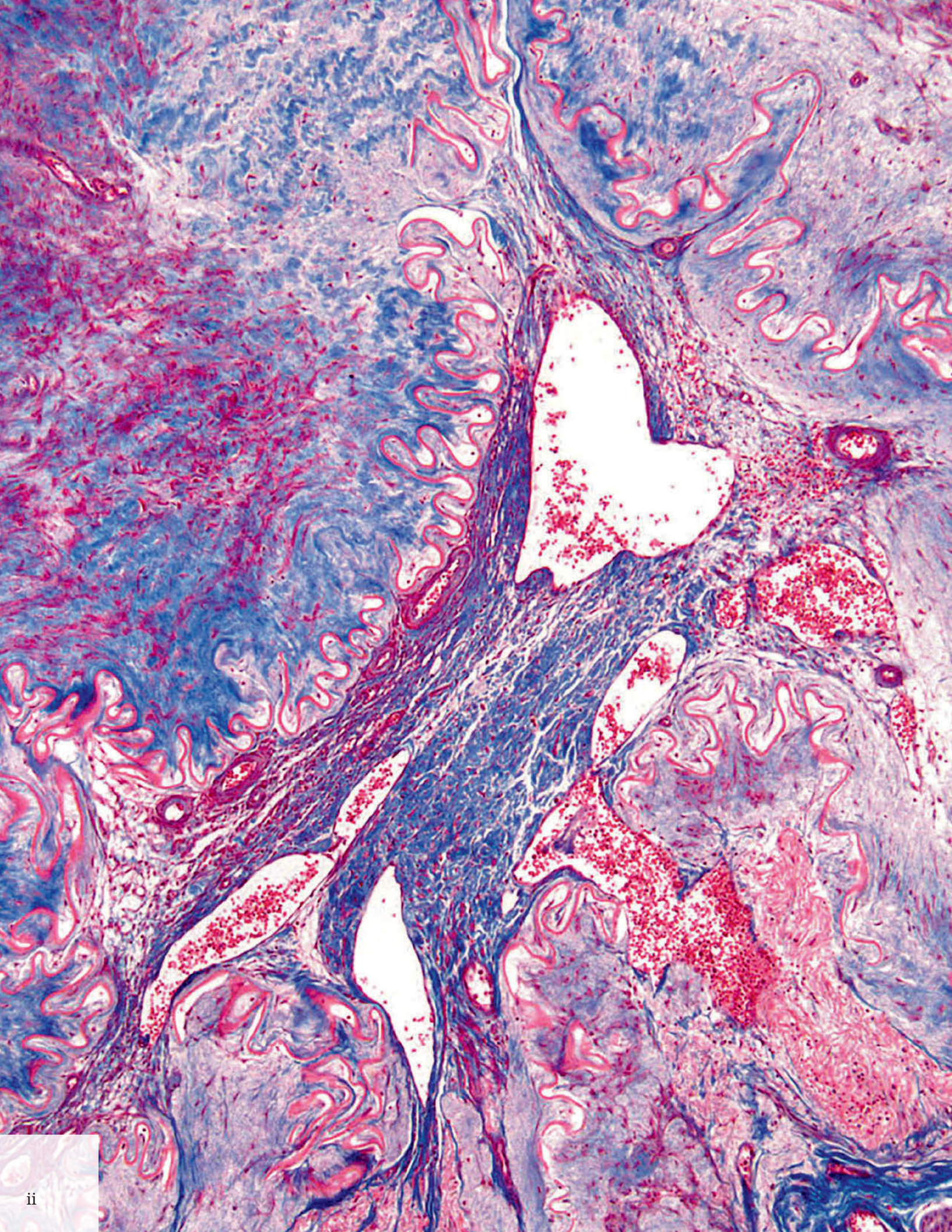

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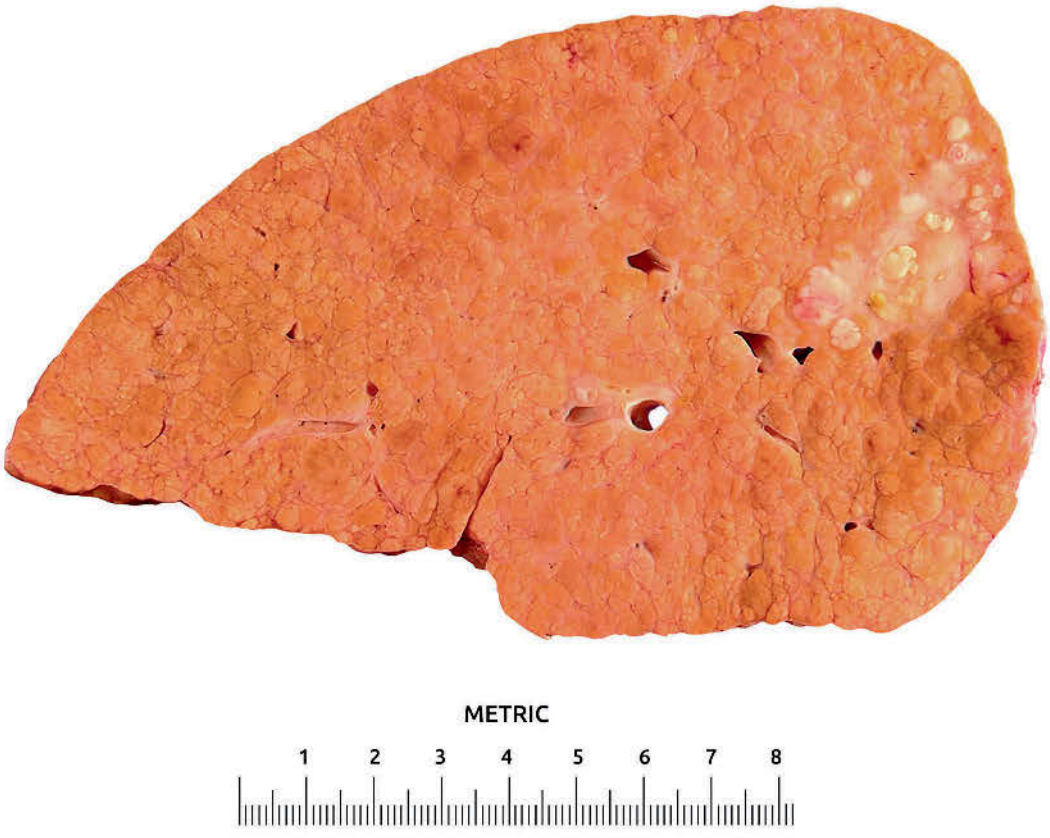
Dedication

