Developmental Stress
&
The Origins Of Adult Disease

Andrea Danese, MD MSc
BACKGROUND

WHAT?

WHEN?

HOW?

WHY?

CONCLUSIONS
BACKGROUND

WHAT?

WHEN?

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WHY?

CONCLUSIONS
BACKGROUND

- What is inflammation?
INFLAMMATION

PROTECTIVE EFFECTS

- Innate immunity

  - Body physical barriers
    (e.g., skin, gastrointestinal tract)

  - Non-self recognition
    (complement system, Toll-like receptors)

  - Activation
    (cytokines, endothelial cells)

  - Response
    (phagocytes, acute phase proteins)
INFLAMMATION
Biomarkers

Primary inflammatory cytokines

- Interleukin-1
- Tumor necrosis factor-α etc.

Extravascular sources
- Adipose tissue
- Chronic infections (gingivitis, bronchitis, etc.)

Angiotensin II

- Messenger cytokine

Interleukin-6

Liver

Endothelial cell

- Selectins
- ICAM-1
- VCAM-1
- sICAM-1
- sVCAM-1
- s-Selectins etc.

Blood vessel

Vascular sources
- Inflamed atheroma
- Hypertensive arteries
- Aortic aneurysms

Serum markers of inflammation
- CRP
- SAA
- Fibrinogen

Taubes G (2002) Science
INFLAMMATION
DAMAGING EFFECTS

INFLAMMATION AND DISEASE

THE SECRET KILLER

- The surprising link between inflammation and heart attacks, cancer, Alzheimer's and other diseases
- What you can do to fight it
BACKGROUND

- What is inflammation?
- How does stress influence inflammation?
STRESS & INFLAMMATION
NEURO-IMMUNE NETWORK

STRESS

SYMPATHETIC

GLUCOCORTICOIDs

PARASYMPATHETIC

+ -
The Nobel Prize in Physiology or Medicine 1950

"for their discoveries relating to the hormones of the adrenal cortex, their structure and biological effects"

Edward Calvin Kendall
Tadeus Reichstein
Philip Showalter Hench
BACKGROUND

- What is inflammation?
- How does stress influence inflammation?
- What are the consequences of early life stress?
EARLY EXPERIENCE & HEALTH
THE EPIGENETIC LANDSCAPE

Genes

E1 (t1)
E1 (t2)
E2 (t3)

TIME (age)

ADULT DISEASE RISK

Waddington CH (1975)
STRESS & INFLAMMATION
IN ADULTS WITH MALTREATMENT HISTORY

STRESS

SYMPATHETIC

GLUCOCORTICOIDs

PARASYMPATHETIC
STRESS & INFLAMMATION
IN ADULTS WITH MALTREATMENT HISTORY

Heim C (2000) JAMA
Increased risk for:

- Chronic lung disease
  - OR: 3.9
  - 95% CI: [2.6-5.8]

- Cardiovascular disease
  - OR: 2.2
  - 95% CI: [1.3-3.7]

- Cancer
  - OR: 1.9
  - 95% CI: [1.3-2.7]

- Diabetes
  - OR: 1.6
  - 95% CI: [1.0-2.5]

THE DUNEDIN STUDY

Representative birth cohort followed up from birth to age 32y
N=972 (at age 32 years)
Childhood maltreatment (multiple informants, multiple time points)
High-sensitive CRP (>3mg/dL, cont), fibrinogen, white blood cell count
Risk factors and potential mediating variables throughout life-course
Cox, OLS regression analysis
CHILDHOOD MALTREATMENT
AGE 3-11 YEARS

Maternal rejection (14%)
Harsh discipline (10%)
Disruptive caregivers changes (6%)
Physical abuse (4%)
Sexual abuse (12%)
MALTREATMENT AND ADULT INFLAMMATION
HIGH RISK GROUP FOR CARDIOVASCULAR DISEASE (CDC, AHA)

No Probable Definite

Childhood maltreatment

hsCRP > 3 mg/L (%)

Danese A (2007) PNAS
MALTREATMENT AND ADULT INFLAMMATION

RR = 1.80 [1.26-2.58]
MALTREATMENT AND ADULT INFLAMMATION
CO-OCCURRING EARLY-LIFE RISKS

Low birth weight. RR = 1.60 [1.00-2.57]
*Low child SES. RR = 1.96 [1.19-3.25]
*Low child IQ. RR = 1.44 [1.03-2.01]

Low birth weight. RR = 0.87 [0.49-1.53]
*Low child SES. RR = 1.89 [1.50-2.39]
*Low child IQ. RR = 2.12 [1.56-2.87]
MALTREATMENT AND ADULT INFLAMMATION

