

*Nutrient Modulation of Epigenetic
Programming and Reprogramming*

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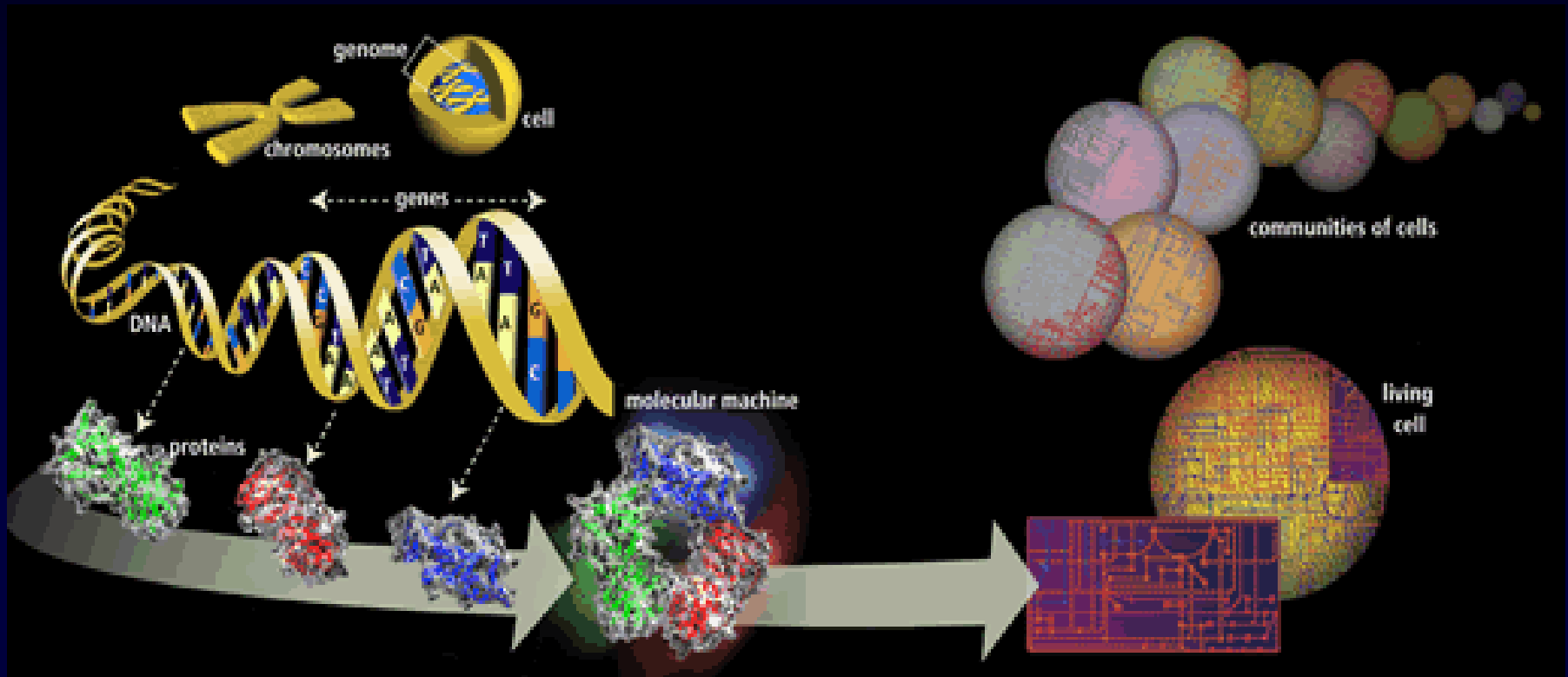
"I expect that in the year 2005 (when the entire human genome is scheduled to be mapped and sequenced), on the back of our foods, there are going to be a lot of things like that, because we are going to know a lot more about ourselves. And I think the field of nutrition, which, in my own opinion now, has not benefited from the advances in molecular genetics, will be a completely different field. That will be the most revolutionized field in the year 2005. And the reason is that we will know lots more, we will actually know something about nutrition so you won't pick up one day and say fat is good for you and the next day fat is bad for you. Because we will know that some people it is good for and some people it is bad for.

"We will be able to know what people can metabolize and what some people can't metabolize.We're going to have a new definition of what it means to be healthy."

