Myocarditis

from the immunological viewpoint

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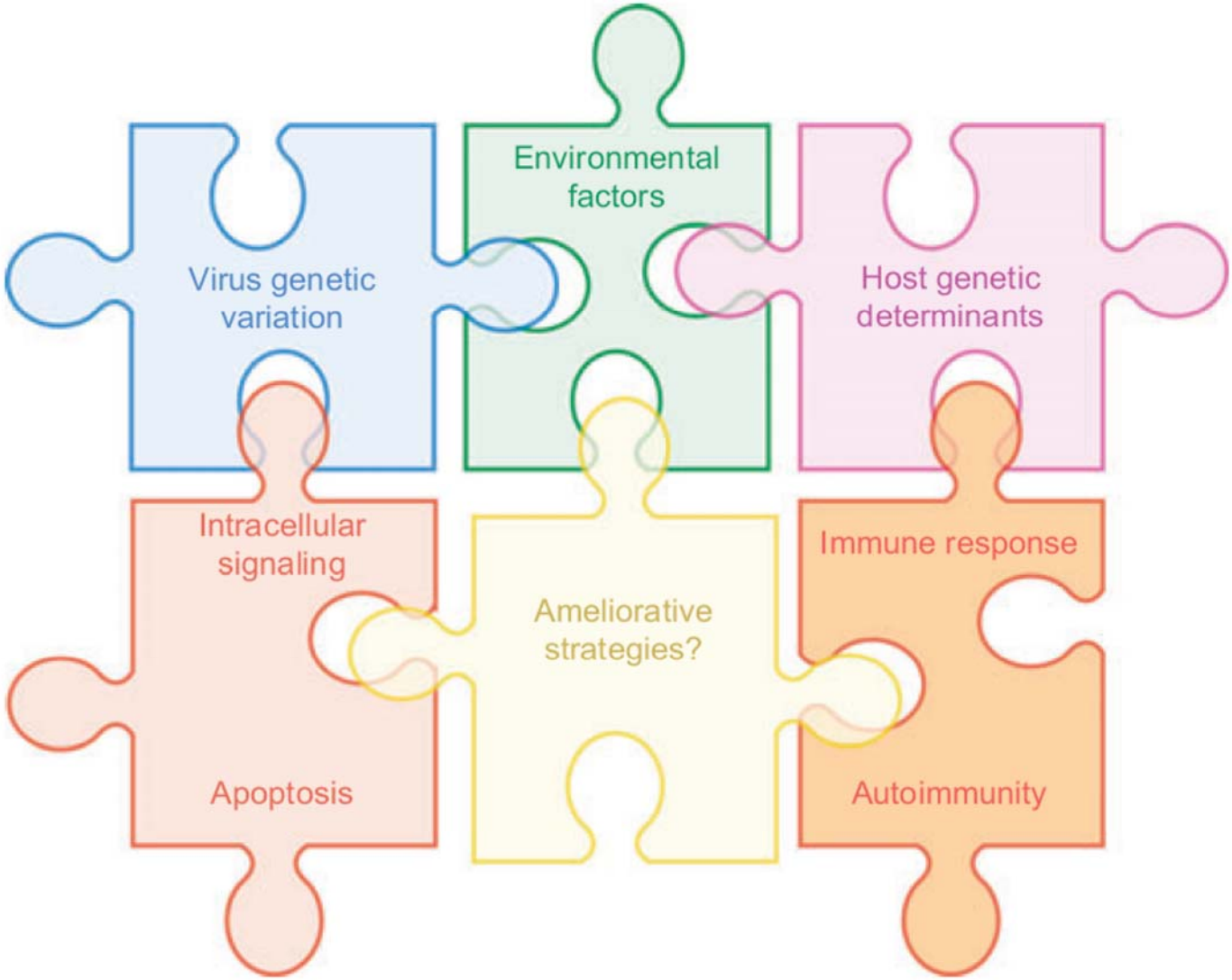
Myocarditis is a cardiac disease
associated with inflammation of the myocardium
and apoptotic degeneration and/or necrosis of adjacent myocytes
in the absence of a localized ischemic event

McManus BM.
Atlas of Cardiovascular Pathology for the Clinician,
Philadelphia, 2000

Myocarditis (with or without a DCM phenotype)
is an acquired, nongenetic disease
of infectious or noninfectious etiology;
among the noninfectious causes
autoimmunity plays a major role
either triggered by a prior infection
(e.g., postviral, post-*Trypanosome cruzi*)
or without an apparent environmental trigger

