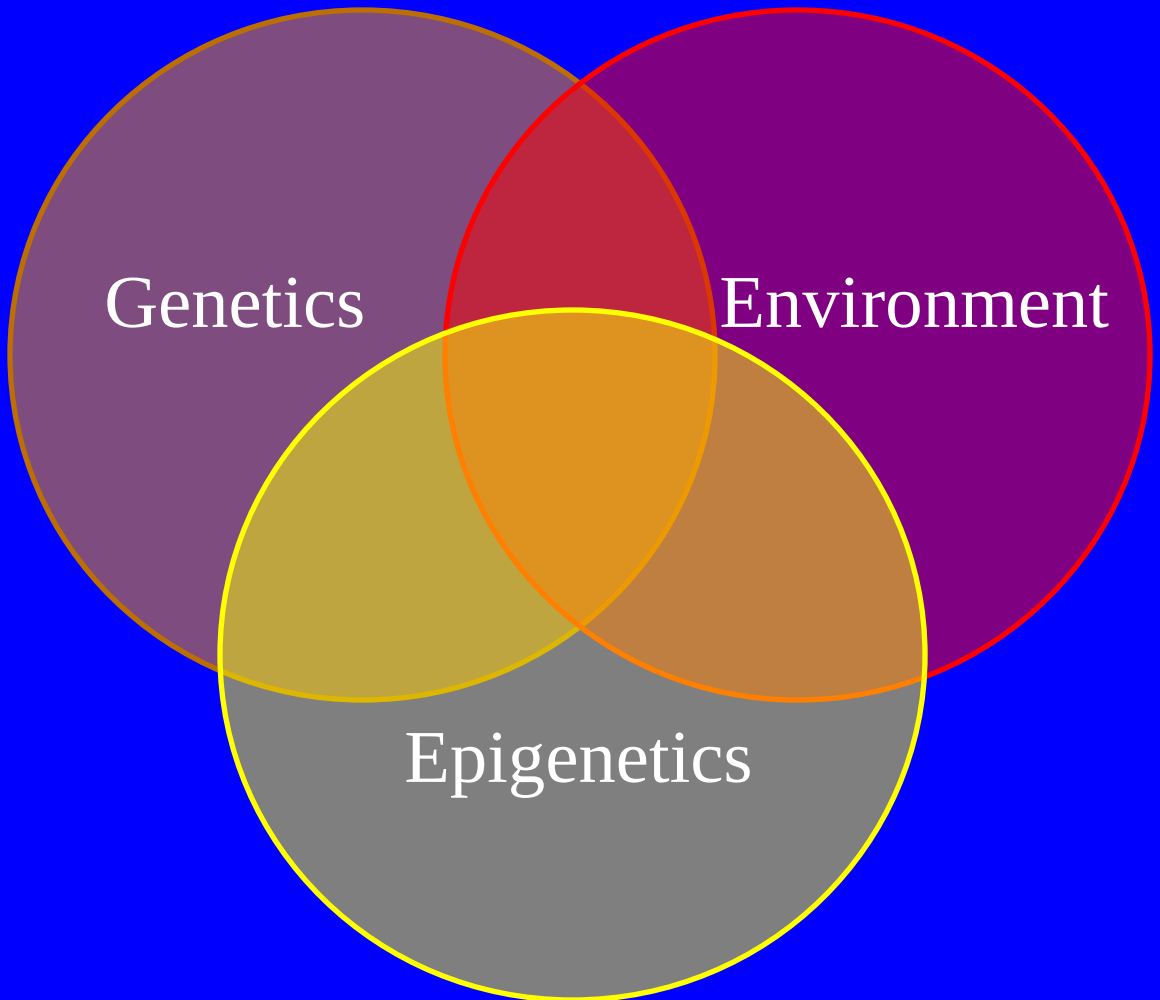
Impact of epigenetics in environmental risk assessment

Kevin Chipman

Phenotype



- Epigenetics plays an important role in the way organisms develop and respond to their environment including stressors and diet

- Epigenetic responses can be beneficial to an organism but can also contribute to disease, often later in life

- We can detect epigenetic responses in the natural environment – can they be related to incidence of disease ? (demonstrate via an example)

- Propose epigenetic fingerprints of life-time exposures (as retrospective biomarkers)

- Epigenetics can contribute in the monitoring of environmental change

Epigenetic responses to stress in plants

Plant development is controlled via epigenetic mechanisms Eg. flowering, sexual reproduction and leaf senescence.

Temperature, salinity, drought etc. all bring about epigenetic stress responses in plants to help them adapt.