<http://www.laskerfoundation.org/rprimers/hgp2.html>

The Human Genome Project: Part Two: Ushering in a new era of molecular medicine
Date of Publication: 1998

Human Genome



http://www.ornl.gov/sci/techresources/Human_Genome/home.shtml

- Assemble & understand cellular networks
- Manipulate cellular networks for benefit
 - Pharmaceuticals & Nutrients
- Capacity to sense and adapt to environment



David Barker

Fetal Origins of Adult Disease or “Barker” Hypothesis

(1986)

Fetal environmental exposures, especially nutrition, act in early life to program risk for adult health outcomes



Genome-Nutrient Interactions in Programming

Chromatin Modification

- Methylation
DNA & Histones
- Acetylation
Histones
- ADP Ribosylation
Histones
- Biotinylation
Histones



Gene Targeting
Signal Strength
Signaling event

Chromatin
Chemical modification
Reversible & (meta)stable?

Nutrients/metabolism

Critical window
Gene Expression → *Genome Programming*
Transient *persistent*

Nutrition, Metabolism Methylation & Epigenetic Modifications

- Does the genome *sense* metabolism/nutrition and *buffer* networks through chromatin modifications?
- Does genetic variation at the level of “*nutrient sensing*” influence epigenetic programming ?
Is there a genetic component to the epigenetic response?
- Do nutrients affect epigenetic responses within the physiological or pharmacological range?

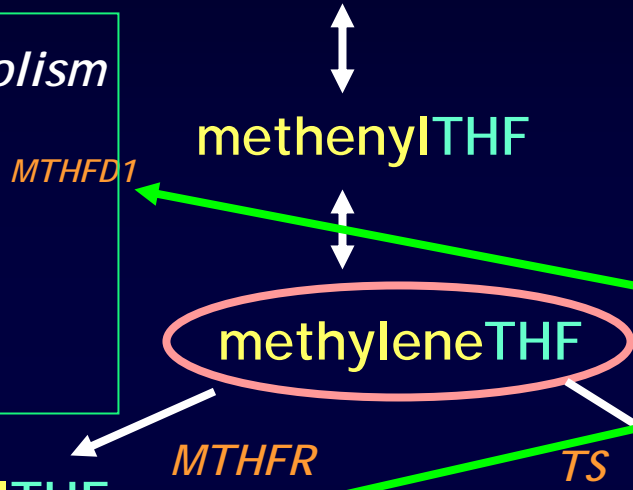
One-Carbon Metabolism

Herbig et al. (2002) J. Biol. Chem. 277; 38381-38389

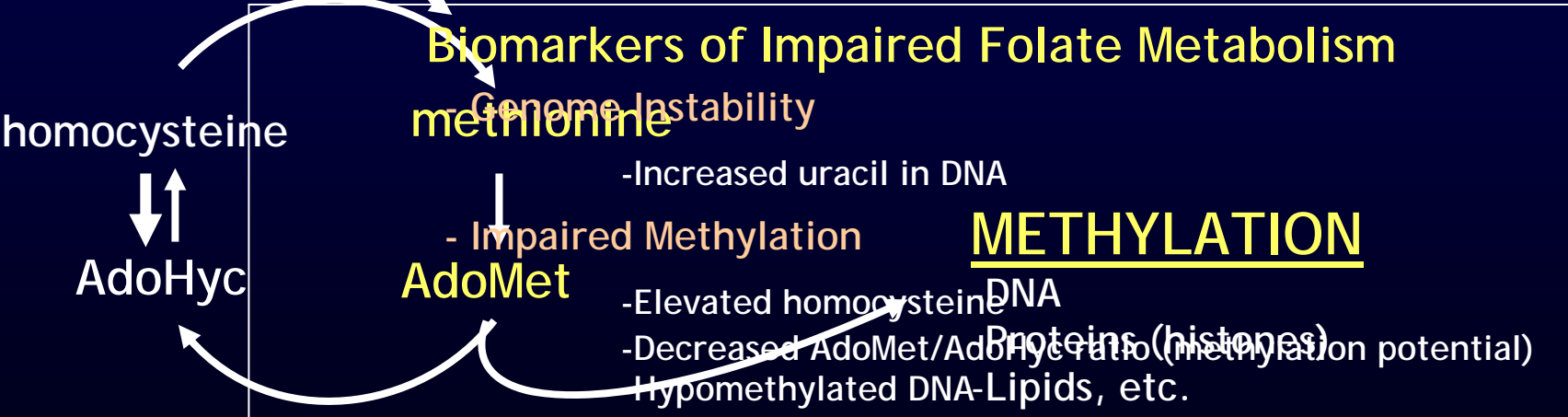
(tetrahydrofolate)



Impaired Folate Metabolism
 Increased risk for :
 - Vitamin deficiencies
 - Developmental anomalies (NTDs)
 - Cancer
 - CVD
 - B6, etc
 - Neurodegenerative/cognitive
 - SNPs ..