Elliott P, et al. *Eur Heart J* 2008; 29:270

The puzzle of myocarditis

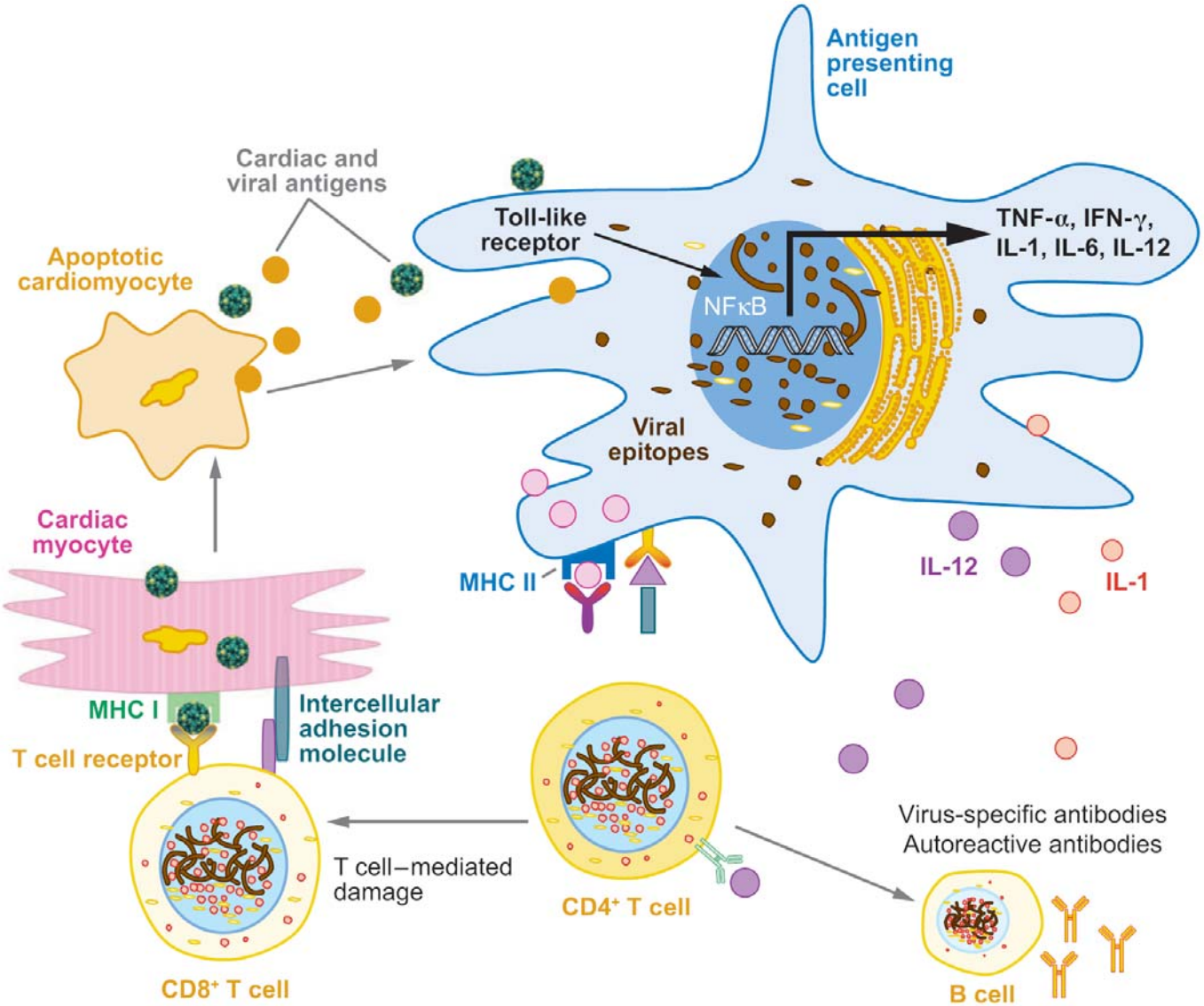


Myocarditis

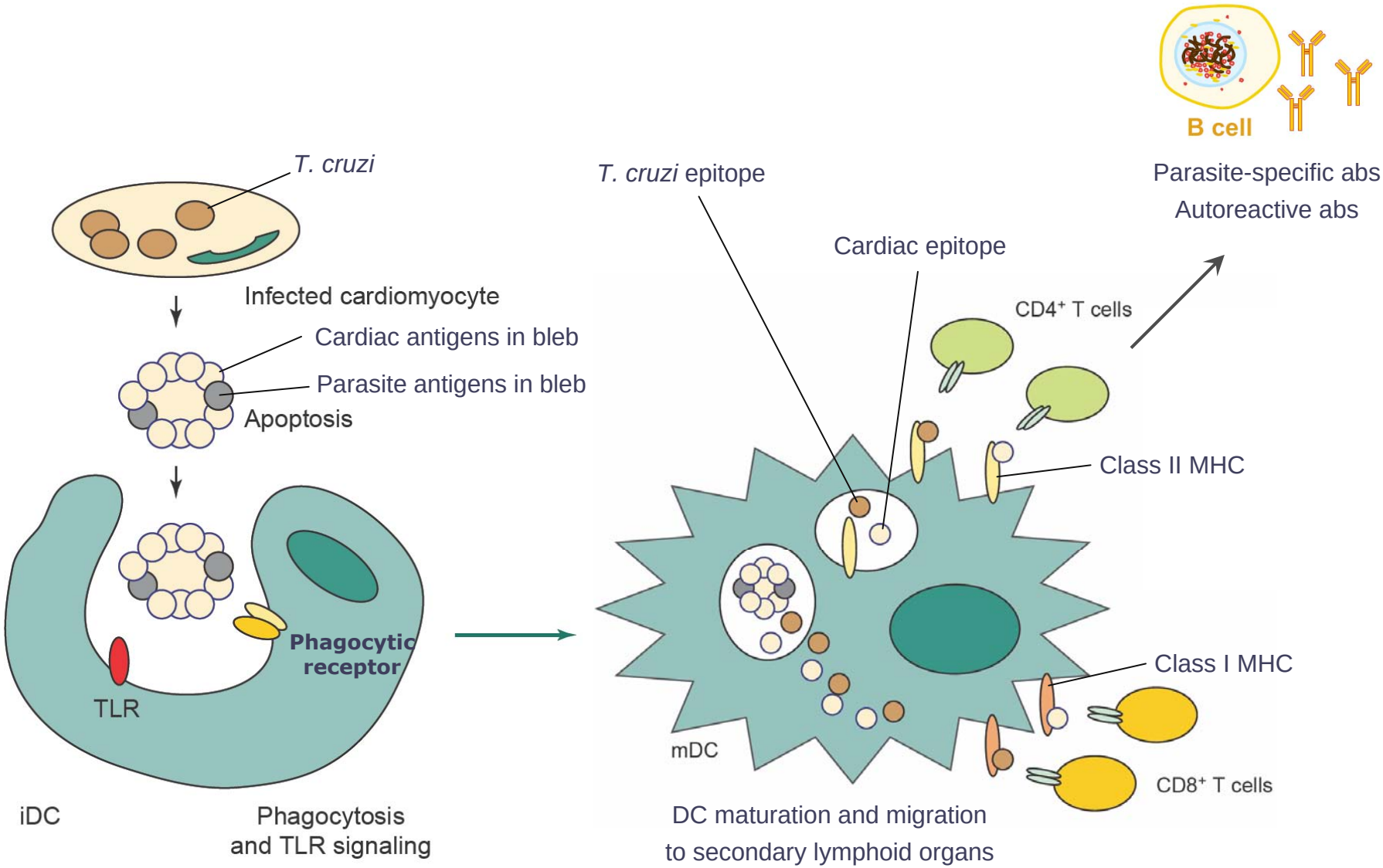
from the immunological viewpoint

1. Pathogen-induced immune-response-mediated myocardial injury
2. Pathogen-induced anti-cardiac autoimmunity
3. Myocarditis as an organ-specific autoimmune disease