Therefore there are positive opportunities to improve stress tolerance and crop yields via epigenetics

Organisms can adapt to stressors in the environment

Kille et al., Soil Biology and Biochemistry 2013

Two lineages of earthworms with arsenic resistance co-existing at metal-contaminated mine sites

A

AFLP analyses showed DNA sequence variations associated with arsenic concentrations,

Suggestive of a major genetic component in adaptation

B

Association of DNA methylation patterns with soil arsenic concentrations

Suggestive of a major epigenetic component in adaptation

Diet and Epigenetics

epigenome.eu

R. Jirtle et al

Agouti mice (yellow; hypomethylated A^{vy} metastable epiallele)

Fed with methionine, folic acid, zinc supplements (increases methylation)

Mice on supplemented diet had darker coats due to increased methylation of A^{vy} gene, and were leaner and healthier

Diet and Epigenetics

The differences in morphology, behaviour and reproductive ability of genetically identical female worker and queen honey bees have been explained by distinct methylation profiles of their brain DNA and subsequent impacts on transcription.

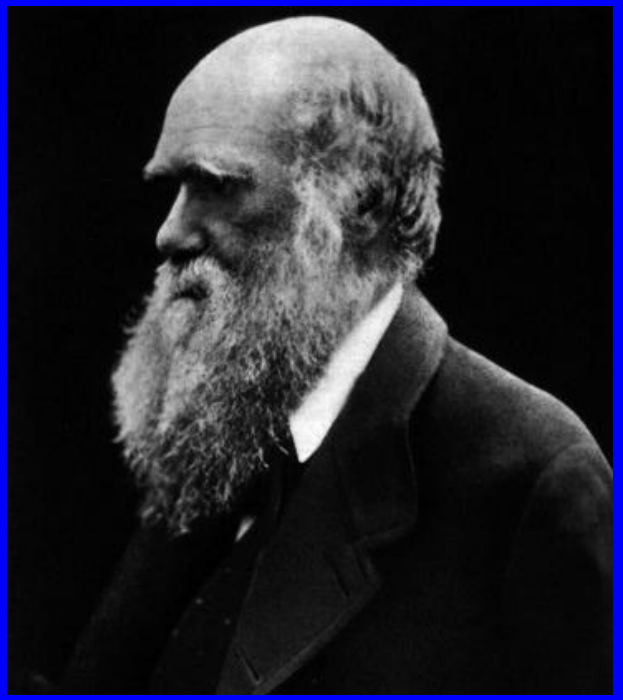
The variation in their methylation profiles has been linked, in part, to their different diets during larval development.

So epigenetic responses in the environment are not necessarily adverse- they can be beneficial, even protective