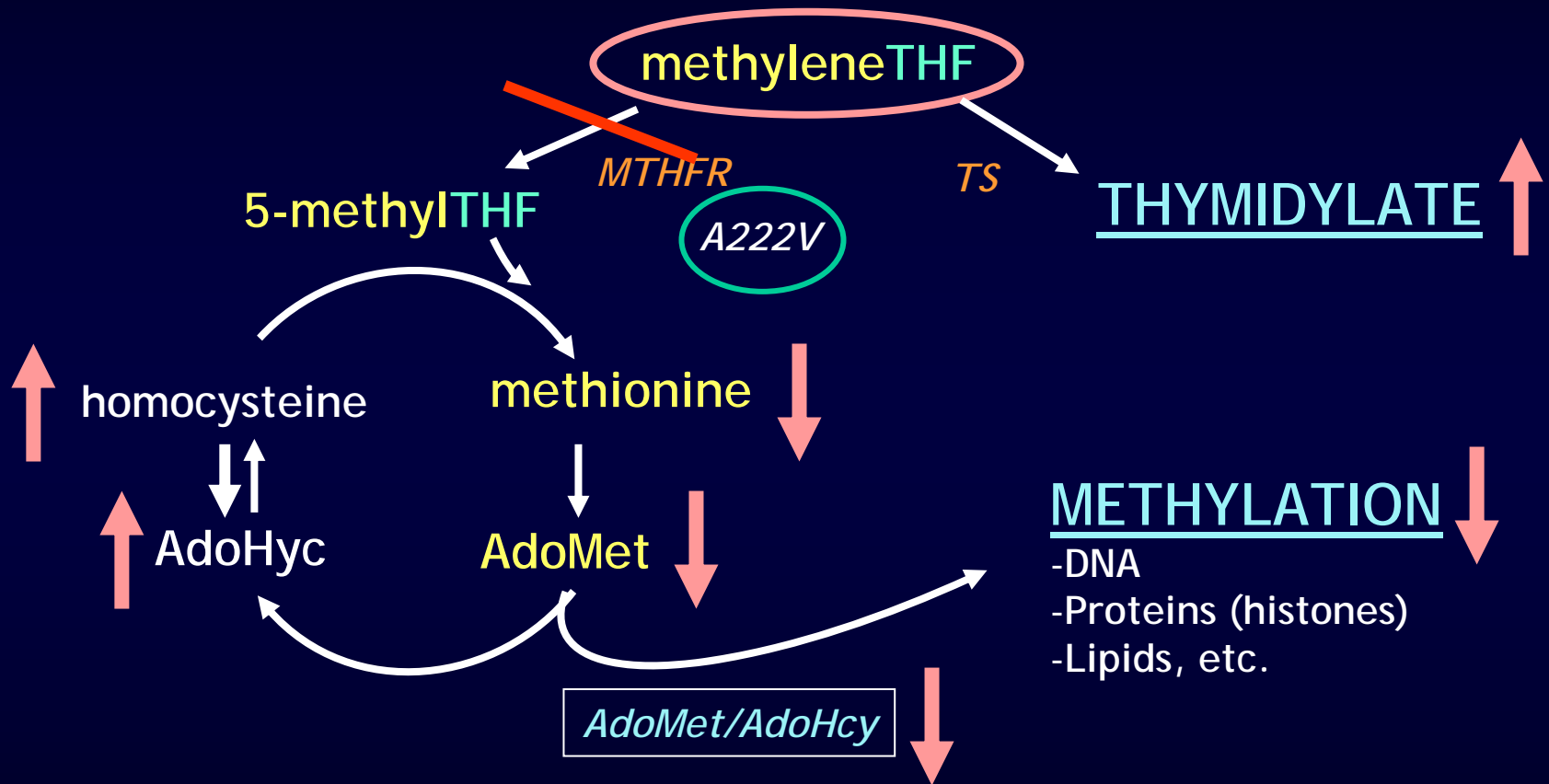
SNPs
 - NTDs
 - miscarriage



One-Carbon Metabolism

Herbig et al. (2002) *J. Biol. Chem.* 277; 38381-38389

MTHFR mutations/SNPs affect genome stability and methylation capacity



Benefit and Risks of MTHFR Polymorphism

COMMON Allele

Gene sequence ..GCG GGA GCC GAT ...