The authors thank our teachers, students, and families who gave us guidance, inspiration, and love. We owe you everything. You know who you are!

We also thank the many investigators, pathologists, and clinicians who created the knowledge we have summarized, and the patients whose biopsies revealed so many of the insights.

Bob and Tony



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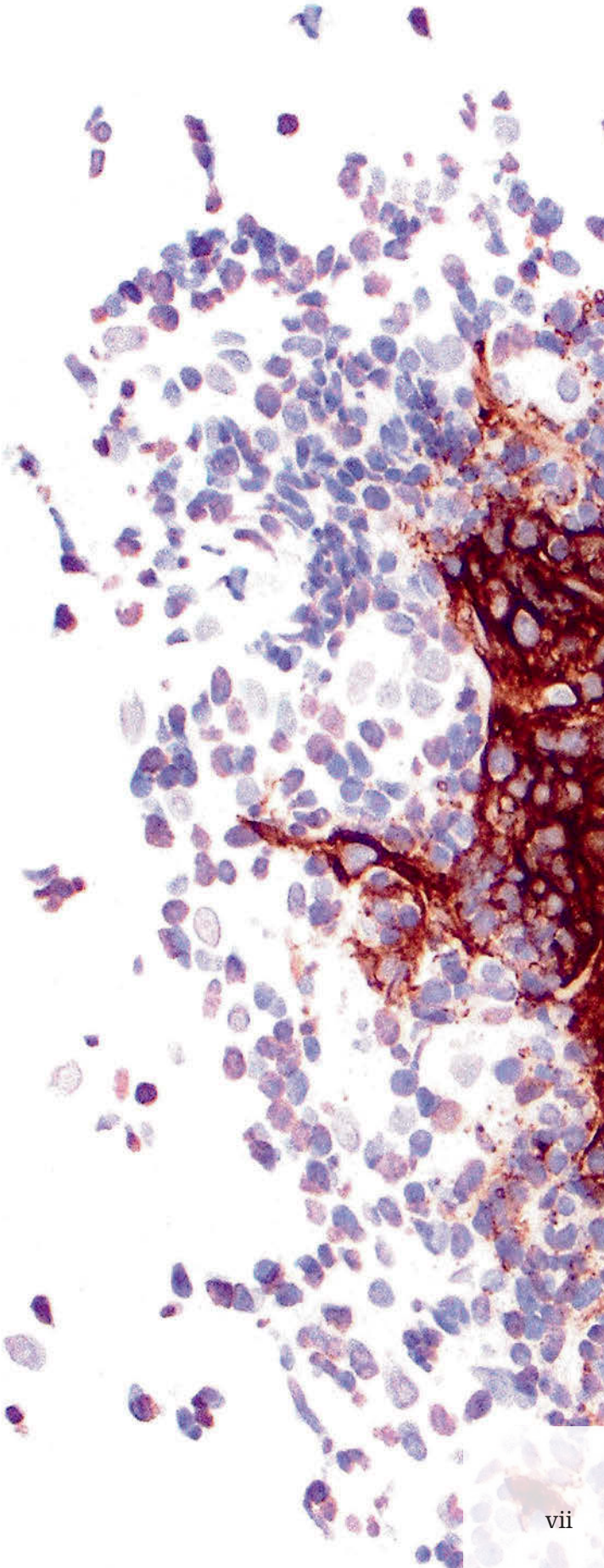