Jean-Baptiste de Lamarck

Inheritance of Acquired Characteristics

How organisms adapt to stress in the environment

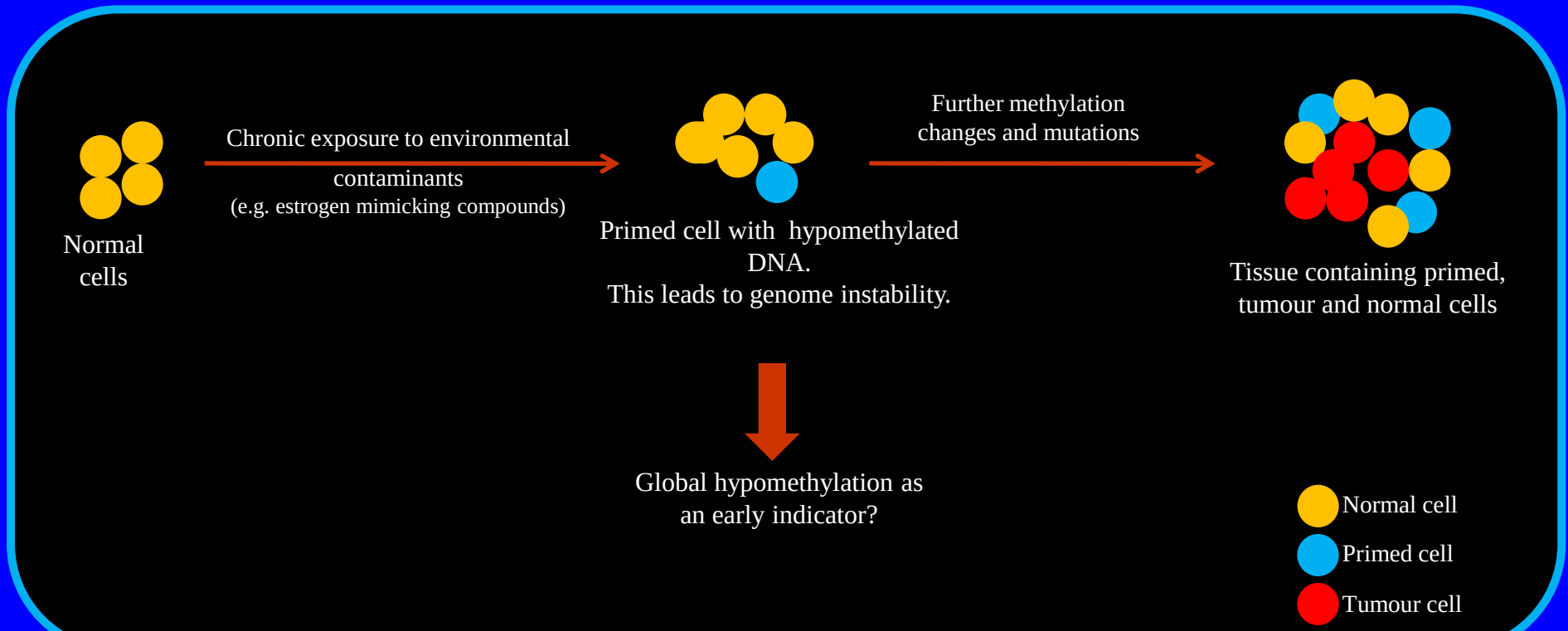


Charles Darwin

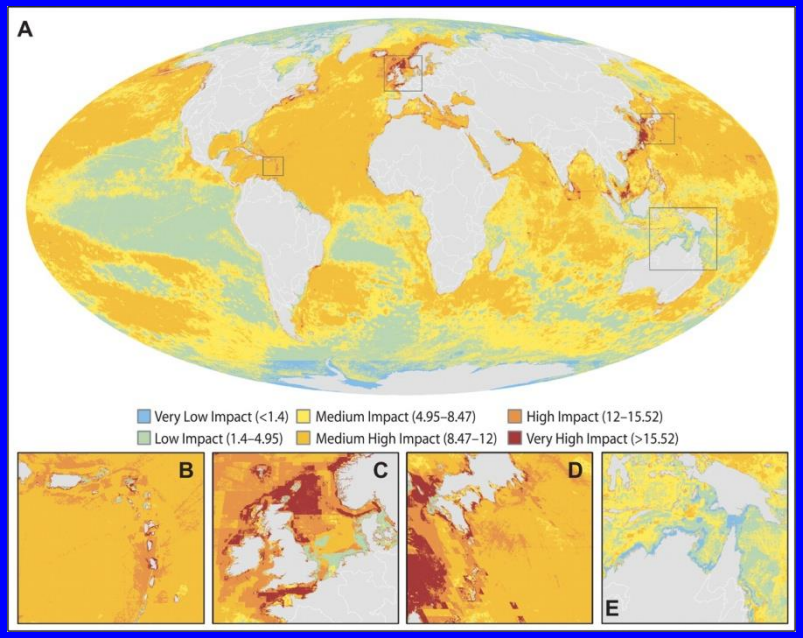
Evolution by Natural Selection

However, in some cases these changes are associated with marked phenotypic endpoints that can be detrimental including delayed onset of disease. Changes during critical windows of embryonic development can be manifested in adulthood and can potentially transfer through generations.

•Eg. the epigenetic progenitor model of cancer. In this model epigenetic changes precede and heighten susceptibility to cancer.



Benjamin S. Halpern et al.
Science 2008:
Vol. 319. pp. 948 - 952



A Global Map of Human Impact on Marine Ecosystems

- **There has been improvement of environmental pollution in many areas but today, attention is turning to subtle effects that may have a long term effect on fitness**

- **Analyses at the molecular level can help**

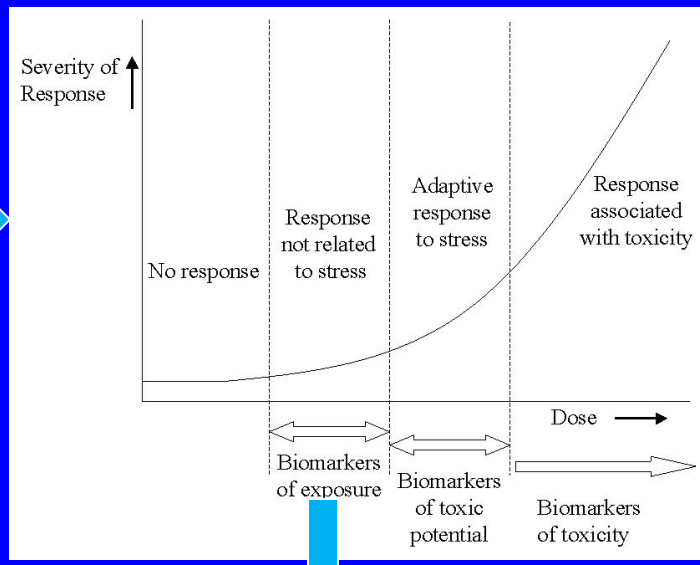
Responses may inform on the Stimuli

ORGANISM

STIMULUS

RESPONSE

In the Environment the stimuli are usually multiple and unknown



Responses may inform on the outcome for the Organism

Responses can be used as Biomarkers of exposure or effect.

