Immune Checkpoint Inhibitor Associated Myocarditis: Pathophysiology

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World of Cardio-Oncology

Cardio-Oncology: Novel Platform for Investigation

- BASIC and TRANSLATIONAL SCIENCE
- Insights in Human Cardiovascular Biology
- New Clinical Entities
- Cardiovascular and Cardio-metabolic Sequelae of Novel Targeted Cancer Therapies

Cardio-Oncology
Immune-Checkpoint Inhibitor Myocarditis: Defining a New Syndrome

Clinical Questions
Incidence?
Clinical presentation?
Treatment?

Who is at risk?
Precision or Personalized Medicine
- CV risk factors
- Autoimmune risk factors
- Tumor risk factors
- ?Genetic risk factors

Immune Checkpoint Inhibitor-Associated Myocarditis
Can better understanding of the molecular pathophysiology help us identify patients at risk?

• What caused T cell infiltration into heart and muscle?
  – Why these organs only?

• Other triggers of myocarditis–
  – Viral?
  – Other insult?

• Genetic Differences?
  – MHC Haplotype?
  – Tumor genetics (whole exome sequencing)?
  – Germline?
Insights into Mechanisms of Toxicity
Insights into Mechanisms of Toxicity

A. Inflammatory gene transcripts

B. Muscle-specific gene transcripts

Graphs showing the distribution of T-cell clones in different tissues before and after treatment.
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Basic biology of PD-1/PD-L1 in the heart
How does the heart interact with the immune system??
Induced Pluripotent Stem Cells (iPSC), Rodent Models
Cardiomyopathy in PD-1 KO Mice

Autoimmune Dilated Cardiomyopathy in PD-1 Receptor–Deficient Mice

Hiroyuki Nishimura, Taku Okazaki, Yoshimasa Tanaka

Dilated cardiac etiology receptor PD-1 cardiomyopathy gestive heart globulin G (IgG) mice exhibit dalyton proteins results indicat prevention of

PD-1 deficiency results in the development of fatal myocarditis in MRL mice

Jian Wang¹, Il-mi Okazaki¹,², Taku Yoshida¹,⁴, Shunsuke Chikuma¹, Yu Kato¹,⁴, Fumio Nakaki¹, Hiroshi Hiai³, Tasuku Honjo¹ and Taku Okazaki¹,²

Programmed Death Ligand 1 Regulates a Critical Checkpoint for Autoimmune Myocarditis and Pneumonitis in MRL Mice¹

Julie A. Lucas,* Julia Menke,* Whitney A. Rabacal,* Frederick J. Schoen,† Arlene H. Sharpe,† and Vicki R. Kelley²*

MRL/MpJ-Fas⁻⁻ (MRL-Fas⁻⁻) mice develop a spontaneous T cell and macrophage-dependent autoimmune disease that shares features with human lupus. Interactions via the programmed death 1/programmed death ligand 1 (PD-1/PD-L1) pathway downregulate immune responses and provide a negative regulatory checkpoint in mediating tolerance and autoimmune disease. Therefore, we tested the hypothesis that the PD-1/PD-L1 pathway suppresses lupus nephritis and the systemic illness in MRL-Fas⁻⁻ mice. For this purpose, we compared kidney and systemic illness (lymph nodes, spleen, skin, lung, glands) in PD-L1 null (⁻⁻⁻⁻) and PD-L1 intact (wild type, WT) MRL-Fas⁻⁻ mice. Unexpectedly, PD-L1⁻⁻⁻⁻;MRL-Fas⁻⁻ mice died as a result of autoimmune myocarditis and pneumonitis before developing renal disease or the systemic illness. Dense infiltrates, consisting of macrophage and T cells (CD8⁺ > CD4⁺), were prominent throughout the heart (atria and ventricles) and localized specifically around vessels in the lung. In addition, once disease was evident, we detected heart specific autoantibodies in PD-L1⁻⁻⁻⁻;MRL-Fas⁻⁻ mice. This
PD-L1 Expression in the Injured Myocardium

A. PD-L1 expression, myocardium (200x)
B. PD-L1 expression, myocardium (400x)

In collaboration with Janis Taube, Bob Anders, Luis Diaz, Johns Hopkins
PD-L1 Upregulation in Myocarditis as a Complication of Anti-PD-1/Anti-CTLA-4 Therapy for Melanoma

Andy Lichtman, Brigham and Women’s Hospital
Myocarditis as a complication of anti-PD1/anti LAG3 Rx of Carcinoma

- Lymphocytic myocarditis
- CD3
- PD-L1
- HL-DR (marker of IFN)
Expression of PD-L1 in mouse heart and mouse heart endothelial cells

**PD-L1 mRNA in heart**


**IFNγ induction of PD-L1**

Mouse Heart EC

Pre-Clinical Platform for Assessing and Understanding Cardiotoxicity of Novel Compounds

• Cell based models –
  – Isolated mouse or rat myocytes or endothelial cells/smooth muscles cells
  – Induced pluripotent stem cells (iPS)
• Genetic manipulation – CRISPR/Cas9
• “Personalized” medicine

• Zebrafish
• Rodent models –
  – Mechanistic understanding of cardiotoxicities
    • Sunitinib, Sorafenib
  – Transgenic mice can allow for defining “on-target” vs. “off-target” effects

Vanderbilt Cardio-Oncology Program
Conclusions

• Myocarditis is a new clinical phenomenon that is a rare (but clinically significant) complication of cancer immunotherapy
  – Initial mechanistic studies show that robust T cell and macrophage infiltrates

• Biological plausibility for this new clinical phenomenon
  – Central role for PD-1/PD-L1 in the heart

• Need for multi-institutional to understand the pathophysiology of myocarditis and multi-pronged approach to understand who is at risk of developing myocarditis
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