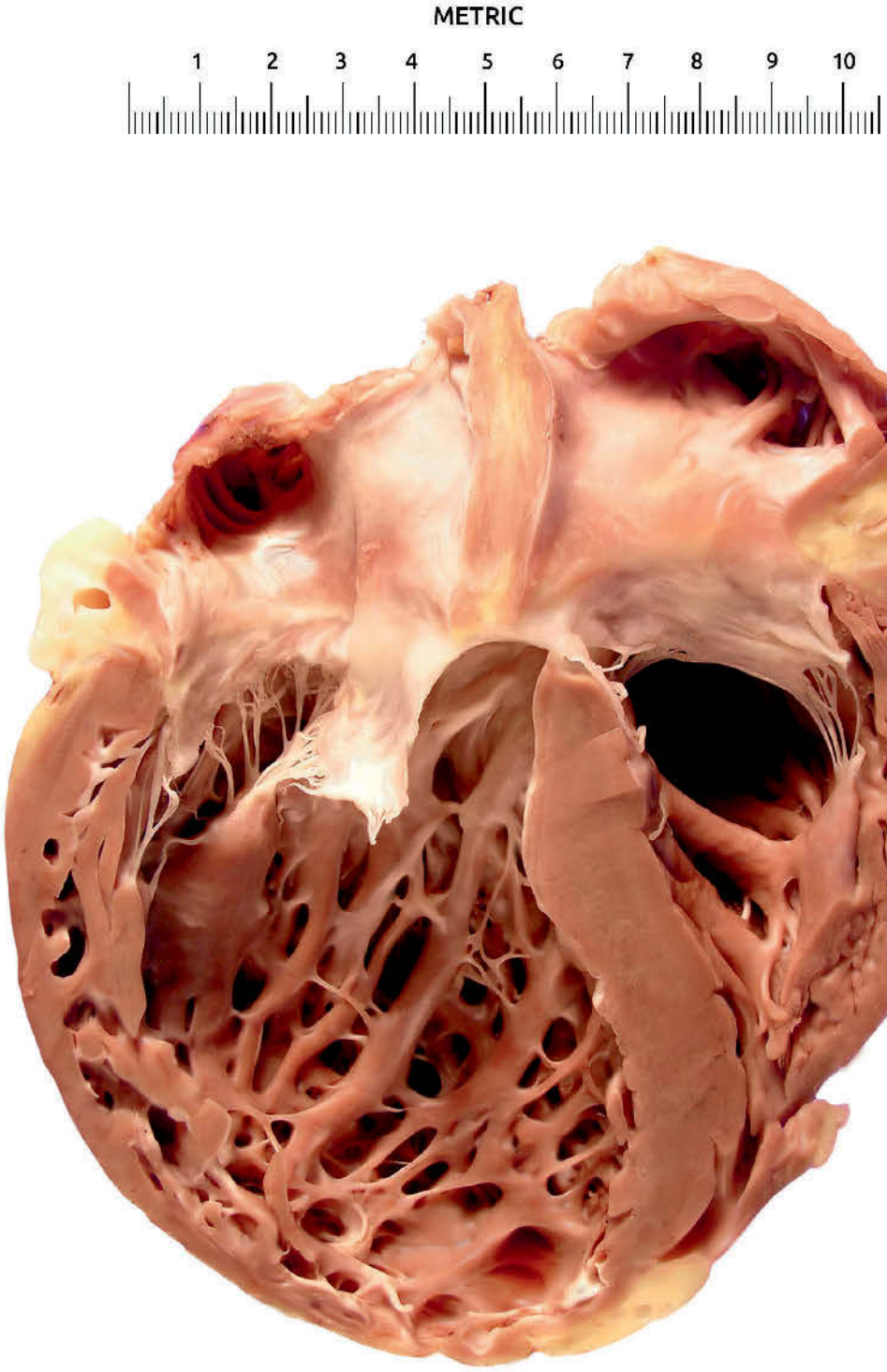
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Preface

Solid organ transplantation represents a monumental achievement of modern medicine and has extended the lives of countless patients. What was once a Herculean challenge is now fairly routine with excellent outcomes, but this could not be possible without major advances in surgical techniques and immunosuppressive agents, as well as improved understanding of transplant immunology and pathology.

Diagnostic Pathology: Transplant Pathology, second edition represents the collective knowledge of over 20 experts of the various transplant organs (kidney, liver, heart, lung, pancreas, intestine, and vascularized composite allografts). For the practicing pathologist, transplant pathology provides the ultimate diagnostic challenge, as numerous injuries, including donor disease, surgical complications, allograft rejection, drug toxicity, opportunistic infections, &/or recurrent or de novo diseases can occur simultaneously or at different times. The content within this textbook serves to guide you through this complex realm. The numerous images and bullet point format aim to aid with current and future dilemmas provided at the microscope by your daily practice. The fascinating world of transplant pathology awaits in the following pages.

