Basic Mechanisms of Myocarditis

KIRK U. KNOWLTON, M.D.

INTERMOUNTAIN MEDICAL CENTER, SALT LAKE CITY, UTAH

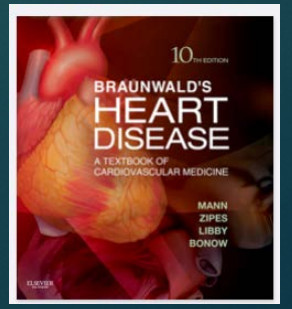
UNIVERSITY OF CALIFORNIA, SAN DIEGO

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

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



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] Yoshimasa Tanaka,[2] Kazuki Nakatani,[6] Masatake Hara,[3] Akira Matsumori,[3] Shigetake Sasayama,[3] Akira Mizoguchi,[4] Hiroshi Hiai,[5] Nagahiro Minato,[2] Tasuku Honjo[1]*

SCIENCE VOL 291 12 JANUARY 2001

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

Taku Okazaki[1], Yoshimasa Tanaka[2,3], Ryosuke Nishio[4,5], Tamotsu Mitsuiye[6], Akira Mizoguchi[7], Jian Wang[1], Masayoshi Ishida[2], Hiroshi Hiai[8], Akira Matsumori[4], Nagahiro Minato[2] & Tasuku Honjo[1]

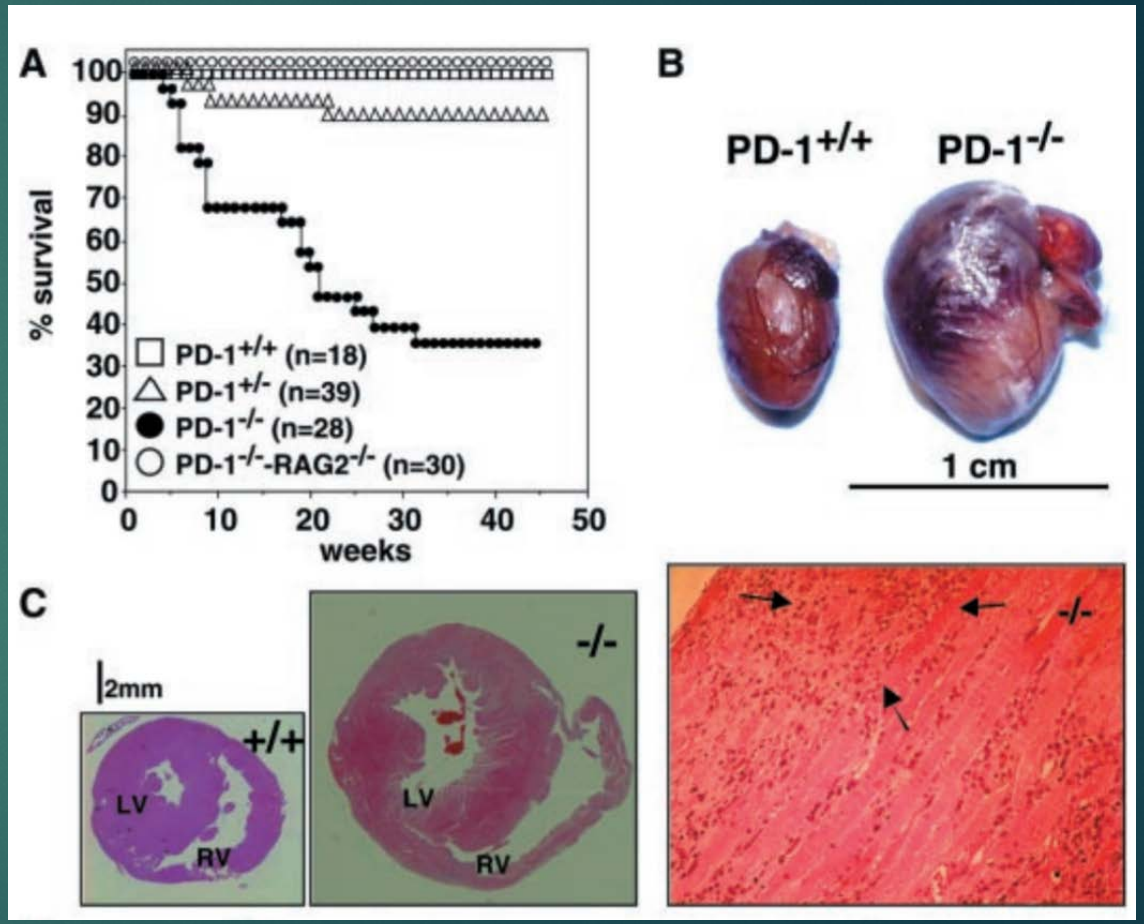
We recently reported that mice deficient in the programmed cell death-1 (PD-1) immunoinhibitory coreceptor develop autoimmune dilated cardiomyopathy (DCM), with production of high-titer autoantibodies against a heart-specific, 30-kDa protein. In this study, we purified the 30-kDa protein from heart extract and identified it as cardiac troponin I (cTnI), encoded by a gene in which mutations can cause familial hypertrophic cardiomyopathy (HCM). 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 Ca^{2+} current of normal cardiomyocytes. These findings suggest that antibodies to cTnI induce heart dysfunction and dilatation by chronic stimulation of Ca^{2+} influx in cardiomyocytes.