Protein Sequence .. Ala Gly Ala ASP...

677 C -> T Allele

Gene Sequence ..GCG GGA GTC GAT...

Protein Sequence ...Ala Gly Val Asp ...

In utero Risk

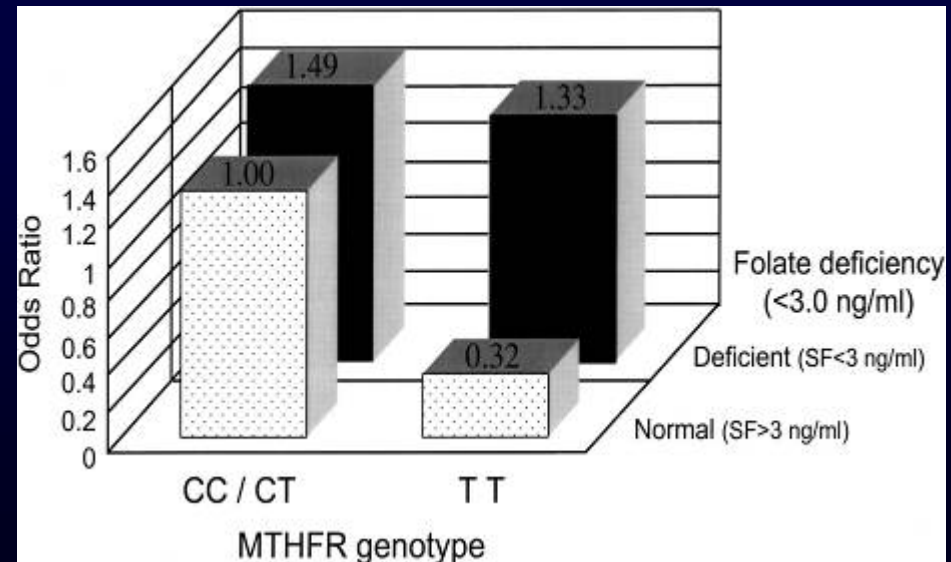
"T" allele
(A222V)

- NTDs
 - In humans, (not in mice)
- Spontaneous abortion
 - Not in HW equilibrium