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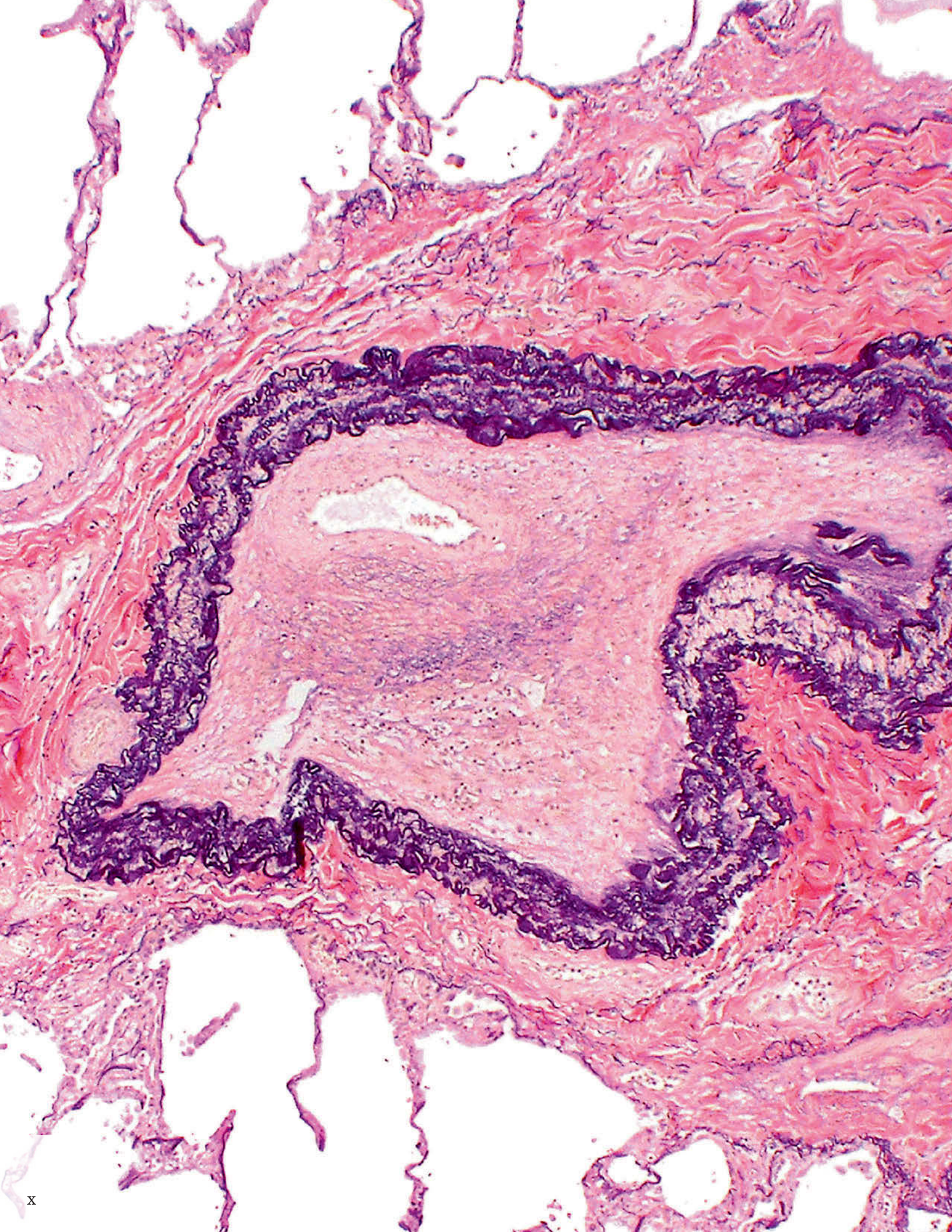

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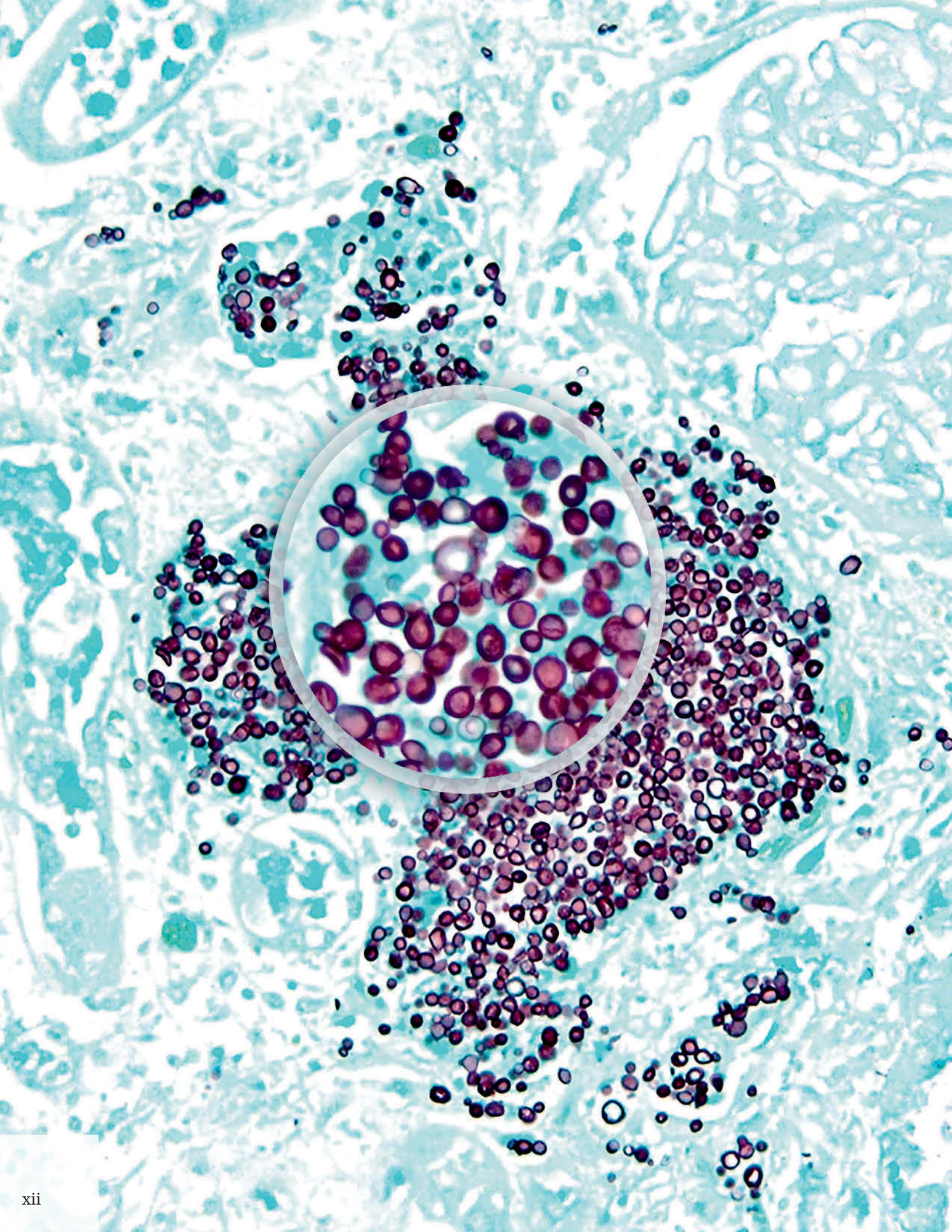