Earliest responses are often alterations in concentrations of biological molecules.

Genomics and Epigenomics can play important roles

Epigenetics in Environmental Cancer???

Dab (*Limanda limanda*)

- High cancer prevalence (~20%) Irish sea & North sea
- Molecular basis of tumourigenesis is unclear---is modulation of DNA methylation contributing to changes in gene expression?

Mirbahai *et al. BMC Genomics* 2011, **12**:3
http://www.biomedcentral.com/1471-2164/12/3

BMC Genomics

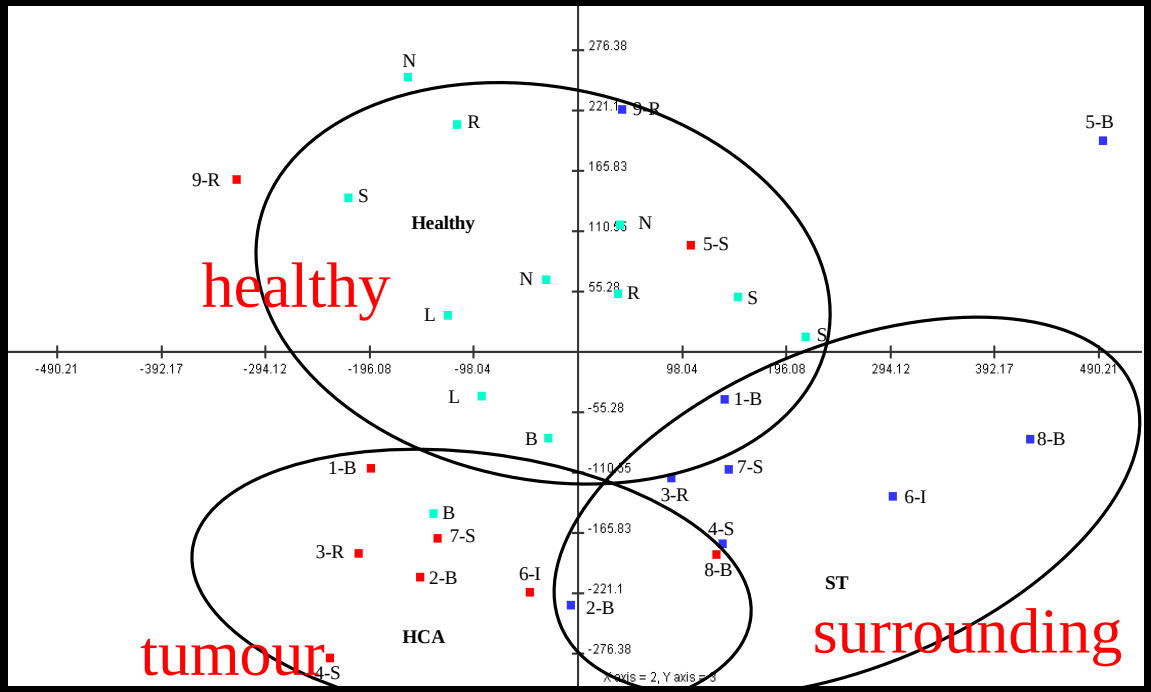
RESEARCH ARTICLE Open Access

Comprehensive profiling of zebrafish hepatic proximal promoter CpG island methylation and its modification during chemical carcinogenesis

Leda Mirbahai[1*], Timothy D Williams[1], Huiqing Zhan[2], Zhiyuan Gong[2], J Kevin Chipman[1]

Adapted a methylation immunoprecipitation and Illumina high throughput sequencing method for this non-model organism

Gene expression from microarray analyses



Key signalling pathways altered in tumour compared to surrounding tissue (FDR<5%)

- Molecular mechanisms of cancer
- Wnt/β-catenin signalling
- Regulation of eIF4 and p70S6K signalling
- Estrogen receptor and estradiols

(e.g. AKT ↑, VTG ↑, c-MYC ↑, HSP90 ↓, CCND2 ↑, MAPK10 ↑)

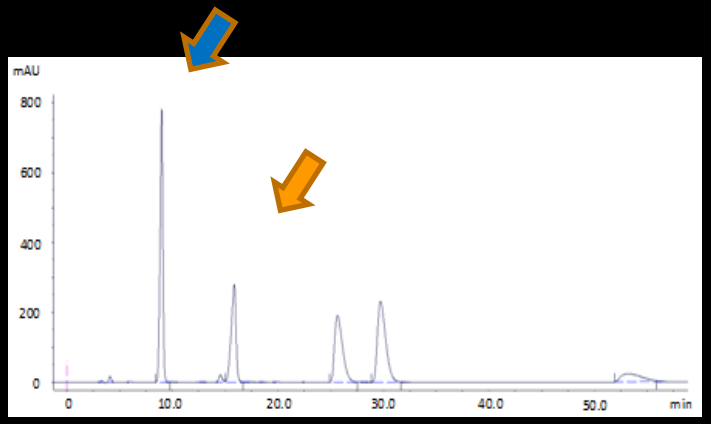
Examples of categories of genes differentially methylated (Tumour versus surrounding tissue)