Nature Medicine December 2003

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

Margarite L. Tarrio,* Nir Grabie,* De-xiu Bu,* Arlene H. Sharpe,*,† and Andrew H. Lichtman*

Journal of Immunology 2012



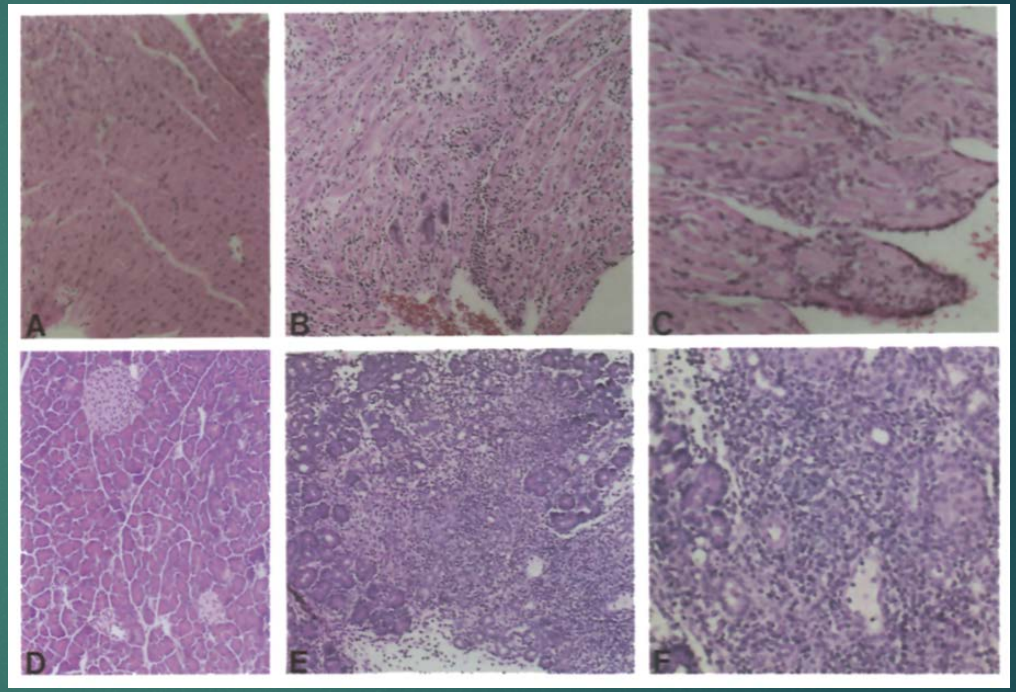
Immunity

Volume 3, Issue 5, November 1995, Pages 541-547

Article

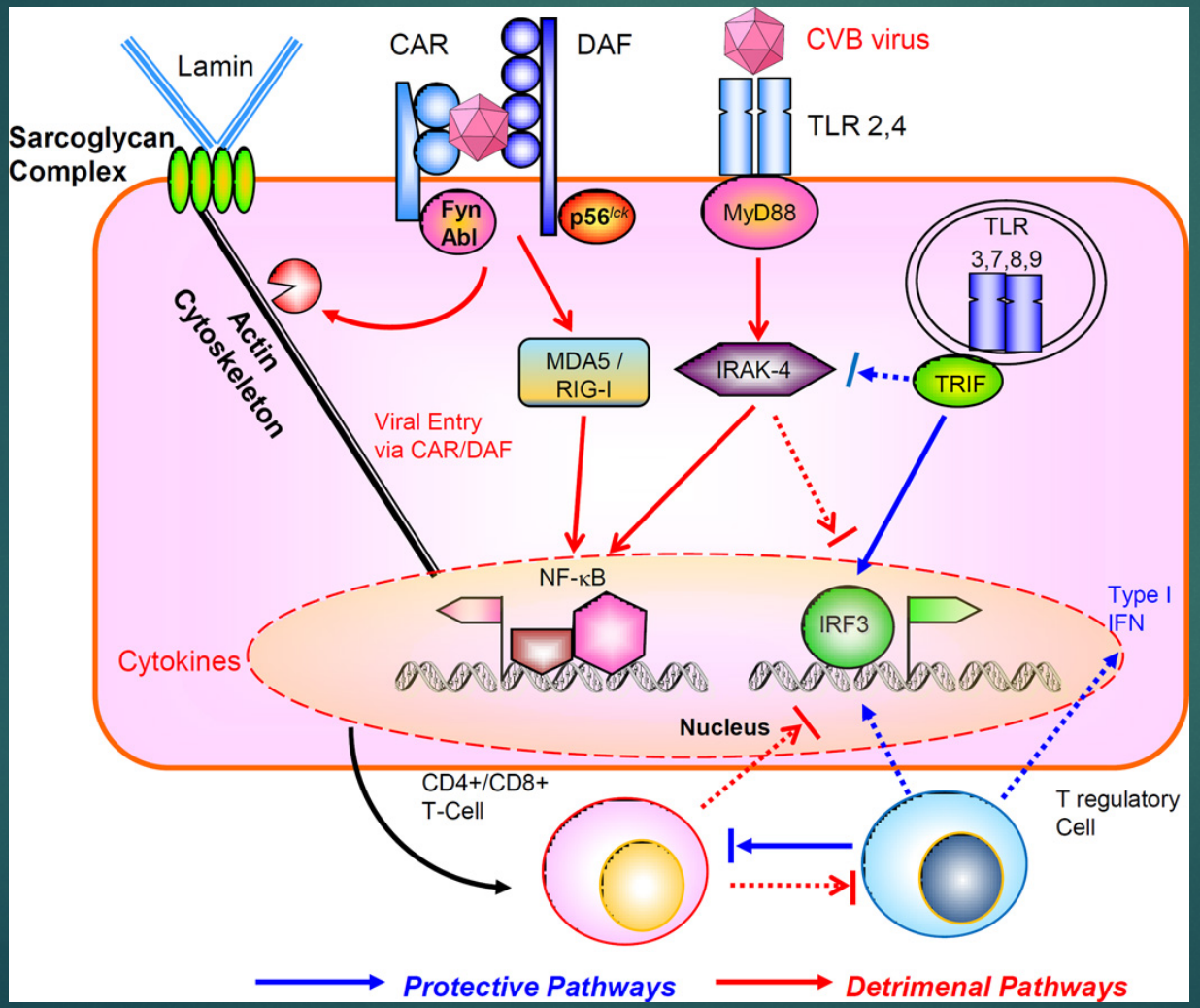
Loss of CTLA-4 leads to massive lymphoproliferation and fatal multiorgan tissue destruction, revealing a critical negative regulatory role of CTLA-4

Elizabeth A. Tivol *, Frank Borriello *, A.Nicola Schweitzer *, William P. Lynch *, Jeffrey A. Bluestone †, Arlene H. Sharpe *