Sections

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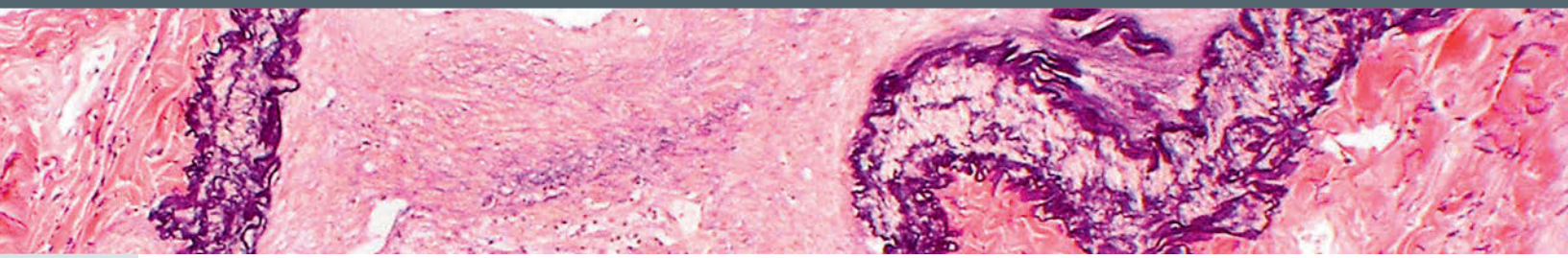

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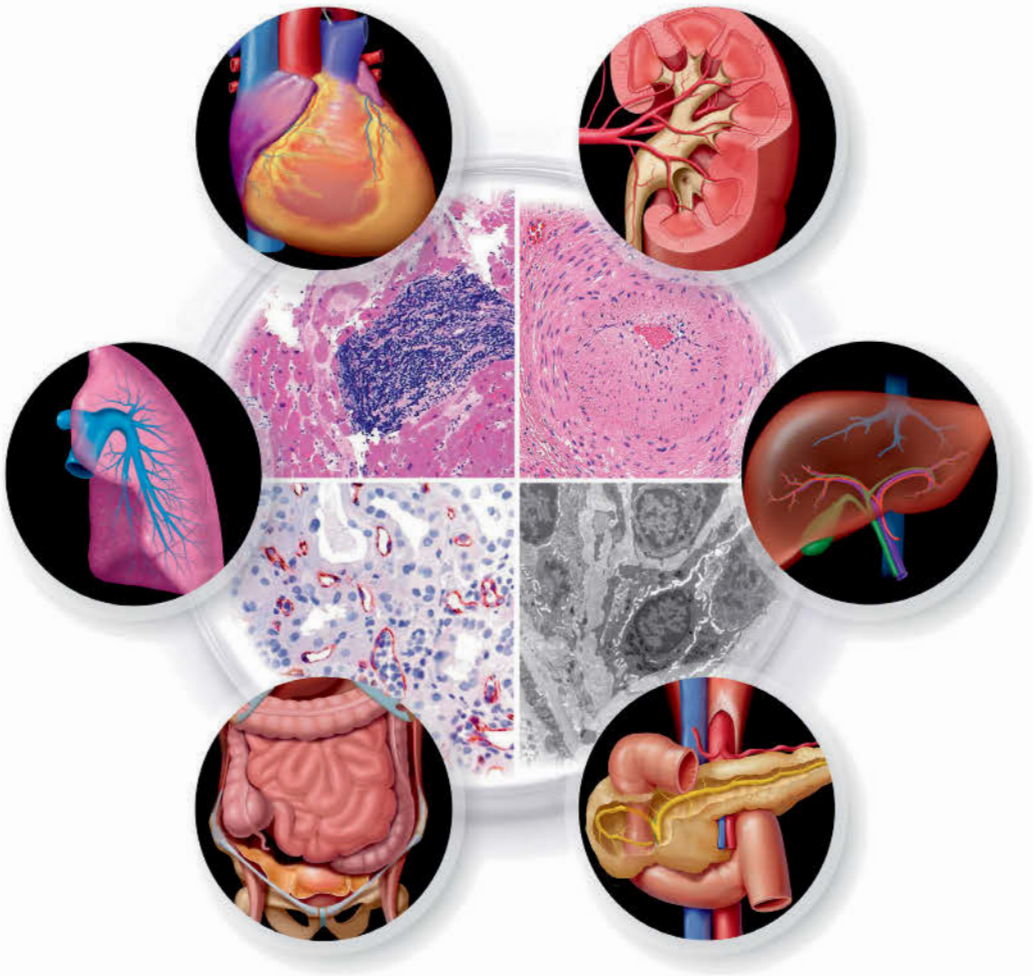