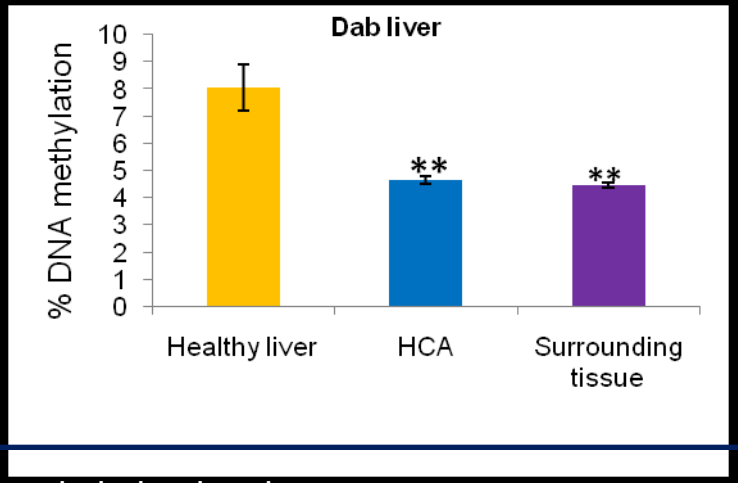
- Cell cycle, proliferation, apoptosis ,cell adhesion and migration
- DNA binding, regulation of transcription
- Methyltransferase activity and histone deacetylation
- Wnt and MAPK kinase pathway
- Inflammatory response
- Decrease in methylation level of oncogenes (e.g. Ras)
- Change in the methylation level of genes involved in methylation pathway