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MALTREATMENT AND ADULT INFLAMMATION
ADULT STRESS EXPOSURE

Low SES. RR = 1.48 [1.23-1.73]
*Major Depression. RR = 1.46 [1.10-1.94]
*High Perceived Stress. RR = 1.43 [1.12-1.82]

Low SES. RR = 1.44 [0.94-2.20]
*Major Depression. RR = 1.45 [1.06-1.99]
*High Perceived Stress. RR = 1.45 [1.08-1.94]
MALTREATMENT AND ADULT INFLAMMATION
ADULT STRESS EXPOSURE

RR = 1.64 [1.13-2.40]

Low SES.                      RR = 1.48 [1.23-1.73]
*Major Depression.       RR = 1.46 [1.10-1.94]
*High Perceived Stress. RR = 1.43 [1.12-1.82]

RR = 1.80 [1.26-2.58]

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*Major Depression.       RR = 1.45 [1.06-1.99]
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MALTREATMENT AND ADULT INFLAMMATION
ADULT HEALTH & HEALTH BEHAVIOURS

*CV risk cluster.  RR = 2.38 [1.84-3.10]
*Smoking.  RR = 1.18 [0.69-2.03]
*Physical inactivity.  RR = 1.57 [1.05-2.34]
*Diet.  RR = 1.01 [0.68-1.48]

RR = 1.48 [1.10-2.00]  *CV risk cluster.
RR = 0.87 [0.69-1.11]  Physical inactivity.
RR = 0.98 [0.78-1.23]  Diet.

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RR = 1.18 [0.69-2.03]  Smoking.
RR = 1.57 [1.05-2.34]  *Physical inactivity.
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ADULT HEALTH & HEALTH BEHAVIOURS
MALTREATMENT AND ADULT INFLAMMATION

?  RR = 1.80 [1.26-2.58]
MALTREATMENT AND ADULT INFLAMMATION
ADULT HEALTH & HEALTH BEHAVIOURS

- CV risk cluster: RR = 1.76 [1.23-2.51]
- Smoking: RR = 1.18 [0.69-2.03]
- Physical inactivity: RR = 1.57 [1.05-2.34]
- Diet: RR = 1.01 [0.68-1.48]

- CV risk cluster: RR = 2.38 [1.84-3.10]
- Smoking: RR = 1.80 [1.26-2.58]
- Physical inactivity: RR = 0.87 [0.69-1.11]
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- Smoking: RR = 1.91 [1.13-3.23]
- Physical inactivity: RR = 0.87 [0.69-1.11]
- Diet: RR = 0.98 [0.78-1.23]
MALTREATMENT AND ADULT INFLAMMATION
CONTINUOUS CRP MEASURE

Danese A (2007) PNAS
MALTREATMENT AND ADULT INFLAMMATION

FIBRINOGEN

Danese A (2007) PNAS
WHITE BLOOD CELLS

MALTREATMENT AND ADULT INFLAMMATION

Danese A (2007) PNAS
MALTREATMENT AND ADULT INFLAMMATION

INFLAMMATION FACTOR

Danese A (2007) PNAS
SUMMARY (1)

- Maltreated children show a significant and graded elevation in inflammation levels 20 years later, in adulthood.

- The effect of childhood maltreatment on adult inflammation is independent of the influence of co-occurring risk factors.

- 10% of the cases of inflammation in the population may be attributable to childhood maltreatment.
EARLY EXPERIENCE & HEALTH
THE EPIGENETIC LANDSCAPE

Waddington CH (1975)
CHILDHOOD MALTREATMENT
AGE 3-11 YEARS

Maternal rejection (14%)
Harsh discipline (10%)
Disruptive caregivers changes (6%)
Physical abuse (4%)
Sexual abuse (12%)

0-1

No

Yes
EARLY-LIFE vs ADULT-LIFE STRESS

C-REACTIVE PROTEIN

Danese A (2008) Arch Gen Psychiatry
EARLY-LIFE vs ADULT-LIFE STRESS
C-REACTIVE PROTEIN

Danese A (2008) Arch Gen Psychiatry
**EARLY-LIFE vs ADULT-LIFE STRESS**

C-REACTIVE PROTEIN

Danese A (2008) *Arch Gen Psychiatry*
EARLY-LIFE vs ADULT-LIFE STRESS
C-REACTIVE PROTEIN

C-REACTIVE PROTEIN

Controls  Depressed-only  Maltreated-only  Depressed+maltreated

Danese A (2008) Arch Gen Psychiatry
EARLY-LIFE vs ADULT-LIFE STRESS

INFLAMMATION FACTOR

Inflammation factor
(N=673) (N=109) (N=56) (N=27)

Danese A (2008) Arch Gen Psychiatry
EARLY-LIFE vs ADULT-LIFE STRESS

INFLAMMATION FACTOR

Danese A (2008) Arch Gen Psychiatry
EARLY-LIFE vs ADULT-LIFE STRESS
INFLAMMATION FACTOR

Danese A (2008) Arch Gen Psychiatry
EARLY-LIFE vs ADULT-LIFE STRESS

INFLAMMATION FACTOR

Danese A (2008) Arch Gen Psychiatry
SUMMARY (2)

- Stress in childhood may modify developmental trajectories and have long-term effect on disease risk.