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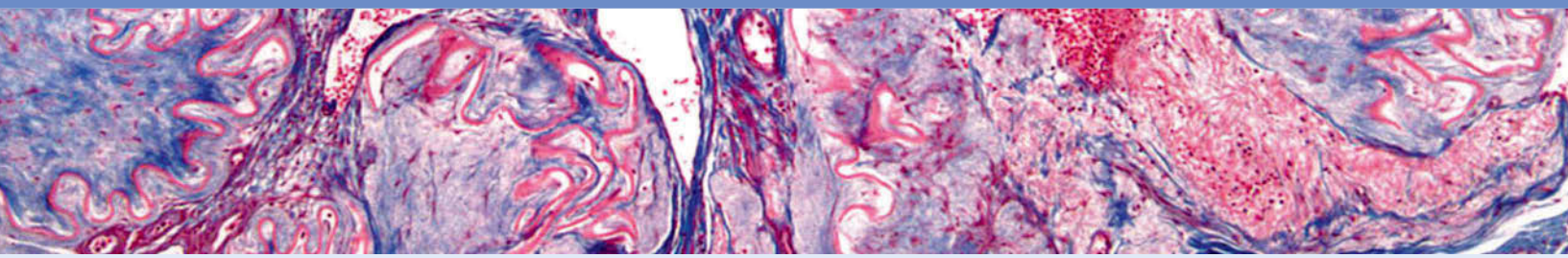
SECTION 1

Immunology



INTRODUCTION

Defining Immune Response in Solid Organ Transplantation

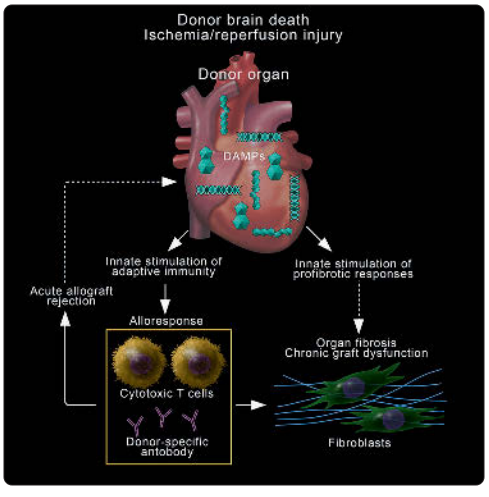
- Solid organ transplantation (SOT) involves graft-host interaction resulting in alloimmune response
- Interaction has 3 key phases
  - Induction: Antigen recognition
  - Effector: Direct allograft injury
  - Resolution: Decrease in immune response to allograft
- T cells defined as key players in SOT
  - Most immunosuppressive therapies target modulation of T-cell immune responses
- Advances in transplantation immunology reveal role for B cells, NK cells, and components of innate immune response in maintaining allograft rejection
  - Complement also plays role in allograft responses and priming alloreactive T cells
  - NK cells have dual roles in SOT
    - Produce inflammatory mediators
    - Regulate immune responses
  - B cells play role in both acute and chronic antibody-mediated rejection
- Nonimmunologic tissue damage (i.e., ischemia-reperfusion injury) and infections
  - Enhance alloreactivity and promote rejection episodes
  - Mediated by production of damage-associated molecular patterns (DAMPs) and pathogen associated molecular patterns (PAMPs)
  - Mediated by modifications of alloreactive T-cell repertoire
- Early inflammatory response to tissue injury depends upon adaptive immunity

INNATE IMMUNE RESPONSES IN SOT

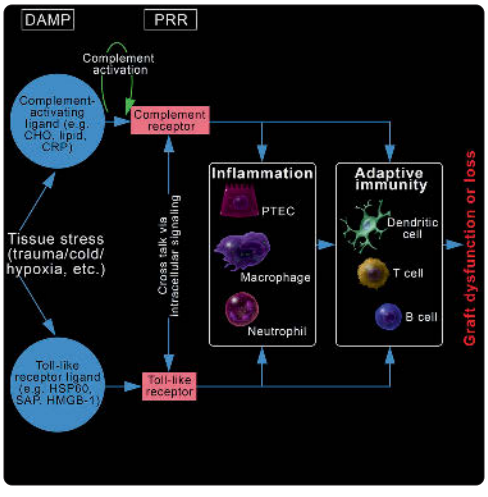
Innate Immunity and Complement in Allograft Rejection and Tolerance

