Universitat Autònoma de Barcelona

FOLLOWING INTRAUTERINE GROWTH RETARDATION

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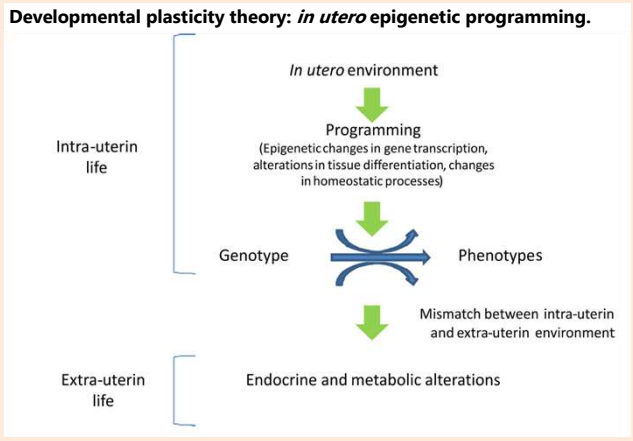
INTRODUCTION

Intrauterine growth retardation (IUGR) is a common complication of pregnancy characterized by decreased body weight and body mass of foetus, related to other foetus at same gestational weeks. Many studies correlate IUGR with the later development of adult diseases (e.g. pregnant women exposed to the Dutch Hunger Winter of 1944-1945 delivered infants with lower birth weight. By age 50, these offspring has impaired glucose tolerance). These studies led to the formulation of the ***'developmental plasticity theory'*** which consists in the ability of the organism to change structure and function in response to environmental signals. IUGR displays a significant risk for:

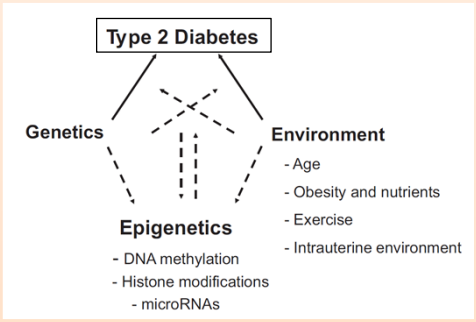
- Obesity
- Hypertension
- Dyslipidaemia
- Insulin resistance
- Type 2 diabetes mellitus

Developmental plasticity theory: *in utero* epigenetic programming.



TYPE 2 DIABETES MELLITUS

A chronic metabolic disease caused by an impaired sensitivity to insulin of insulin-responsive tissues coupled with insufficient β-cell compensation, characterized by hyperglycaemia and altered lipid metabolism. Therefore, the pancreas is a key player for the development of T2DM.



MITOCHONDRIAL DYSFUNCTION

Molecular process in mitochondria

IUGR

↓ $[O_2]$

↓ activity of complexes of the electron chain

↑ [reactive oxygen species (ROS)]

Oxidative reactions

Damage mitochondrial DNA (mtDNA)

↓[ATP]

β-cells:

- **Are especially vulnerable to ROS**
- **Have a high oxidative energy requirement**

- **Impair insulin secretion**
- **Decrease gene expression**
- **β-cell death**

T2DM adulthood

EPIGENETIC MODIFICATIONS IN KEY GENES OF T2DM DEVELOPMENT

T2DM associated loci
GLUT4
HNF4A
PDX1
H19/IGF2
KNCJ11

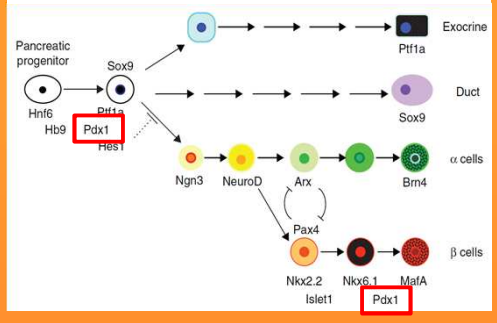
PANCREATIC DUODENAL HOMEOBOX 1 (PDX1)

A transcription factor that plays an essential role in:

- Early pancreas development
- β-cell differentiation
- Maintenance of mature β-cell function

Pdx1 is a gene susceptible to increased epigenetic modifications (especially DNA methylation).

Pdx1 role in early pancreas development and β-cell differentiation



EPIGENETIC SILENCING OF PDX1

Histone deacetylation (loss USF-1 binding + repressor complex recruitment)

↓ (a), (b)

DNA methyltransferase 1 (Dnmt1) recruitment

↓ (c)

↓H3K4 trimethylation / ↑H3K9 dimethylation

DNA methyltransferase 3a (Dnmt3a) recruitment

DNA methylation CpG islands

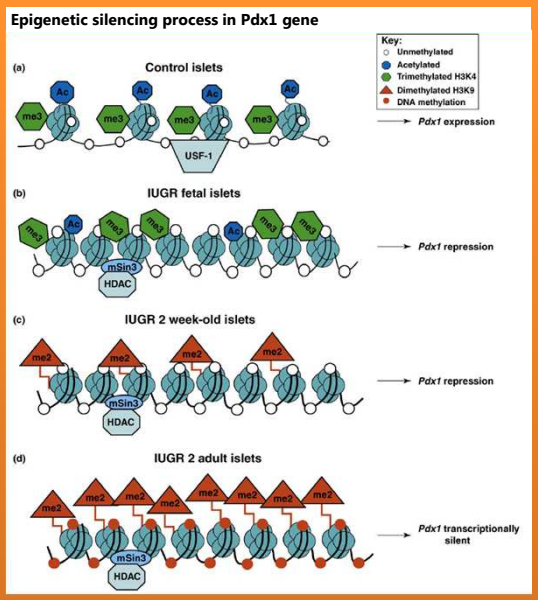
↓ (d)

Permanent repression of Pdx1

- **β-cell dysfunction**
- **Impair insulin secretion**

T2DM adulthood

Epigenetic silencing process in Pdx1 gene



CONCLUSIONS

IUGR leads to a reprogramming process that persists throughout life and to a progressive development of a T2DM phenotype. Mitochondrial dysfunction plays an important role in β-cells because of their vulnerability to ROS. On the other hand, the epigenetic silencing of Pdx1 suggests therapeutic agents for the prevention of common diseases with late-onset phenotypes.