Immune-mediated myocardial injury in CVB3 myocarditis



Immune-mediated myocardial injury in *T. cruzi* myocarditis



Autoreactivity after *T. cruzi* infection

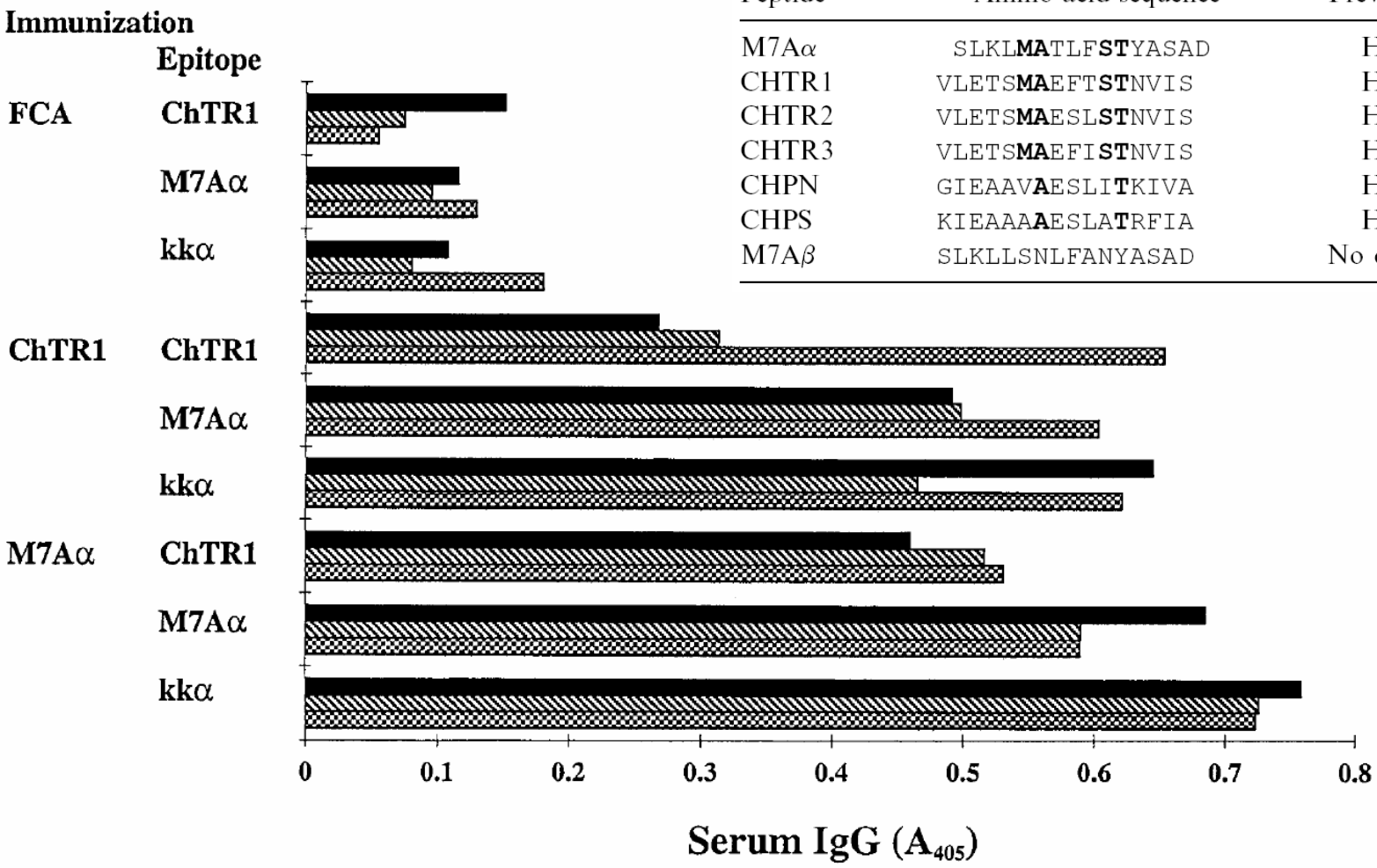
Host Component	Host	Molecular Definition
Neurons	H	Serum IgG
Sciatic nerve homogenate	H	Serum IgG
Heart homogenate	H	T cells
Cardiomyocytes	H, Rb	T cells
Heart homogenate	M	T cells
Cardiac myosin	M	CD4+ T cells, serum IgG
43-kDa Muscle glycoprotein	M	Serum IgG
Nervous tissue, heart and skeletal muscle	M	Serum IgG
Second extracellular loop, M2 cholinergic receptor	H,M	Serum IgG
Second extracellular loop, β1 adrenergic receptor	M	Serum IgG
Small nuclear ribonucleoprotein	H	Serum IgG

Marin-Neto JA et al. *Circulation* 2007;115:1109

Antigenic mimicry

Chlamydia-derived peptides that mimic heart-specific α-mhc-derived peptides

Peptide	Amino acid sequence	Prevalence	Severity
M7Aα	SLKL**MA**TLF**ST**YASAD	High	High
CHTR1	VLETS**MA**EFT**ST**NVIS	High	Mild
CHTR2	VLETS**MA**ESL**ST**NVIS	High	Mild
CHTR3	VLETS**MA**EFI**ST**NVIS	High	Mild
CHPN	GIEAAV**A**ESLI**T**KIVA	High	Mild
CHPS	KIEAAA**A**ESLA**T**RFIA	High	Mild
M7Aβ	SLKLLSNLFANYASAD	No disease	—