- Innate, antigen-independent proinflammatory events occur soon after SOT
  - May be regulated and enhanced by graft-specific adaptive immune response
- Innate immune responses primarily mediated by PAMPs or pathogen-recognition receptors (PRRs)
  - PAMPs or PRRs recognize pathogen-derived molecules and host-derived molecules from damaged/stressed tissues
  - Ischemic and surgical trauma can trigger release of endogenous molecules capable of activating PRRs
  - Toll-like receptors (TLRs) are important PRRs that activate innate immunity and direct adaptive immune responses
    - TLRs are expressed on following cells
      - Dendritic cells (DCs)
      - B cells
      - Mast cells
      - T cells
      - Endothelial cells
      - Organ parenchymal cells
    - TLR expression modulated by inflammatory mediators and other localized or systemic activation signals
    - TLR stimulation results in activation of key transcription factors, such as NF-κB
    - Results in production of many mediators and augmented functions
      - Proinflammatory cytokines
      - Chemokines
      - Antimicrobial peptides
      - Adhesion molecules
      - Enhanced antigen presentation
      - Upregulation of costimulatory molecules on antigen-presenting cells (APCs)
  - Other PRRs include
    - Nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs)
      - Direct role as intracellular sensors of cellular stress
      - Components of inflammasome, which control activation of proinflammatory cytokines, IL-1β, and IL-18
    - RIG-like helicases (RLHs)

Danger-Associated Molecular Signals



Innate Immune Response and Mechanisms of Injury



(Left) *Damage-associated molecular patterns (DAMPs) can accumulate in a donor organ through ischemia-reperfusion injury or time from death. DAMPs act via toll-like receptors (TLRs) or specific receptors to activate innate immunity.* **(Right)** *TLRs recognize DAMPs, while complement receptors recognize complement effector molecules. Stress-induced signals through pattern-recognition receptors (PRR) mediate injury to tissue.*

  - Receptor for advanced glycation end products (RAGE)
  - Scavenger receptors
  - Complement receptors
  - Mannose-binding lectin
- Cells of innate immune compartment are critical in alloantigen presentation
  - Mature, activated DCs perform many functions
    - Secretion of proinflammatory cytokines
    - Upregulation of MHC class II on cells
    - Increased expression of T-cell costimulatory molecules
    - In absence of "danger" signals, DCs remain immature and mediate tolerance via induction of anergy or apoptosis on cognate interaction with antigen-specific T cells
  - Macrophages do not effectively prime naive T cells but play key role in immediate posttransplant period
    - Donor and recipient macrophages infiltrate allografts and proliferate
    - Absolute numbers of macrophages decrease in absence of rejection
  - In acute rejection, macrophage infiltration accounts for 40-60% of cellular infiltrate and performs following roles
    - Production of proinflammatory cytokines
    - Phagocytose necrotic cell debris
    - Production of reactive oxygen species (ROS)
    - Presents antigen to effector T cells
  - Neutrophils also mediate tissue injury via cytotoxic and proinflammatory mechanisms
  - NK cells are important innate lymphocytes, and while unlikely to solely mediate allograft rejection, they act as facilitators by amplifying early graft inflammation and supporting T-cell alloreactivity
- Complement activation, when unchecked, can result in tissue (allograft) injury
  - Plays key role in antibody-mediated rejection by promoting alloantigen-specific B-cell maturation and reducing threshold for B-cell stimulation by antigens
- Peripheral synthesis of complement characteristic of newly transplanted organs
  - Determines allograft response to surgical and other stressors
  - Contributes to T-cell priming and shaping of adaptive immune response related to transplant rejection
- Roles of complement
  - Complement triggered by binding of alloantibodies to donor organ endothelial cells
  - Significant variability in endothelial cell response to pathogenic antibody and complement
  - 3 possible outcomes
    - Immediate thrombosis and allograft infarct
    - Lesser injury with gradual decline of allograft function due to complement deposition
    - No injury
  - All these phenomena can contribute to allograft damage and rejection

INFECTION, TISSUE DAMAGE, AND IMMUNE RESPONSE IN SOT

Infections and Alloreactivity

- Infections (viral) in pretransplant period can induce memory T cells that cross react with allogeneic MHC through direct allorecognition (heterologous immunity)
  - Alloreactive memory T cells are more important in allograft rejection because of
    - Propensity for rapid expansion
    - Production of inflammatory and cytotoxic effector mediators
  - Pretransplant frequency of donor-specific memory T cells (producing IFN-γ) in renal transplant patients correlates with risk of posttransplant rejection episodes
- Posttransplant bacterial, fungal, and viral infections also associate with development of acute or chronic rejection, depending on type of SOT and infection
- Activation of PRRs by infection results in eventual T-cell activation and differentiation, with downstream activation of other hematopoietic cells that may participate in rejection
- Different pathogens elicit different classes of immune response
- Type I IFNs produced during viral and intracellular bacterial infections and stimulate immune responses
  - Treatment of recurrent hepatitis C viral infections with IFN-α in transplant patients facilitates viral clearance but increases risk of allograft rejection
- Besides bystander effects of infections (via cytokines) on T-cell activation, infections directly influence uptake and presentation of alloantigens
- Certain infections (e.g., CMV) may have immunosuppressive effect systemically, which predisposes to opportunistic superinfections
- New therapeutic approaches focus on blocking innate immune responses that stimulate alloreactivity but not protective immunity to infections
  - e.g., rapamycin (sirolimus) increases magnitude and quality of effector and memory CD8 T-cell responses to infection but inhibits alloreactive CD8 T-cell responses

