Resilience, resistance, and health: Insights from animal models of social determinants of health

Disclosures: None

Steve W. Cole, Ph.D.
UCLA School of Medicine
Department of Psychiatry & Biobehavioral Sciences
Department Medicine, Division of Hematology-Oncology
Semel Institute for Neuroscience & Human Behavior
Norman Cousins Center for Psychoneuroimmunology
Jonsson Comprehensive Cancer Center
Social Determinants of Health

- Poverty / low SES
- Social loss / bereavement
- Post-traumatic stress
- Early life deprivation
- Loneliness / isolation
- Social instability / violence
- Chronic stress
- Discrimination
- Low social rank
- Disease burden
- Anxiety

Resilience

Resistance / robustness
Animal modeling value:

**Insult / SDOH adversity**
- CNS response
- Peripheral neural response
- End-organ regulation
- Disease pathogenesis
- Cell/molecular mechanisms
- Social resources/interventions
- Pharm/behav. interventions

**Health / well-being / function**
Mouse modeling of CNS stress resilience:

The dopaminergic reward system
Mouse modeling of CNS stress resistance

Neurobiology of Resilience: Interface Between Mind and Body
Cathomas et al., Biological Psychiatry 2019
Mouse models of disease: Adding “social determinants”
Mouse models of disease: mapping SDOH cell/molecular mechanisms

- CNS threat perception
- SNS neurons, NE
- Bone marrow
  - Stem Cell
  - Lymphoid
  - Myeloid
  - Monocyte
  - Granulocyte

- Viral infection
  - Lymph nodes - neoinnervation - IFN, Th2/Th17
  - Lung / airway - pneumonia - asthma
  - Vasculature - atherosclerosis
  - CNS - inflammation - neurodegen
  - Solid tumor - breast - ovarian
  - Metastasis

- Systemic circulation

References:
Cole et al. PNAS 2011
Powell et al. PNAS 2013
Heidt et al. Nature Medicine 2014
Cole et al. PNAS 2015
McKim et al. Cell Reports 2018
Primate modeling of social processes: resilience

Monkey lockdown

Inflammation:
Classical monocytes

Antiviral:
Type I IFN RNA

Cole et al. PNAS 2021
Primate modeling of social processes:
Resilience to early life adversity

Reactivity:
1.2 vs. 3.2 critical points (d'), \( p < 10^{-10} \)
1.9 vs. 3.7 inflection points (d''), \( p < 10^{-10} \)

681 Diverged by mo. 6
650 Recovered? - 95%
Øf Embedded? - 5%

Suomi et al., unpublished, 2015
Take-home points / knowledge gaps / research opportunities

Animal models provide exquisite experimental control and mechanistic analyses of SDOH
• Causal effects of modeled “social determinants” on behavior and health outcomes
• Cellular/molecular/genetic mechanisms in vivo
• Genetic/developmental/social resilience factors
• Rapid proof-of-concept testing for resilience remedies/interventions/solutions

CAVEAT: “animal SDOH” differ ethologically from human SDOH (…AND other animals)
  e.g., isolation (safety vs threat), loneliness (social safety signaling), caregiving, neural/endocrine

Implication: NO single animal model will provide a full-cycle, high-fidelity model of human SDOH
Solution: blend different models for different components, with particular attention to ethological validity

• Mice = good for disease modeling and molecular dissection (genetic manipulability, short lifecycle)
• Mice = bad as models of human social behavior (e.g., isolation, caregiving, cognition, etc.)
• Rats = good for “broadly human-similar” social behavior
• Rats = bad as models of human disease (generally not genetically manipulable)
• Non-human primates = great models of human-similar social, cognitive, motor behavior
• Non-human primates = variable fidelity models of disease, expensive & long lifecycle, ethically constrained, generally not genetically manipulable