Basic Mechanisms of Myocarditis

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Major mechanisms that contribute to myocarditis

- Infection
  - Virus
  - Bacteria
  - Parasites
- Immune activation against infectious pathogens
  - Innate immunity
  - Adaptive immunity
- Primary immune mechanisms
  - Myocyte injury
  - Antigen mimicry
  - Hypersensitivity reactions
# Causes of Myocarditis

<table>
<thead>
<tr>
<th>VIRUSES/VIRAL DISORDERS</th>
<th>BACTERIA/BACTERIAL DISORDERS</th>
<th>CARDIOTOXINS</th>
<th>HYPERSENSITIVITY MEDIATORS/FACTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenovirus</td>
<td>Chlamydia</td>
<td>Ethanol*</td>
<td>Cephalosporins</td>
</tr>
<tr>
<td>CVB*</td>
<td>Cholera</td>
<td>Anthracycline drugs*</td>
<td>Clozapine</td>
</tr>
<tr>
<td>Cytomegalovirus*</td>
<td>Mycoplasma</td>
<td>Arsenic</td>
<td>Diuretics</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>Neisseria</td>
<td>Carbon</td>
<td>Insect bites</td>
</tr>
<tr>
<td>Hepatitis C virus</td>
<td>Salmonella</td>
<td>monoxide</td>
<td>Lithium</td>
</tr>
<tr>
<td>Herpes simplex virus</td>
<td>Staphylococcus</td>
<td>Catecholamines</td>
<td>Snake bites</td>
</tr>
<tr>
<td>HIV*</td>
<td>Streptococcus</td>
<td>Cocaine*</td>
<td>Sulfonamides</td>
</tr>
<tr>
<td>Influenza virus</td>
<td>Tetanus</td>
<td>Heavy metals</td>
<td>Tetanus toxoid</td>
</tr>
<tr>
<td>Mumps</td>
<td>Tuberculosis</td>
<td>Copper</td>
<td>Tetracycline</td>
</tr>
<tr>
<td>PVB19</td>
<td>Spirochetal</td>
<td>Mercury</td>
<td>Systemic disorders</td>
</tr>
<tr>
<td>Poliovirus</td>
<td>Leptospirosis</td>
<td>Lead</td>
<td>Hypereosinophilia</td>
</tr>
<tr>
<td>Rabies</td>
<td>Lyme disease</td>
<td>Protozoa</td>
<td>Kawasaki disease</td>
</tr>
<tr>
<td>Rubella</td>
<td>Relapsing fever</td>
<td>Chagas disease</td>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>Varicella-zoster virus</td>
<td>Syphilis</td>
<td>Leishmaniasis</td>
<td>Wegener</td>
</tr>
<tr>
<td>Yellow fever</td>
<td></td>
<td>Malaria</td>
<td>granulomatosis</td>
</tr>
</tbody>
</table>

*Checkpoint inhibitors
Are there common questions between viral myocarditis and checkpoint-inhibitor mediated myocarditis?
Low incidence of myocarditis in patients treated with checkpoint inhibitors

- A very small percentage of patients that receive checkpoint inhibitors develop myocarditis- 0.09% or 0.27% of patients treated single checkpoint inhibitors or combination checkpoint inhibitors, respectively.
Low incidence of myocarditis in patients infected with viruses that are known to cause myocarditis

- While many patients are infected with common viruses such as Coxsackievirus, adenovirus, parvovirus, herpes virus, Epstein-Barr virus, only a very small percentage actually develop myocarditis.
Why?

- Potential genetic variants/mutations
  - Innate immunity
  - Adaptive immunity
  - Sarcolemmal membrane integrity

- Other factors
  - Underlying infection
  - Nutrition
  - Age
  - Pregnancy
  - Hormones

- The incidence of disease is likely affected by a combination of multiple influences
Therefore,

- Review mechanisms that have been shown to cause myocarditis
- And, those that increase susceptibility to myocarditis
Autoimmune Dilated Cardiomyopathy in PD-1 Receptor–Deficient Mice

Hiroyuki Nishimura,¹ Taku Okazaki,¹ Yoshimasu Tanaka,² Kazuki Nakatani,¹ Masatake Hara,³ Akira Matsumori,³ Shigetake Sasaayama,³ Akira Mizoguchi,⁴ Hiroshi Hiai,⁵ Nagahiro Minato,⁶ Tasuku Honjo¹

