The Cardiosplenic Axis in Heart Failure

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DISCLOSURES: None
Cytokine Hypothesis of Heart Failure (HF)

- Sympathetic nervous system
- Stimulation
- Reduced cardiac output
- Damaged myocardium
- Activated monocyte
- Cytokines impairing myocardial function
- Natriuretic peptides
- Cytokines
  - Cytokines impairing myocardial function
  - Proinflammatory cytokines
- Release into bloodstream
- Hypoperfused skeletal muscle

References:
Monocytes/Macrophages and Dendritic cells (DCs)


Ferenbach and Hughes, *Kidney Int*, 2008
Monocytes/Macrophages and Dendritic cells (DCs)

Shi and Pamer, Nat Rev Immunol, 2011
Hilgendorf et al, Circ Res, 2014
How is the mononuclear phagocyte network altered in chronic HF?

What is contribution of splenic mononuclear cells to pathological LV remodeling

Cell populations
  - Appropriate lineage exclusion
  - Macrophages CD11b^+ F4/80^+ (CD206^-/+)
  - Monocytes CD11b^+ F4/80^+/low (Gr-1^{hi/low})
  - Classical DCs (cDCs) CD11c^+ B220^-
  - Plasmacytoid DCs (pDCs) CD11c^{+/-} B220^+ (Siglec-H^+)

Ismahil et al, Circ Res 2014
Ischemic HF model
8 Weeks Post-Infarction

Sham

Heart Failure

Sham

HF

Trichrome stain

WGA stain

Sham

HF

0.2 mm

200 μm

0.2 mm

200 μm
Macrophage Populations in the Failing Heart

Heart Failure – Remote Zone

WGA Mac-1
Arginase

Phalloidin

M1
M2
Macrophage Populations in HF

Heart

Peripheral Blood

- Activated Monocytes
  - CD11b+F480+ cells (% Lymphocyte-Monocyte population)
  - Sham: 5, HF: 10

- Proinflammatory monocytes
  - Lin-CD11b+F480+Gr-1hi cells (% Lymphocyte-Monocyte population)
  - Sham: 5, HF: 10

- Anti-inflammatory monocytes
  - Lin-CD11b+F480+Gr-1low cells (% Lymphocyte-Monocyte population)
  - Sham: 5, HF: 10

- Resident classically activated Mφ
  - CD11b+F480+ CD206+ cells (% cell population)
  - Sham: 5, HF: 10

- Resident alternatively activated Mφ
  - CD11b+F480+ CD206+ cells (% cell population)
  - Sham: 5, HF: 10

- Mac-1 positive cells
  - High power field
  - Sham: 4, HF: 16
Dendritic Cell Populations in HF
Circulating Cytokines in HF

- IL-6 pg/ml: Wt = 4, HF = 3, p = 0.428
- MCP-1 pg/ml: Wt = 3, HF = 4, p = 0.250
- IFN-γ pg/ml: Wt = 4, HF = 4, p = 0.0143
- IL12p70 pg/ml: Wt = 3, HF = 4
- IL10 pg/ml: Wt = 4, HF = 4
- TNF-α pg/ml: Wt = 3, HF = 4

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Spleen Histology

Cesta MF, *Toxicol Pathol*, 2006


Cesta MF, *Toxicol Pathol*, 2006
Splenic Remodeling in HF – Monocyte Populations

Sham

HF

Spleen wt/tibia length (mg/cm)

p=0.0126

Sham HF

Spleen cells/HF

p=0.0068
Splenic Remodeling in HF – DC Populations
Is the spleen necessary for pathological remodeling in heart failure?
Robust Cardiosplenic Axis in HF

8 W HF-before Spx

16 W HF- 8 W After Spx
Robust Cardiosplenic Axis in HF

CD45

HF

HF with spleen

HF without spleen

CD11b DAPI

5µm

20µm

5µm

20µm

CD11b fluorescence intensity

p=0.0002

Spleen

+ -

HF

4 3

OMY

100ms 2mm
Robust Cardiosplenic Axis in HF
Are splenocytes in HF independently sufficient to induce pathological remodeling?
HF Splenocytes Induce LV Remodeling in Naïve Mice

Sham Splenocyte Tx

HF Splenocyte Tx
HF Splenocytes Induce LV Remodeling in Naïve Mice
Baseline

PBS-Splenocytes

100ms

LPS-Splenocytes

100ms

8 Wks

PBS-Splenocytes

100ms

LPS-Splenocytes

100ms

n = 7 per group
**HF Splenocytes Induce Systemic Inflammation in Naïve Mice**

**CD11b+CD8+ T Cells**
- **Sham**
- **HF**

**Spleen wt/tibia length**
- **Sham-Splenocyte**
- **HF-Splenocyte**

**Images**
- Sham splenocyte transfer
- HF splenocyte transfer

**Graphs**
- **CD11b-F480+ (Percent monocyte/lymphocyte population)**
- **Spleen wt/tibia length**
HF Splenocytes Home to the Heart and Induce Tissue Injury
Splenocytes Are Intensely Activated in HF
HF Splenocytes do not Increase Serum Cytokines in Naïve Mice
CARDIOSPLENIC AXIS IN ISCHEMIC HEART FAILURE

Heart
- ↑ Pro-inflammatory MΦ = Anti-inflammatory MΦ
- ↑ Classical DC
- ↑ Plasmacytoid DC
- ?(Other Immune cells?)

Blood
- ↑ Pro-inflammatory Mo = Anti-inflammatory Mo
- ↑ Classical DC
- ↑ Plasmacytoid DC
- ↑ CD4 & CD8 T cells
- ?(Other Immune cells?)

Spleen
- ↓ Pro-inflammatory Mo
- ↑ Anti-inflammatory Mo
- ↑ Classical DC
- ↑ Plasmacytoid DC
- ↑ CD4 & CD8 T cells
- ?(Other Immune cells?)

Heart Failure
- Fibrosis
- LV Dysfunction
- Apoptosis
- LV Remodeling

HF-Spleen
- Increased WP follicles
- Larger germinal centers
- Increased marginal zone
- Activated splenocytes
Implications

• Activation of mononuclear phagocytes is indispensable for the progression of pathological remodeling/fibrosis. The splenic and cardiac microenvironment in HF play critical roles in this process.

• Progression of cardiac remodeling and fibrosis is dependent, at least in part, on autoimmune injury in the heart, i.e., ischemic cardiomyopathy is an immune cell-mediated cardiomyopathy.

• Targeting specific mononuclear cell populations within the spleen and heart (e.g., monocyte/macrophages and DCs), or the specific antigens responsible for their activation, may comprise a more feasible approach to therapeutic immunomodulation in HF.
Acknowledgements

Prabhu Lab
Ameen Ismahil, PhD
Justin Kingery, MD, PhD
Robert Lewis, MD, PhD
Guihua Zhou, MD, PhD
Ernest Cardwell, BS
Mehak Goel, BS
Bindiya Patel, BS
Yuanyuan Ma, PhD
Hai Zhong, BS
Yixin Wu, BS
Angela De Almeida, MS
Shyam Bansal, PhD

Collaborators
Tariq Hamid, PhD

Support
NIH R01 HL-99014
NIH P01 HL-78825
VA Merit Award
UAB CCVC and Stem Cell Institute