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

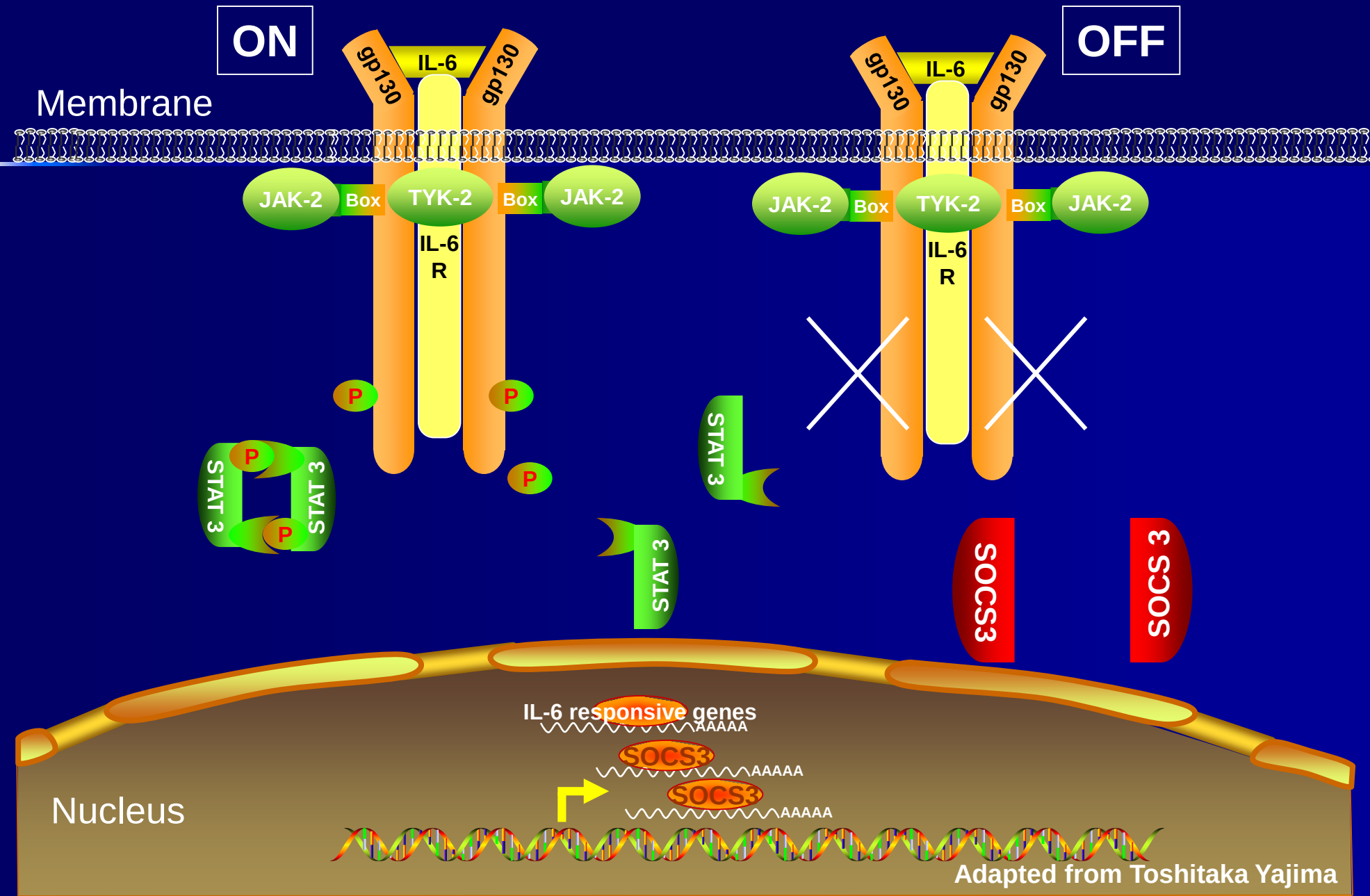
Toll-like receptors (TLRs)

Table 2. TLRs and Viral Ligands

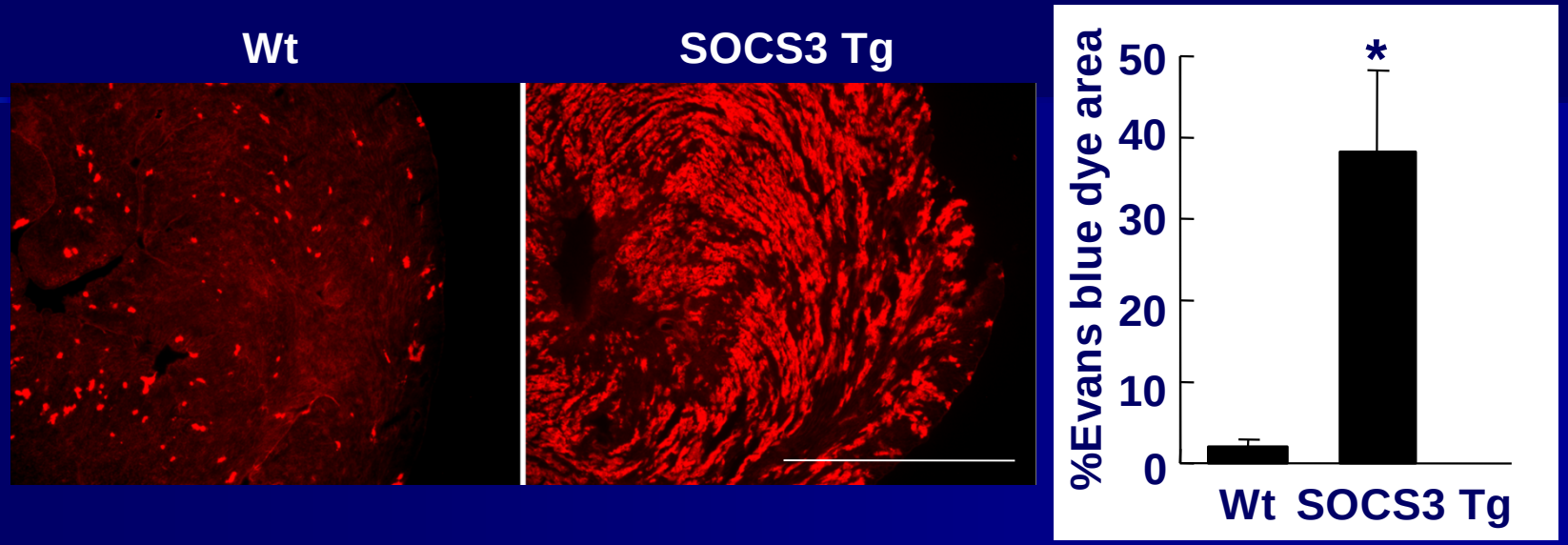
TLR	Localization	Viral Ligands
2	Cell surface	Envelope proteins of measles virus, human cyto megalovirus, and herpes simplex virus type 1
4		F protein of respiratory syncytial virus
		Envelope protein of mouse mammary tumor virus
3		Viral dsRNA, synthetic dsRNA (Poly I:C)
7/8	Endosome	ssRNA, Synthetic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