Dab

Three categories of samples

1. HCA (T) **2. Surrounding tissue (ST)** **3. Healthy liver**

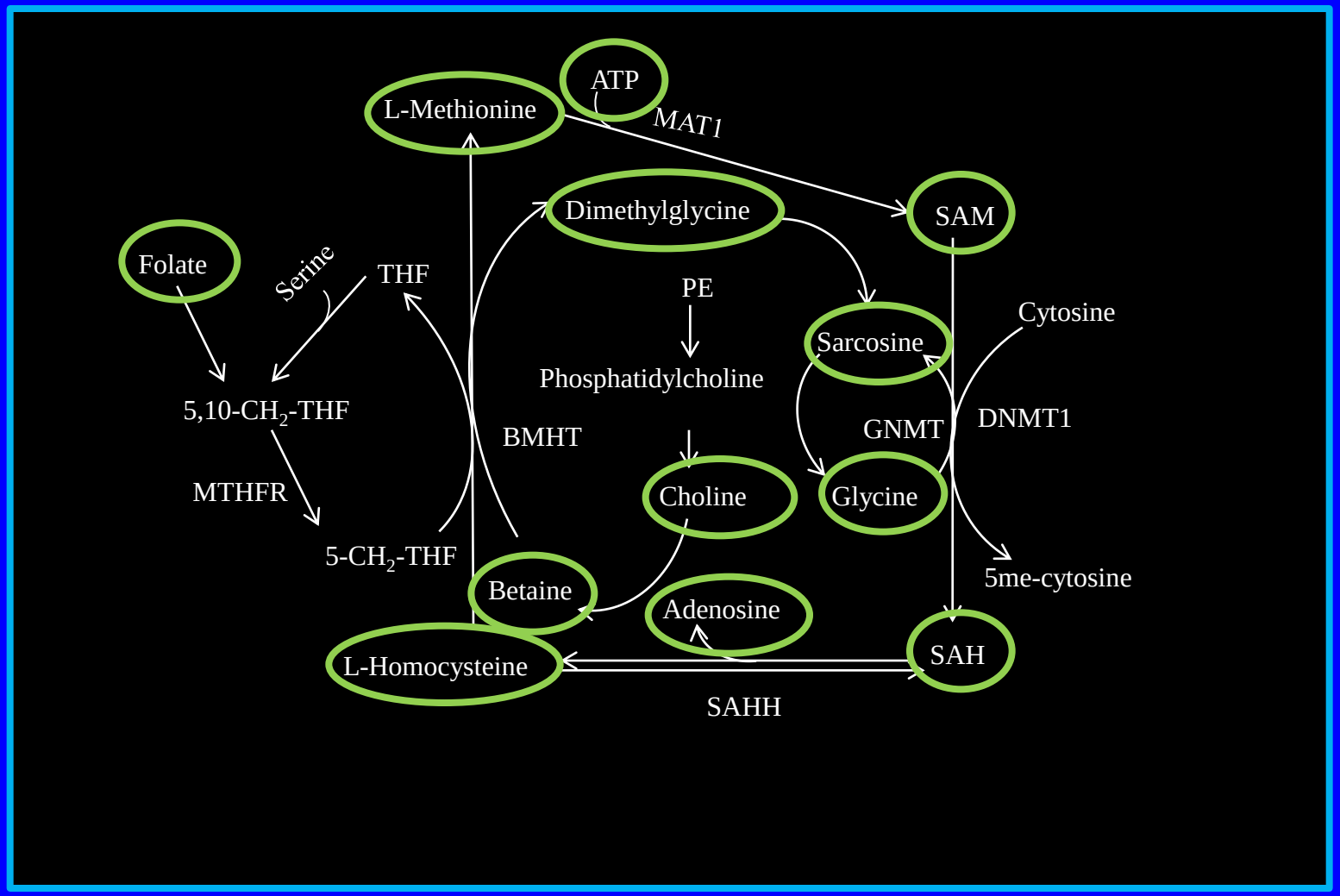




Measurement of global methylation levels using HPLC (n=5, p-value<0.01)

Targeted quantification of metabolites involved in 1-carbon cycle

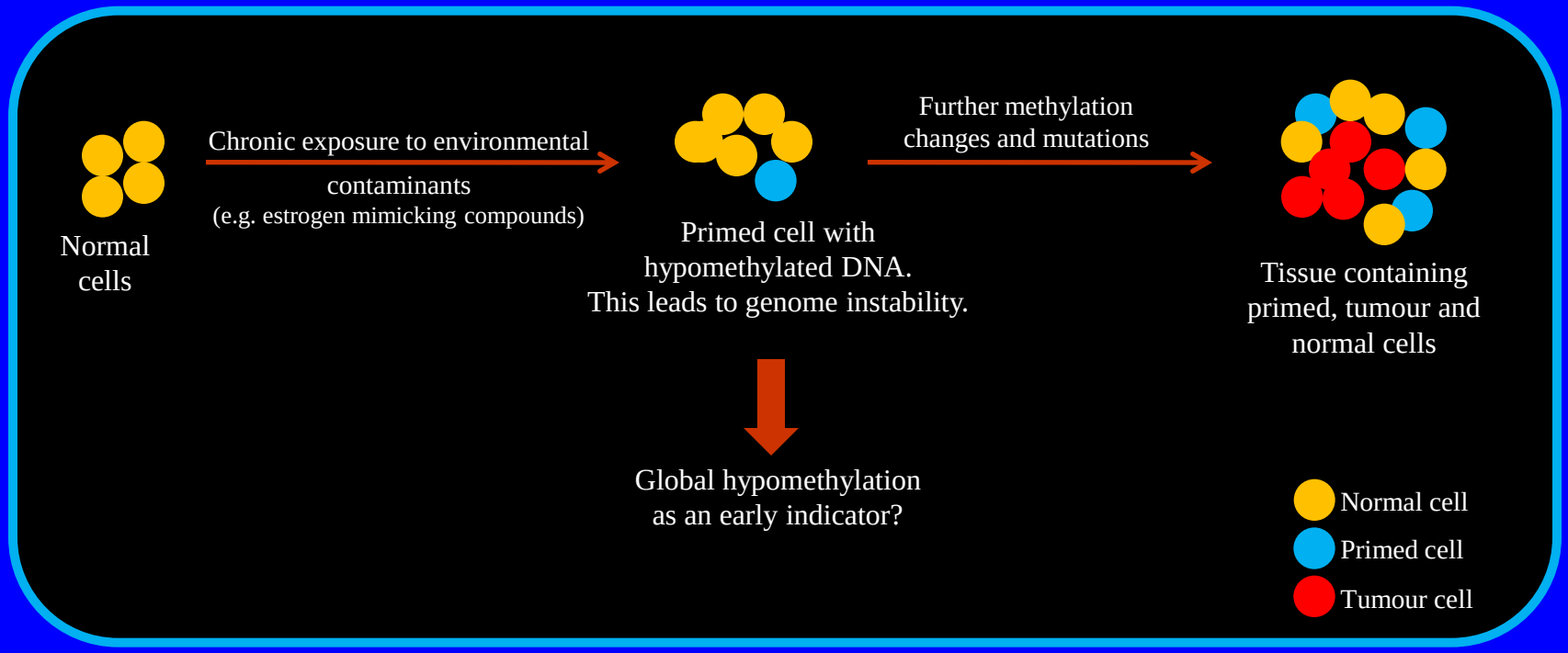
SAH (inhibitory to DNA methyltransferases) is elevated in both ST and tumours



Surrounding tissue hypomethylation:

- One possibility is that surrounding tissue effects are secondary to tumour presence.