Penninger JM, Bachmaier K. *J Infect Dis* 2000;181(Suppl 3):S498

Myocarditis

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Major Rose-Witebski criteria for autoimmunity fulfilled in myocarditis

a. Mononuclear cell infiltration and abnormal HLA expression in the target organ in the absence of infectious agents or known inflammatory causes

b. Disease induced in animals by immunization with relevant autoantigen, and/or passive transfer of serum, purified autoantibody and/or lymphocytes

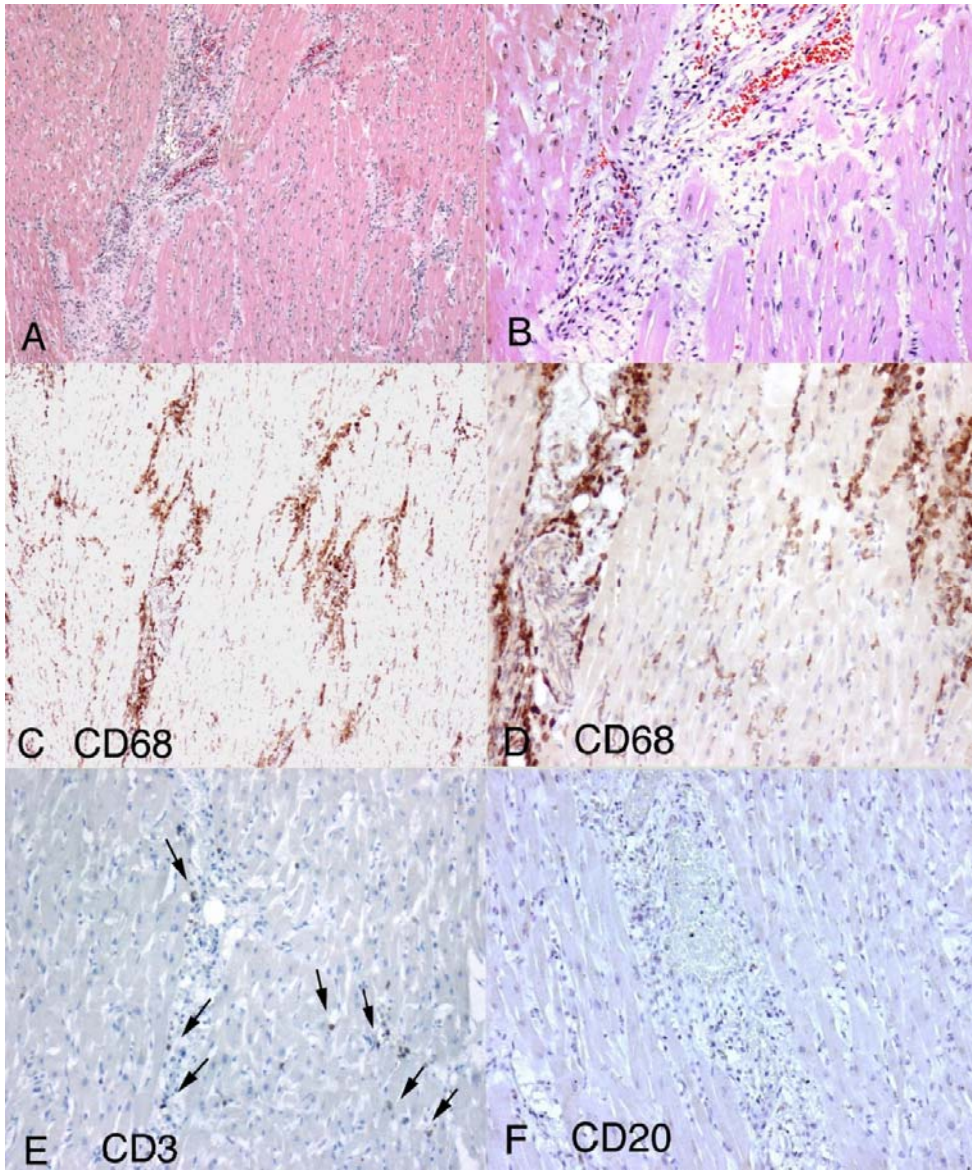
c. Autoantibody and/or autoreactive lymphocytes in situ within the affected tissue

d. Identification and isolation of autoantigen(s) involved

e. Circulating autoantibodies and/or autoreactive lymphocytes in patients and in unaffected family members

f. Efficacy of immunosuppressive therapy

Histopathological manifestations of myocarditis



A. Diffuse interstitial myocardial inflammatory infiltrate more prominent around interstitial capillaries and composed of macrophages and lymphocytes.