Autoantibodies against cardiac troponin I are responsible for dilated cardiomyopathy in PD-1-deficient mice

Taku Okazaki¹, Yoshimasu Tanaka¹²³, Ryosuke Nishino⁴³, Tamotsu Mitsuura⁴, Akira Mizoguchi⁵, Jian Weng¹, Masayoshi Ishida², Hiroshi Hiai⁴, Akira Matsumori³, Nagahiro Minato⁶ & Tasuku Honjo¹

We recently reported that mice deficient in the programmed cell death-1 (PD-1) immunoinhibitory coreceptor develop autoimmune dilated cardiomyopathy (DCM), with production of high-titer autoantibodies against a heart-specific, 30-kDa protein. In this study, we purified the 30-kDa protein from heart extract and identified it as cardiac troponin I (cTnI), encoded by a gene in which mutations can cause familial hypertrophic cardiomyopathy (FHC). Administration of monoclonal antibodies to cTnI induced dilatation and dysfunction of hearts in wild-type mice. Monoclonal antibodies to cTnI stained the surface of cardiomyocytes and augmented the voltage-dependent L-type Ca²⁺ current of normal cardiomyocytes. These findings suggest that antibodies to cTnI induce heart dysfunction and dilatation by chronic stimulation of Ca²⁺ influx in cardiomyocytes.

PD-1 Protects against Inflammation and Myocyte Damage in T Cell–Mediated Myocarditis

Margarite L. Tarrio,⁸ Nir Grabie,⁸ De-xiu Bu,⁹ Arlene H. Sharpe,⁶ and Andrew H. Lichtman⁸

Nature Medicine December 2003

Journal of Immunology 2012
Die within 3-4 weeks of age
Examples of factors that affect susceptibility to myocarditis

From Epelman, Liu and Mann
Nat Rev Immunol. 2015 Feb
Innate immunity

- Interferons
- NFκB
- Toll-like receptors
- JAK-STAT signaling
  - IL-6/gp130/Suppressors of cytokine signaling (SOCS)
- Inflammasomes – IL-1β
## Toll-like receptors (TLRs)

<table>
<thead>
<tr>
<th>TLR</th>
<th>Localization</th>
<th>Viral Ligands</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Cell surface</td>
<td>Envelope proteins of measles virus, human cytomegalovirus, and herpes simplex virus type 1</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>F protein of respiratory syncytial virus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Envelope protein of mouse mammary tumor virus</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>Viral dsRNA, synthetic dsRNA (Poly I:C)</td>
</tr>
<tr>
<td>7/8</td>
<td>Endosome</td>
<td>ssRNA, Synthetic imidazoquinoline derivatives (antiviral drugs)</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>CpG DNA</td>
</tr>
</tbody>
</table>

Poly I:C indicates polynucleoside-polyriboinosinic acid-polyribocytidylic acid; ssRNA, single-strand RNA. Adapted from Uematsu and Akira, copyright © 2008, with permission of Springer Science+Business Media.
SOCS3 tightly regulates gp130 signaling

Adapted from Toshitaka Yajima
SOCS-3 Tg markedly increased the susceptibility to CVB3 infection

Yajima and Yasukawa et al., Circulation Dec 2006
What would happen with infection in the setting of dystrophin deficiency (mdx mice)
Increased cardiomyopathy as evidenced by Evans blue dye in infected mdx mice

Xiong, Lee et al. Nature Medicine
Autosomal Recessive Cardiomyopathy Presenting as Acute Myocarditis

- Homozygous but not heterozygous rare variants in genes associated with inherited cardiomyopathies were significantly enriched in acute myocarditis patients compared with healthy individuals \( (p = 2.22 \times 10^{-03}) \) or patients with other diseases \( (p = 1.08 \times 10^{-04}) \).

- Seven of 42 patients with acute myocarditis or acute viral myocarditis (16.7%) carried rare biallelic (homozygous or compound heterozygous) nonsynonymous or splice-site variations in 6 cardiomyopathy-associated genes (BAG3, DSP, PKP2, RYR2, SCN5A, or TNNI3).

Serkan Belkaya et al. Journal of the American College of Cardiology, April 2017
Acquired immune response

There are a multitude of basic studies in mice that demonstrate the importance of the adaptive immune response in myocarditis.