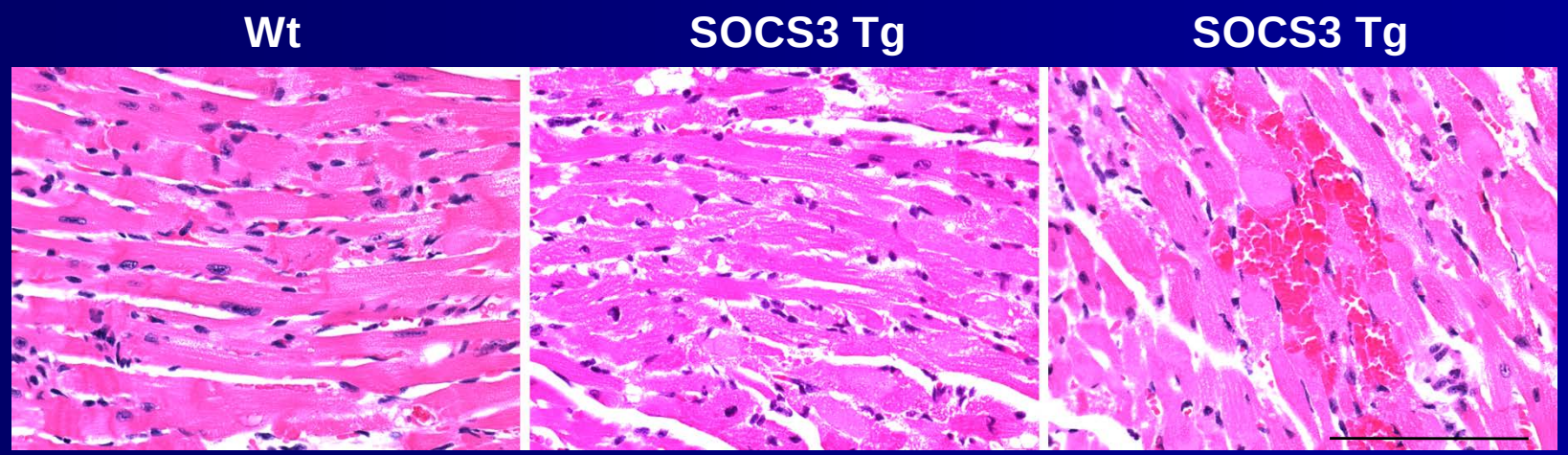
Poly I:C indicates polyriboinosinic:polyribocytidylic acid; ssRNA, single-strand RNA. Adapted from Uematsu and Akira,[62] copyright © 2008, with permission of Springer Science+Business Media.