B. Vasocentric inflammation (H&E stain).

C-D. $CD68^+$ macrophages were the most abundant cells present.

E. Rare $CD3^+$ lymphocytes.

F. Essentially $CD20^-$ immunohistochemical stain.

Tavora et al. *Diagn Pathol* 2008;3:21

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J Mol Cell Cardiol. 2007 June ; 42(6): 1054–1064.

Spontaneous myocarditis mimicking human disease occurs in the presence of an appropriate MHC and non-MHC background in transgenic mice

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*Department of Immunology, Mayo Clinic College of Medicine, Rochester, USA

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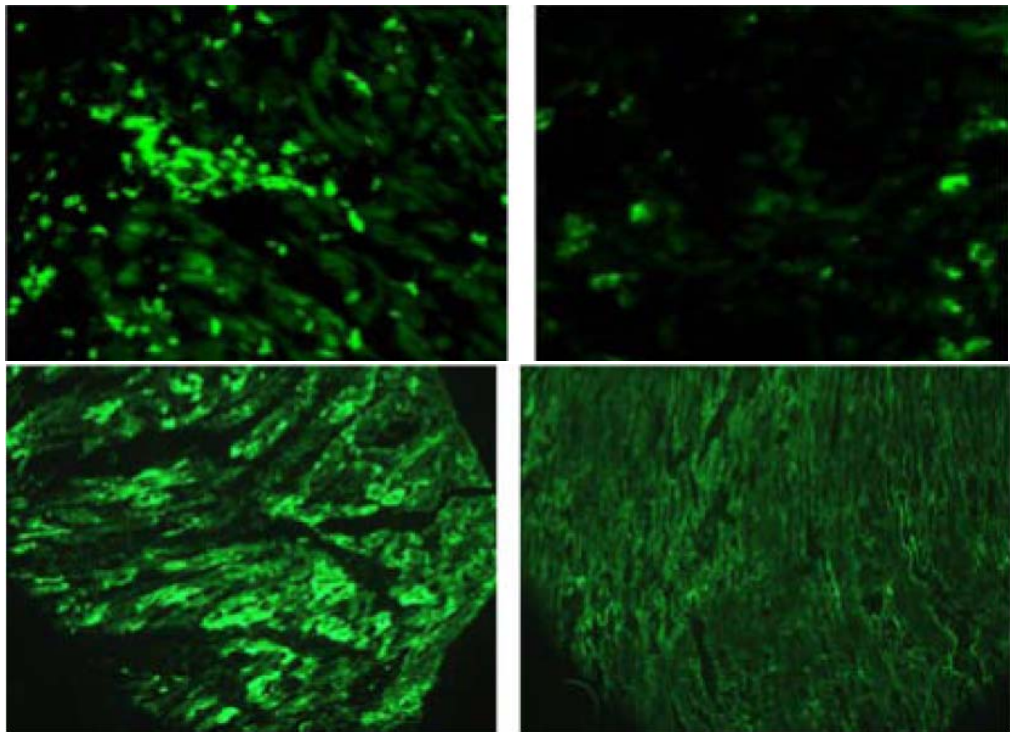