Danger Signals and Role in SOT

- PAMPs allow innate recognition of invading pathogens
- DAMPs also activate innate immunity
  - Via recognition of endogenous cellular stress "danger" signals
- DAMPs can be subclassified based on physiological presence and properties
  - Intracellular molecules, including nucleic acids, and heat-shock proteins (HSPs)
    - Not accessible normally to immune system
    - Only released into extracellular environment or expressed on cell surface after cell damage
  - Extracellular molecules, including extracellular matrix components, altered by cellular stress or injury
- Process of organ harvesting and transplantation alone can generate DAMPs and activate innate immunity

- Most DAMPs signal through TLRs, resulting in NF-κB activation and activation of inflammatory response genes, production of inflammatory cytokines, neutrophil recruitment, preparation of APC, and upregulation of costimulatory molecules and MHC
  - Other than TLRs, DAMPs also signal through non-PRRs, e.g. ligation of RAGE, which can act in concert with TLR activation to modulate inflammatory response
- DAMPs can drive fibrosis-based tissue restructuring in allograft
  - Generate different downstream signals compared to PAMPs
- Effect of DAMPs on rates of rejection and graft dysfunction provide avenues for therapeutic intervention
  - Either via decreasing DAMP expression, enhancing clearance, or blocking signaling
- Important DAMPs in SOT, depending on transplant organ: HMGB1, ATP, HSPs, nucleic acids, Heparan sulfate, hyaluronan, fibronectin, haptoglobin

NK CELLS AND IMMUNE RESPONSE IN SOT

NK-Cell-Mediated Responses in Rejection and Tolerance

- Activated NK-cell production of IFN-γ augments early adaptive immune responses
  - NK-produced IFN-γ postulated to provide costimulation to antigen-experienced T cells
    - NK cells serve as bridge between innate and adaptive immunity in rejection
- NK activating receptors, such as NKG2D, promote rejection by recognition of activating ligands on allografts
- Mature DCs resist NK-mediated cytotoxicity through upregulation of MHC class I
  - Result in enhanced Th1-specific allogeneic responses by selecting mature DCs
- Immature DCs eliminated by NK cell killing
- Counterpoint to NK cell function in rejection is their role in tolerance induction
  - Both activating and inhibitory NK cell receptors required for mediating tolerance
  - Secretion of IL-10 in response to infection is example of NK cell regulation in systemic inflammation
- NK cell regulation of immune response requires both cytotoxicity and cytokine production
- NK cell immune responses regulated in turn by Tregs
  - TGF-β produced by Tregs suppresses cytotoxic profile of NK cells, inhibits granzyme A and B and CD16 expression, and downregulates activating receptor, NKG2D
    - Depletion of Tregs enhances NK-cell proliferation and cytotoxicity
- Unique role of NK cells determine if downstream T-cell response skews toward tolerance or rejection, based on their effector function

B-CELL IMMUNE RESPONSES IN SOT

Acute and Chronic Antibody-Mediated Rejection and Immunosuppression

- Role of donor-specific alloantibodies (DSA) well established in allograft rejection
  - Non-donor-specific HLA antibodies reported and appear earlier compared to DSA
- Weaning IS or homeostatic repopulation after immune cell depletion can lower threshold for B-cell activation
  - May facilitate DSA production, C4d(+) injury, and chronic rejection
- Several commonly used transplant IS agents influence B-cell activation and DSA production to varying degrees
  - Alemtuzumab, monoclonal anti-CD52 antibody when used as induction agent, especially in absence of CNI immunosuppression
    - Causes B-cell suppression for 3-12 months
    - But associates with increased incidence of antibody-mediated rejection in patients with preformed DSA
  - Belatacept, CTLA4 fusion protein
    - Binds CD80/CD86
    - Blocks interaction with CD28 (inhibiting T-cell costimulation)
    - Decreases incidence of de novo alloantibody production
  - Bortezomib, proteasome inhibitor
    - Shown in early studies to reverse antibody-mediated rejection and decrease DSA after plasmapheresis
- Additional studies needed to achieve robust elimination of DSA and durable allograft maintenance
  - Especially in subset of patients who have high levels of DSA pretransplant or either unresponsive or transiently responsive to treatment

NF-KB AND T CELLS IN SOT

Role of NF-κB and T Cells in Transplant Immune Response

- NF-κB, pleiotropic transcription factor, ubiquitously expressed
  - Post SOT, NF-κB in allograft parenchymal cells activated due to ischemic reperfusion injury (IRI)
    - Also expressed in intragraft-infiltrating cells (activated allogeneic T cells) during acute allograft rejection
    - Produces proinflammatory cytokines
  - NF-κB activation is not single event but happens repeatedly in cyclical manner
    - Endogenous DAMPs (intracellular proteins, DNA, RNA and nucleotides that perpetuate noninfectious inflammatory response) produced during IRI
      - Result in TLR-2/TLR-4-dependent activation of NF-κB
      - Induces expression of proinflammatory cytokines such as IL-1 and TNF in myeloid cells and other cells, depending on nature of immune response
      - Downstream signaling of these cytokines
      - Activation of NF-κB (2nd wave)
    - This round of NF-κB upregulates effector molecules (IL-8, MCP-1)
      - Attracts leukocytes to site of inflammation
      - Promotes tissue injury (release of ROS)
- T-cell activation through T-cell receptor signals NF-κB activation and eventually *IL2* gene transcription and T-cell proliferation
- Alloantigen recognition and T-cell activation in allograft rejection includes