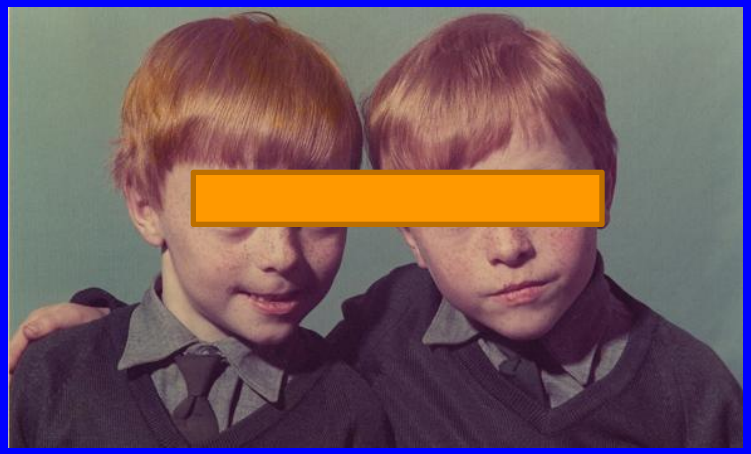
- However, our findings are in accord with the epigenetic progenitor model of cancer. In this model epigenetic changes precede and heighten the risk of susceptibility to cancer.



In relation to risk assessment:

Reflection of exposure to environmental stressors via the epigenome

Epigenetics and Identical Twins



The Times, 7th January 2010

Much greater epigenetic differences at age 50 than at age 3

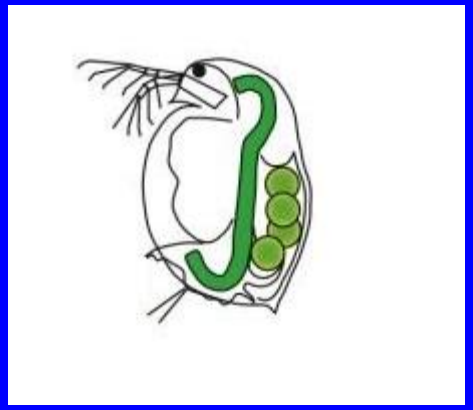
i.e. Epigenetic changes build up over a lifetime –implications for phenotypic differences between monozygotic twins

Fraga, M. F. *et al. Proc. Natl Acad. Sci.* **102**, 10604–10609 (2005)

Can we use changes in the epigenome retrospectively as a "footprint" (MEMORY) of previous exposures in environmental impact assessment in organisms from impacted environments?

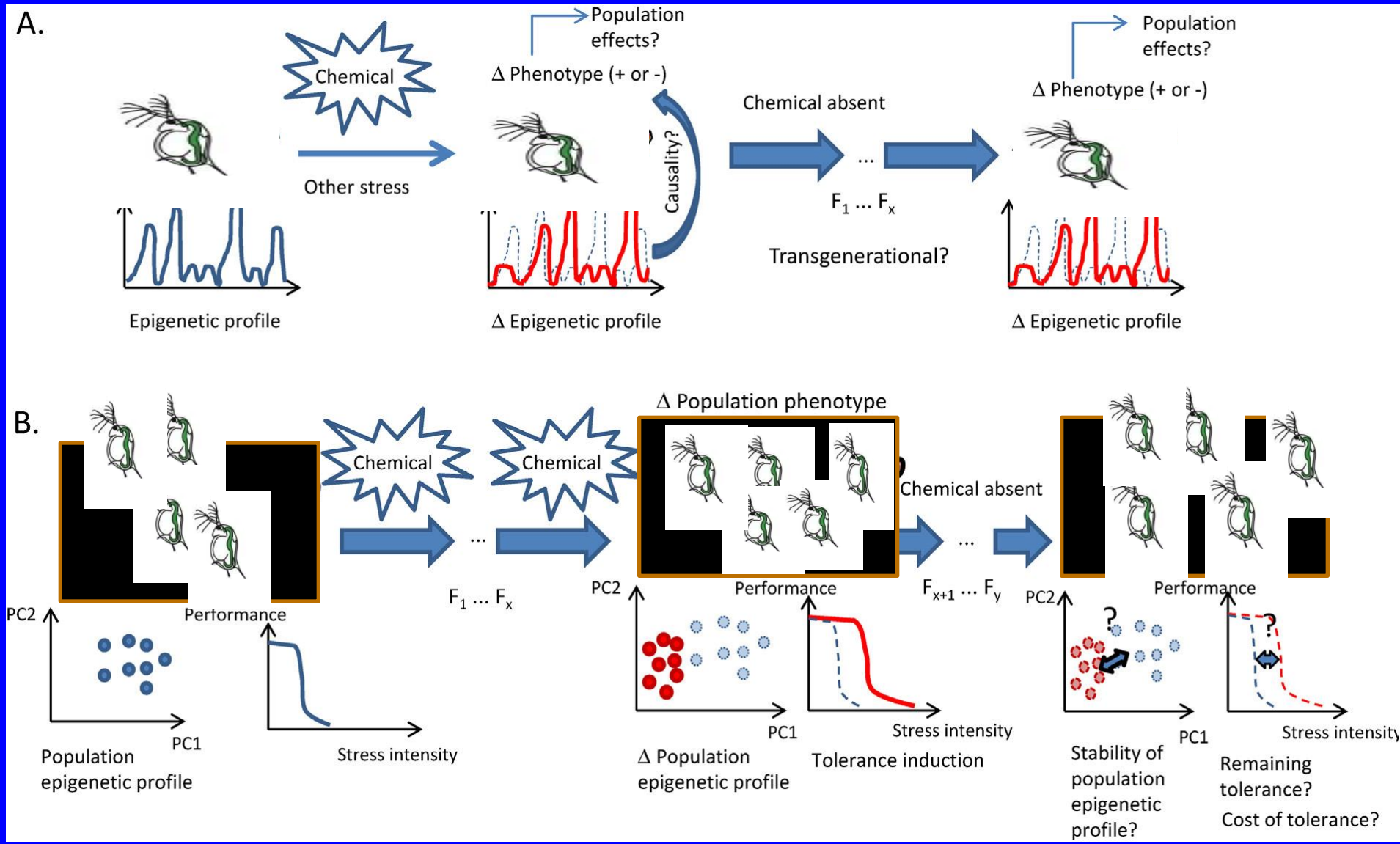
Highlighting opportunities:

- Proposal to use epigenetic changes as a “footprint” of previous exposures contributing to impact assessment in impacted environments



Daphnia is a superb model:

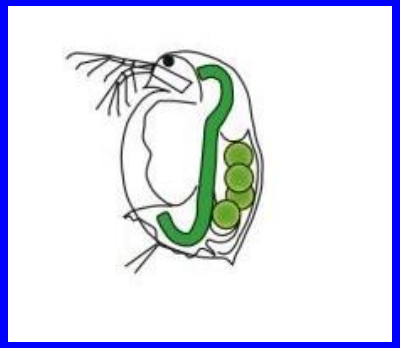
- Can be clonal
- Sexual and asexual reproduction can be controlled
- Used for environmental toxicology
- Resident worldwide in polluted aquatic environment
- Known epigenetic responses to estrogens and metals etc.
- Can be resurrected from historical sediments of different pollution status



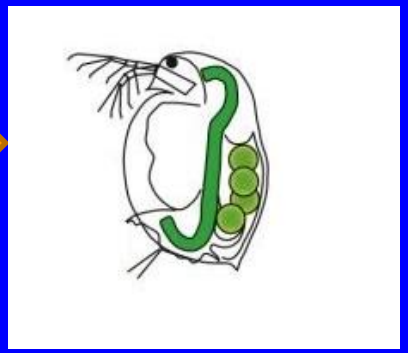
Adapted from Vandegehuchte and Janssen, Mutation Research 2013 And Kille et al., Soil Biology and Biochemistry 2013

Finally.... An exciting opportunity for assessing impact of historical environmental change and stress

Paleoecology (resurrection ecology) may provide a unique opportunity for investigating the role of epigenetic mechanisms in population diversity and adaptation to environmental changes.



Eggs maintained in sediments for hundreds of years (Hairston et al 1995)



CONCLUSIONS

Does the rapidly expanding knowledge of epigenetics and toxicity warrant a major change to risk assessment in the environment ?

We do need to be taking epigenetic responses into account as part of the full picture when assessing the effects of chemicals in the environment

Particular concerns are in delayed onset of disease in populations and in potential transgenerational effects

Epigenetic responses as biomarkers already have a place to play in environmental monitoring (including retrospective exposure assessment).

However, it is premature to propose that epigenetic endpoints can be used in routine risk assessment

Role in risk assessment : Still too many gaps in knowledge

Differentiation between protective adaptive epigenetic changes and adversity

Degree and determinants of reversibility

Site-specificity of epigenetic changes induced by stress

Complexity of multiple DNA and histone modifications

Dependency of potential transgenerational effects on extreme high dose exposures, critical stages of development and species (genetics) (too many studies have claimed transgenerational effects without checking to the level of F3 generation which is essential)

Epigenetics in Dab tumours

University of Birmingham

- Leda Mirbahai
- Kevin Chipman
- Tim Williams
- Mark Viant
- Ulf Sommer
- Adam Hines

Beijing genome institute

- Ning Li
- Ling Li

Cefas

- Brett Lyons
- John Bignell
- Grant Stentiford

NATURAL ENVIRONMENT RESEARCH COUNCIL