CD4⁺ T cells

IgG antibodies

...against
cardiac myosin α heavy chain

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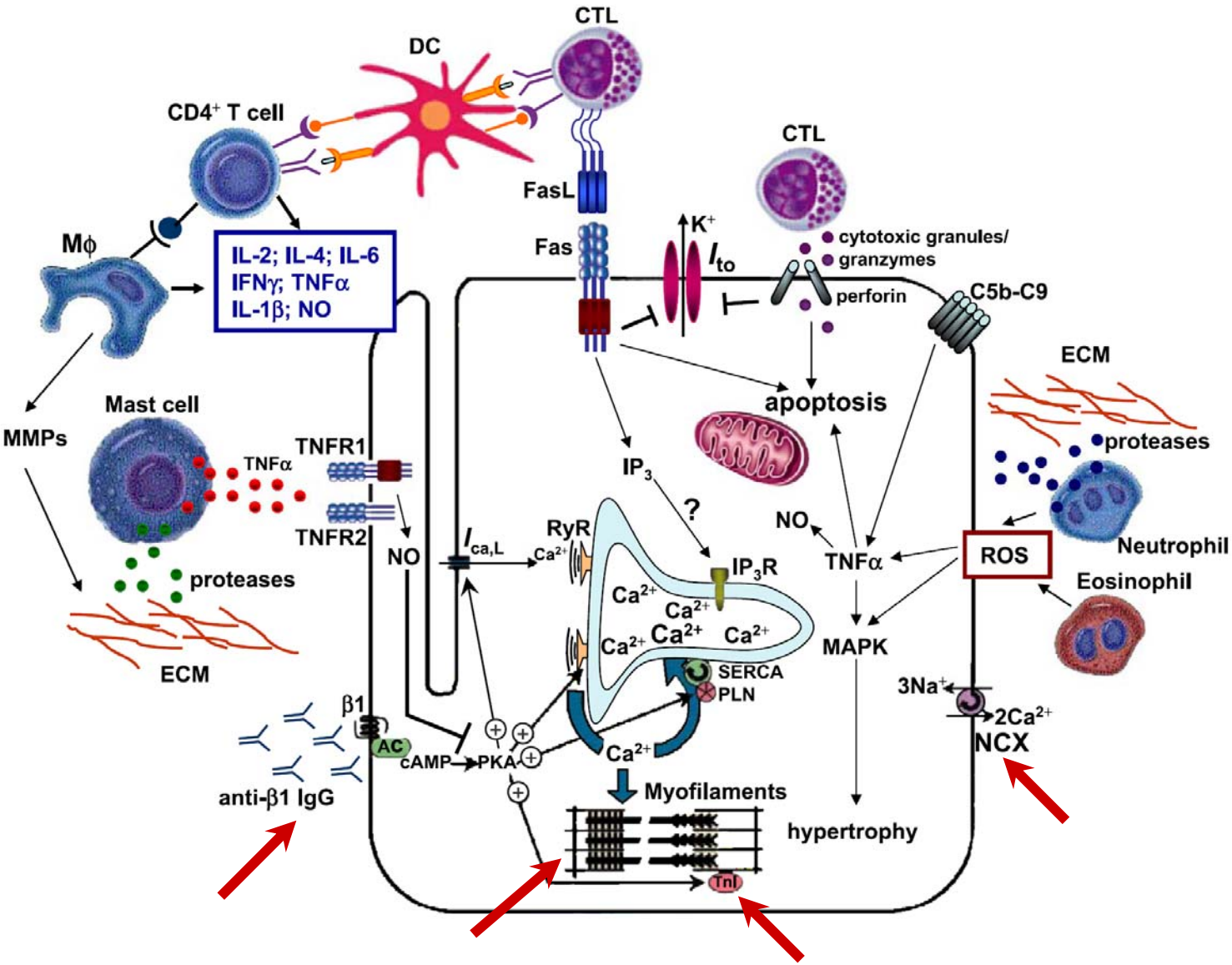
Targets of immune-mediated damage of cardiomyocyte



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Antiheart autoantibodies in myocarditis/DCM

Antibody	Technique	Percentage antibody-positive AM	DCM	OCD	Normals
Muscle-specific					
ASA	s-I IFL	47	10	NT	25
AMLA	AMC	41	9	NT	12
AFA	s-I IFL	28	24	NT	6
IFA	s-I IFL	32	41	NT	3
Heart-reactive	s-I IFL	59	20	NT	0
	s-I IFL	NT	12–28	2133	4
Anti-s.Na/K-ATPase	ELISA + western blot	NT	26	NT	2
Organ-specific cardiac	s-I IFL + abs	41	26	1	3
Antimitochondrial					
M7	ELISA	13	31	10	0
ANT	SPRIA	91	57	0	0
BCKD-E2	ELISA	100	60	4	0
Antilaminin	ELISA	73	78	25–35	6
Anti-β1 receptor					
Inhibiting	LBI	NT	30–75	37	18
Inhibiting	ELISA	NT	31	0	12
Stimulating	Bioassay	96	95	8	0
	ELISA	NT	26	10	1
	FRET	NT	73	23	0
Anti-M2 receptor	ELISA	NT	39	NT	7.5
Anti-α and β MYHC	Western blot	NT	46	8	0
Anti-MLC 1v	Western blot	NT	35	25	15
Non-myofibrillar	Western blot	NT	46	17	0
Anti-MYHC	Western blot	NT	67	42	NT
Anti-MLC 1	Western blot	NT	17	0	NT
Antitropomyosin	Western blot	NT	55	21	NT
Antiactin	Western blot	NT	71	21	NT
Anti-HSP-60	Western blot	NT	85	42	NT
Anti-HSP-60, 70	Western blot	NT	10–14	1–2	3
Anti-β MYHC	ELISA	37	44	16	2.5
Anti-α MYHC	ELISA	17	20	4	2