SOCS3 tightly regulates gp130 signaling



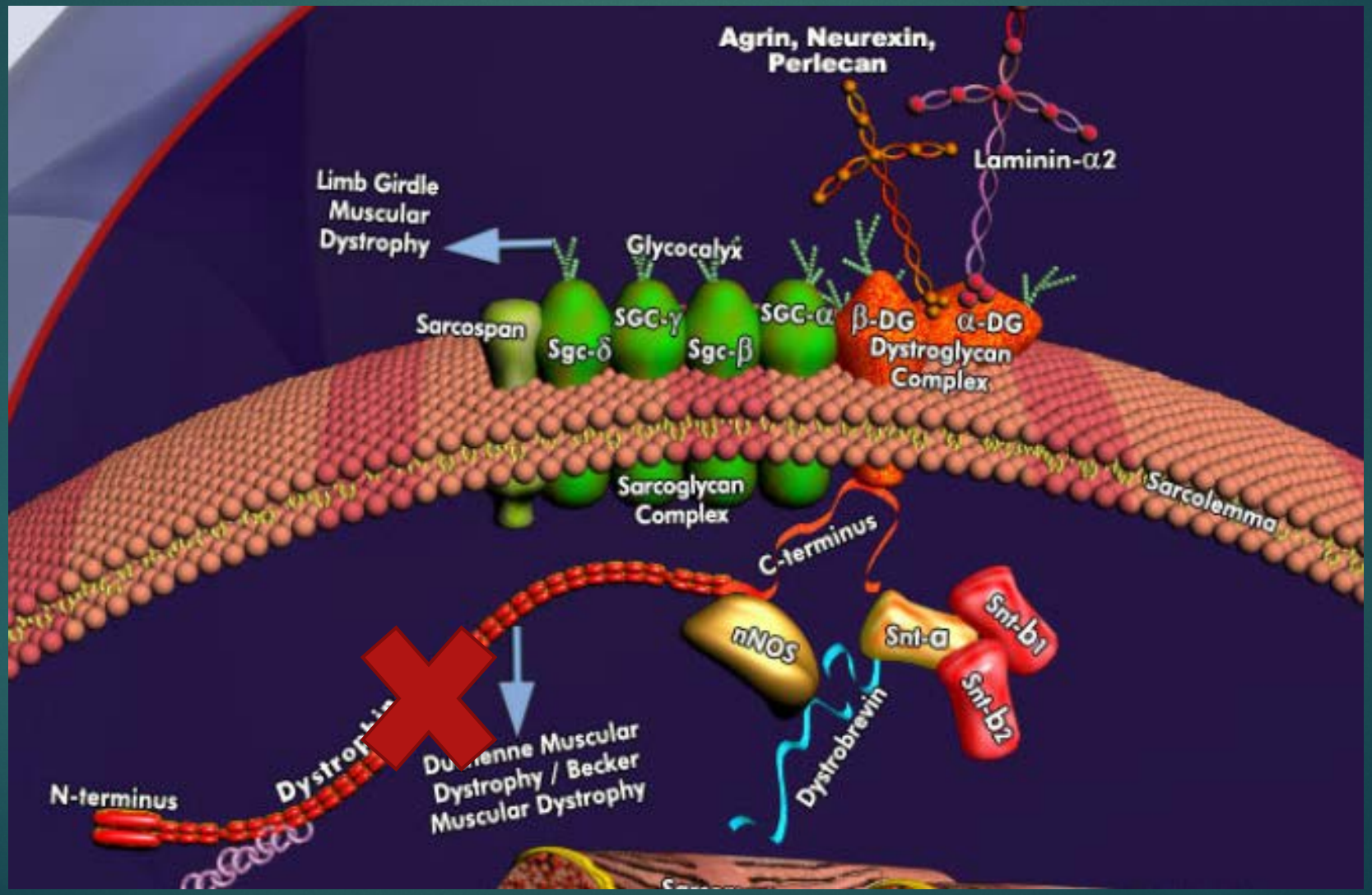
SOCS-3 Tg markedly increased the susceptiblity to CVB3 infection