- If stress does modify developmental trajectories, more favourable conditions later in life may have little effect on disease risk.

- Stress later in life may have a smaller effect on disease risk, because it acts on a more developed system.
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CONCLUSIONS
EARLY EXPERIENCE & HEALTH
THE EPIGENETIC LANDSCAPE

Genes

E1 (t1)
E1 (t2)
E2 (t3)

TIME (age)

ADULT DISEASE RISK

Waddington CH (1975)
EARLY EXPERIENCE & HEALTH
THE EPIGENETIC LANDSCAPE

Waddington CH (1975)
G-E INTERPLAY & INNATE IMMUNITY

- The innate immune response is under the control of genes highly conserved throughout evolution (default).

- Environmental factor may adjust the innate immune response to maximize adaptation, particularly during development (fine-tuning).

- Gene-environment interactions may therefore underlie the observed epidemiological findings.

DNA METHYLATION. Methylation of CpG islands in gene promoter regions inhibits the binding of transcriptional factors, thus gene transcription.
EPIGENETICS & INFLAMMATION

- Early-life stress may induce methylation of the promoter region of the glucocorticoid receptor gene and persistent impairment of glucocorticoid sensitivity in mice.

- This has potential implications for inflammation.

- The relevance of epigenetic mechanisms with regard to the long-term effect of early-life stress on adult inflammation is currently unknown.

EARLY EXPERIENCE & INFLAMMATION
THE ACUTE-PHASE RESPONSE

SUMMARY (3)

- Early-life stress may modify the effect of genetic predispositions to inflammation, acting as an environmental pathogen.

- Early-life stress might also affect adult inflammation by inducing epigenetic changes in the glucocorticoid receptor gene.

- A better understanding of gene-environment interplay will be critical to characterize mechanisms through which early-life stress can affect adult health.
EARLY EXPERIENCE & HEALTH
THE EPIGENETIC LANDSCAPE

E1 (t1)
E1 (t2)
E2 (t3)

GENES

TIME (age)

ADULT DISEASE RISK

Waddington CH (1975)
Specific environmental stimulations during a sensitive period of the development might induce long-term physiological changes.

These changes may be aimed to maximize infant adaptation to conditions in which he/she is likely to live.

However, mismatch between early-life and adult-life living conditions may turn adaptive changes into damaging processes.

PREDICTIVE ADAPTIVE RESPONSE

METABOLISM

CARdiovascular Disease,
Type 2 dIABetes

Health

INNATE IMMUNITY

PREDICTIVE ADAPTIVE RESPONSE

INFECTIONS ?

INFLAMMATION-RELATED DISEASE ?

HEALTH

Danese A (in preparation)
Early-life stress might act as ‘trigger’ for long-term changes in body defences against communicable and non-communicable environmental threats.

Alertness and reactivity of the innate immunity may confer evolutionary advantages in the short term and at young age.

In contrast, increased innate immunity activity may become damaging later in life and lead to disease.
CONCLUSIONS

- Inflammation could be an important biological mediator of the effect of childhood maltreatment on adult health.

Danese A (2007) PNAS
CONCLUSIONS

Effective preventive strategies for adult disease should start from an early age.

Danese A (2008) Arch Gen Psychiatry
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“The past is not dead. In fact, it is not even past”

W. Faulkner
EARLY-LIFE STRESS AND ADULT INFLAMMATION

PRIMATES STUDIES
EARLY-LIFE STRESS AND ADULT INFLAMMATION

MR: maternally reared, still with mother
EW(1): maternally reared and weaned into a peer group
EW(2): maternally reared and weaned into an individual cage
HR: human reared and then peer-reared

Coe C (1989) Brain Behav Immun
EARLY-LIFE vs ADULT-LIFE STRESS
(STD) INFLAMMATION MARKERS

Danese A (2008) Arch Gen Psychiatry
Inflammation factor

Danese A (2008) Arch Gen Psychiatry
MALTREATMENT
AND THE ADULT HYPOTHALAMIC-PITUITARY-ADRENAL (HPA) AXIS

STRESS & INFLAMMATION
NEURO-IMMUNE NETWORK

STRESS RESPONSE
IN ACUTE STRESS

EVOLUTION
CULTURAL vs GENETIC MISMATCH?

LIFE EXPECTANCY
1 million years ago: 12-25 years

The lengthening of human lifespan may have uncovered long-term damaging consequences of processes advantageous in a shorter timeframe.