Caforio ALP, Iliceto S. *Curr Opin Cardiol* 2008; 23:219

Organ-specific IgG AHAs

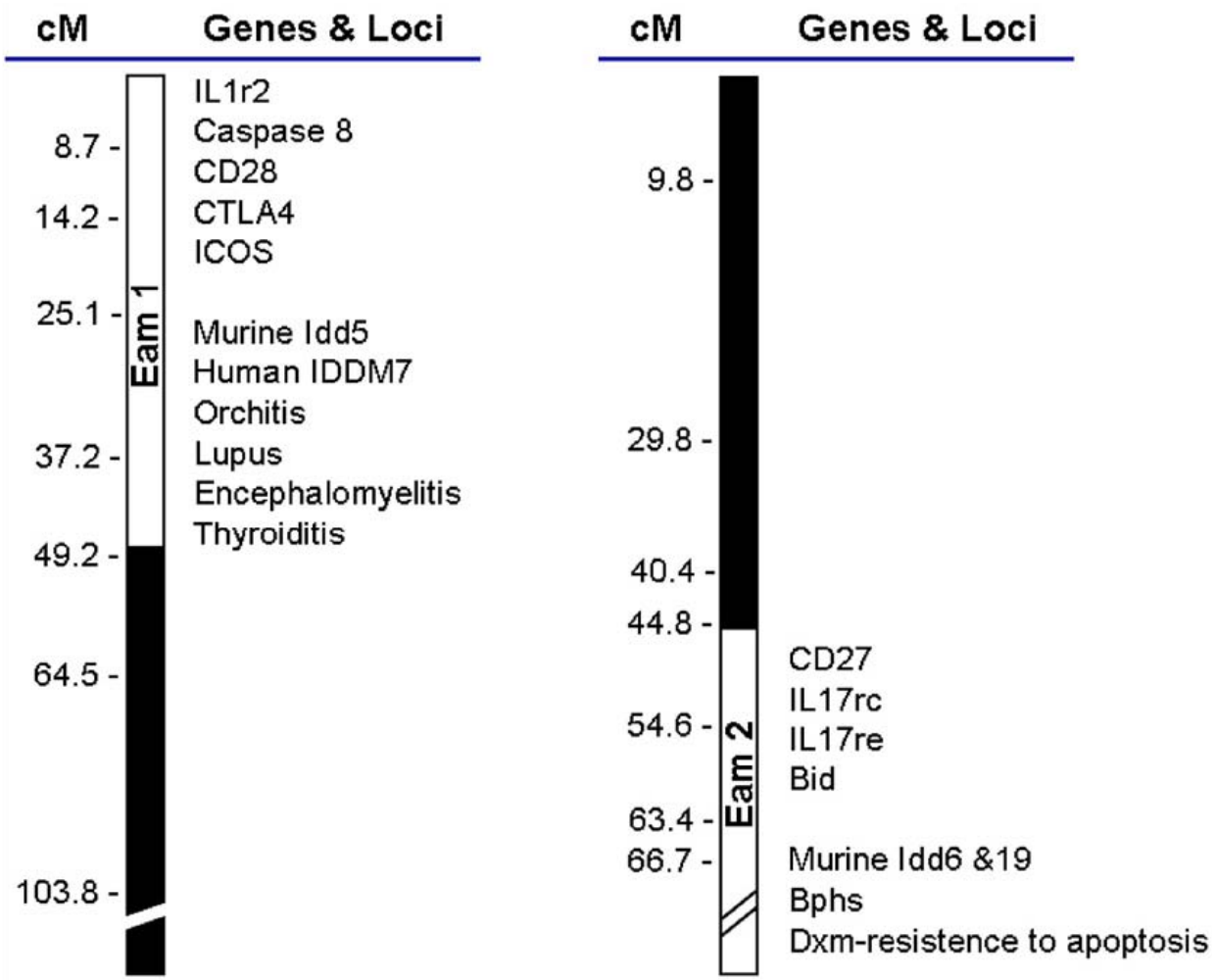
- **30–40%** of myocarditis/DCM patients and their symptom-free family members
- **1%** of patients with other cardiac disease
- **3%** of normal subjects
- **17%** of patients without cardiac disease, but with autoimmune polyendocrinopathy

Staging of preclinical DCM

- **No pre-DCM:** negative AHA, normal echocardiogram
- **Early:** positive AHA, normal echocardiogram
- **Advanced:** positivity for one or more AHA
- **Late pre-DCM:** at least one antibody marker, LVE, or dFS

Caforio ALP, et al. *Circulation* 2007; 115:76

Loci important in autoimmune myocarditis



Chr. 1 Chr. 6

Li HS, et al. *Autoimmun Rev* 2008; 7:168

Thank you for your attention

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