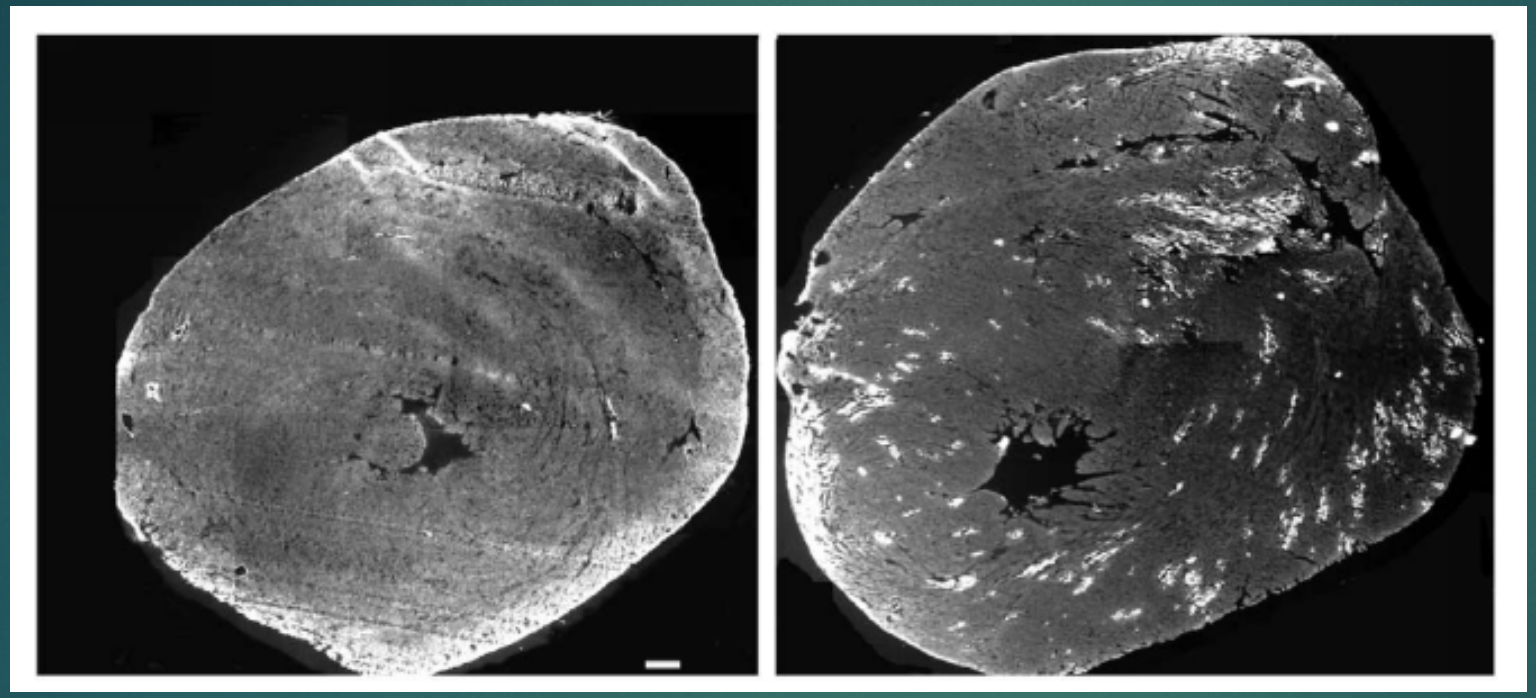


Yajima and Yasukawa et al., Circulation Dec 2006

What would happen with infection in the setting of dystrophin deficiency (mdx mice)



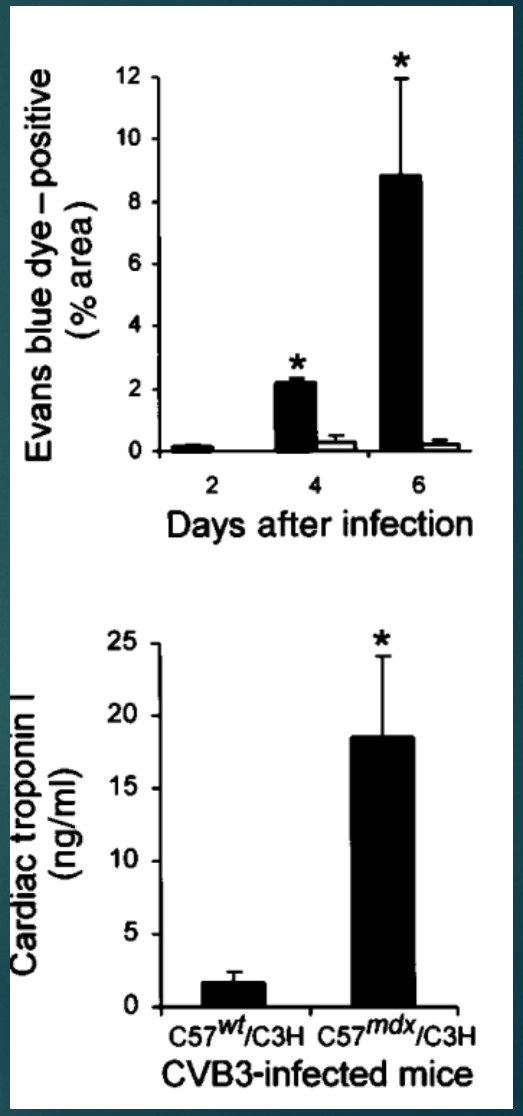
Increased cardiomyopathy as evidenced by Evans blue dye in infected mdx mice



