Epigenetic and cardiovascular disease

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The Barker hypothesis
The Barker hypothesis

Environmental insults occurring during the fetal / perinatal period

Low birth weight / maternal undernutrition

Augmented risk of cardiovascular diseases in adulthood

Coronary heart disease, Hypertension

Systemic vascular dysfunction
Also valid for the pulmonary circulation?
Healthy young adults having suffered of transient hypoxia during their first week of life
Transient perinatal hypoxia predisposes to exaggerated hypoxic pulmonary hypertension later in life.

Sartori et al, Lancet 1999;353:2205-07
La Paz Bolivia
3600 m

Offspring of mother with preeclampsia
Offspring of mother with preeclampsia display pulmonary hypertension at high altitude

Jayet et al., Circulation 2010;122;488-94
Offspring of mother with preeclampsia display systemic vascular dysfunction

Jayet et al., Circulation 2010;122;488-94
Vascular dysfunction later in life

Premature cardiovascular diseases
Assisted Reproductive Technologies

Have been done for almost 4 decades
Account for a steadily increasing number of births
Make up for 1-4% of the population in developed countries
Assisted reproductive technologies (ART) involves the manipulation of embryo during a period where they may be particularly vulnerable.
Hypothesis

Early embryonal

Assisted Reproductive Technologies

Long-term vascular dysfunction?
Methods

65 healthy children (11±2 y) born by ART
57 age-, sex-, birth weight- and gestational age-matched controls

3450 m for 72 hours

Pulmonary and systemic vascular function
Pulmonary-artery pressure
Flow-mediated vasodilation
Pulse wave velocity
Carotid intima-media thickness
Cardiovascular alterations in ART children

- Structural changes (↑ IMT)
- Endothelial dysfunction (↓ FMD)
- ↑ Arterial blood pressure
- ↑ Arterial stiffness (PWV)
- Insulin resistance (↓ Insulin stimulation of substrate delivery)
- Hypoxic PH and RV dysfunction

Vascular dysfunction later in life

Premature cardiovascular diseases
Mechanisms?
Long-term outcome?

• Difficult to investigate in healthy children
• No information (first ART child born in 1978, 38 y)
• Mouse model of ART
Endothelium-dependent mesenteric-artery vasodilation in vitro in ART and control mice

![Graph showing vasodilation in response to acetylcholine concentrations. The graph compares ART and control groups, with a statistically significant difference indicated by P<0.0001.](image)
Mean arterial blood pressure in ART and control mice

P = 0.017
Underlying mechanisms?
Epidemiological data in humans and experimental data in animals suggest that epigenetic mechanisms may play a role in the pathogenesis of fetal programming of adult diseases.
Epigenetic mechanisms

The term of epigenetic indicates stable changes of gene expression that are not related to modifications of the sequence of the DNA.
DNA methylation represents the principal epigenetic mechanisms.

Normal transcription
RNA polymerase

Insult
DNA Methylation

Inhibition of transcription
What is the evidence that epigenetic mechanisms underpin vascular dysfunction in offspring of ART?
Characteristics of epigenetic alterations

• Occur during embryonal-early fetal and during the perinatal period
Epigenetic activity

EMBRYONAL ART

LATE FETAL - PERINATAL

PREECLAMPSIA HYPOXIA

Activity
Epigenetic mechanisms

- Occur during embryonal-early fetal and during the perinatal period
- Consist in a DNA dysmethylation of gene promoters
- Induce stable changes of the gene expression
Endothelial nitric oxide synthase (eNOS) plays a major role in the regulation of vascular function.
Increased methylation of eNOS gene promoter in ART mice
Impaired eNOS gene expression and transcription in ART mice

Gene expression

Plasma NOx

B

eNOS

β-actin

Control ART

P=0.048

C

NOx (μmol/L)

Control ART

P<0.0001
Epigenetic mechanisms

• Occur during embryonal-early fetal and during the perinatal period
• Consist in a DNA dysmethylation of gene promoters
• Induce stable changes of the gene expression
• Transmissible throughout life and to the next generation
Endothelium-dependent mesenteric-artery vasodilation in offspring of ART

Acetylcholine (M)

Vasodilation (%)

ART F1

Control

P <0.001
Endothelium-dependent mesenteric-artery vasodilation in offspring of ART

$P < 0.001$
Epigenetic mechanisms

• Occur during embryonal-early fetal and during the perinatal period
• Consist in a DNA dysmethylation of gene promoters
• Induce stable changes of the gene expression
• Transmissible throughout life and to the next generation
• Potentially reversible (inhibitors of the histone deacetylase)
DNA dysmethylation can be reversed by histone deacetylase inhibitors.
Butyrate restores eNOS promoter methylation in the aorta of ART mice

![Graph showing methylation levels in control, ART, and ART + Butyrate groups]
Effects of Butyrate on endothelium-dependent mesenteric-artery vasodilation in ART and control mice

P < 0.001 ART + vehicle vs. ART + Butyrate
Effects of Butyrate administration to male ART mice on endothelial function in their progeny

![Graph showing vasodilation (%)]

- Offspring of ART + vehicle
- Offspring of ART + Butyrate
- Control

P <0.001 ART vs. ART+Butyrate
Conclusion

We demonstrate for the first time that ART induces premature vascular dysfunction in mice by an epigenetic mechanism
Speculation

ART induced vascular dysfunction in humans is caused by a similar epigenetic mechanism
Long-term consequences?
Cardiovascular disease

Subclinical atherosclerosis

Clinical atherosclerosis

Atherosclerosis burden

FMD
PWV
IMT

1st clinical event premature CV disease

Time [years]

10
55
Flow-mediated vasodilation in children born from ART, children with type I diabetes, offspring of preeclampsia
Survival rate in ART and control mice fed a normal chow (NC) or a high-fat diet (HFD)
Speculation

ART may represent a novel cardiovascular risk factor.
Prevention of ART-induced epigenetic changes and vascular dysfunction?
Melatonin in the culture media increases the efficiency of ART in programs of endangered species survival
Melatonin has epigenetic actions

Hypothesis

Addition of melatonin to the culture media prevents ART-induced epigenetic changes and vascular dysfunction in the offspring
Melatonin prevents defective eNOS gene expression and vascular nitric oxide synthesis in ART mice
Melatonin prevents ART-induced endothelial dysfunction and hypertension in mice

A

B

Vasodilation [%]

Mean Blood Pressure [mmHg]

Acetylcholine [M]

P=0.008

P=NS

P=0.003

Control

ART

ART + Melatonin
Addition of melatonin to the culture media prevents epigenetic changes and vascular dysfunction in ART mice

Similar effect in humans ??
Is this all?
Altered epigenetic regulation in ART mice

- Arterial hypertension
- Shortened life span
- Renal disease
- Cognitive dysfunction
- Transgenerational transmission
- Diabetes / Obesity
- Cancer
Altered epigenetic regulation in ART mice

Early markers of diseases?

Arterial hypertension
Shortened life span

Diabetes / Obesity

Renal disease

Cancer

Cognitive dysfunction

Transgenerational transmission
Summary

- Childhood: Malnutrition, Inflammation, Poor weight gain
- Adult health risk factors: Hypertension, Vascular dysfunction, Obesity, Insulin resistance
- Adult health outcomes: Cardiovascular diseases, Type 2 diabetes

Curr Opin Cardiol 2015, 30:393–397
Parenting from before conception

Michelle Lane, Rebecca L. Robker, Sarah A. Robertson

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A mountain of new questions

Thank you!
Thank you!

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Thank you!