WT + CVB3

mdx + CVB3

Evans blue dye = white above



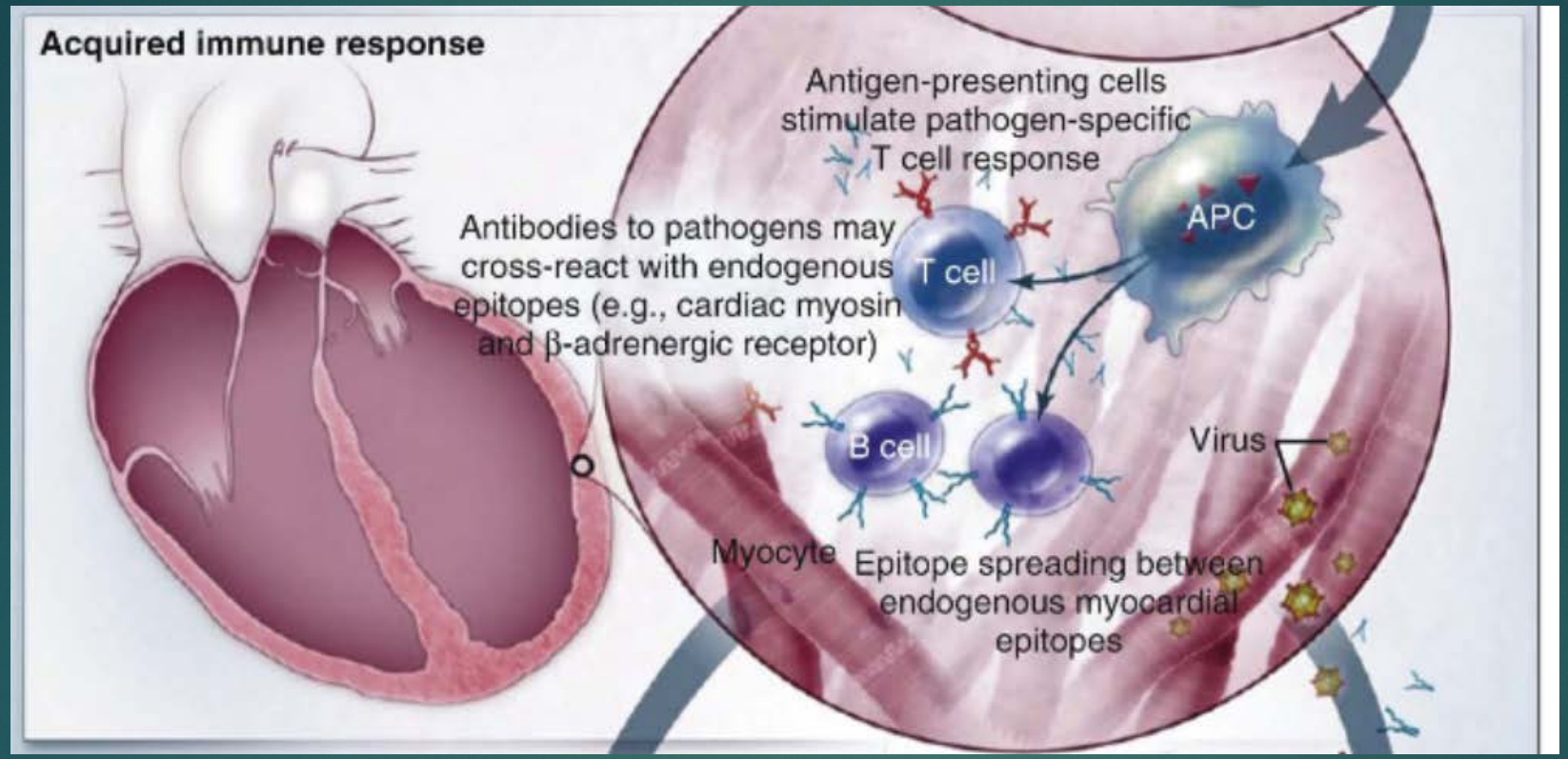
Xiong, Lee et al. Nature Medicine

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 ($p = 2.22E-03$) or patients with other diseases ($p = 1.08E-04$).
- 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



from Cooper LT: Myocarditis. N Engl J Med 360:1526, 2009

- There are a multitude of basic studies in mice that demonstrate the importance of the adaptive immune response in myocarditis
  - Autoimmunity in viral myocarditis. Reddy J, Massilamany C, Buskiewicz I, Huber SA. Curr Opin Rheumatol. 2013 Jul;25(4):502-8
  - Rose NR. Viral myocarditis. Curr Opin Rheumatol. 2016 Jul;28(4):383-9