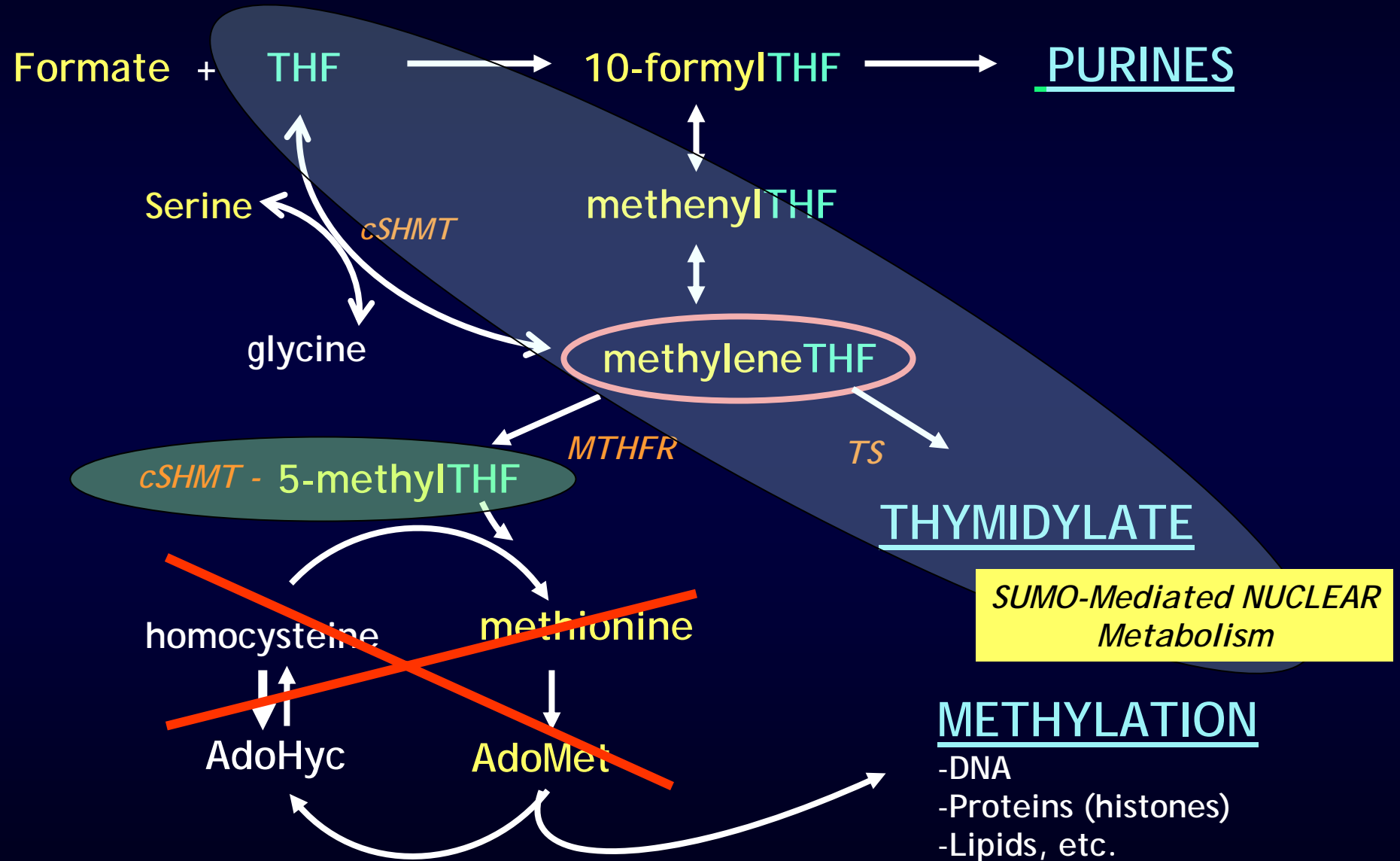
Adult Benefit

"T" allele

- **Physician's Health Study** –
Colon Cancer Risk

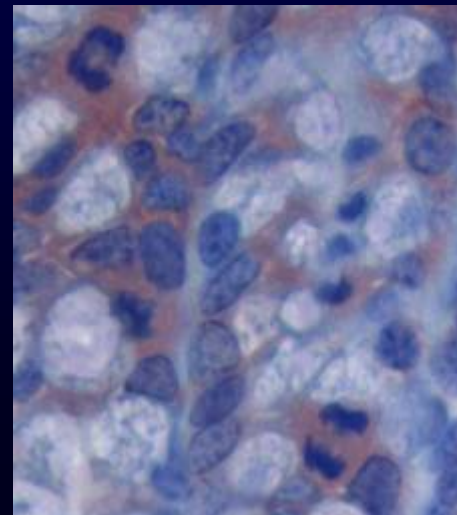
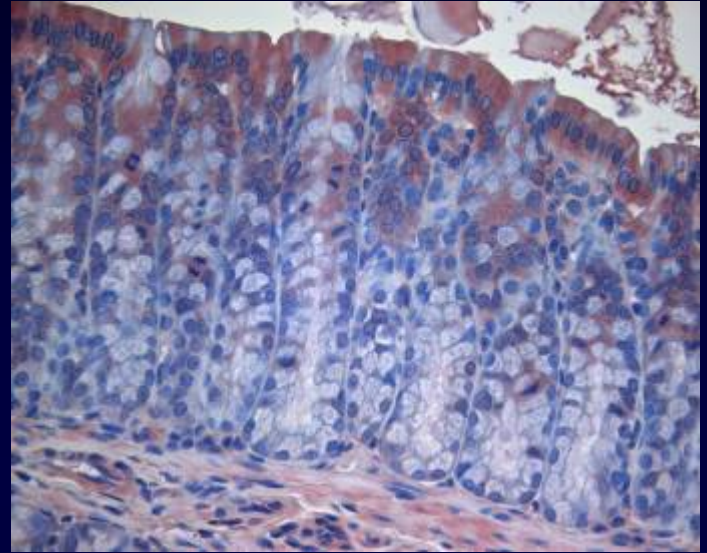
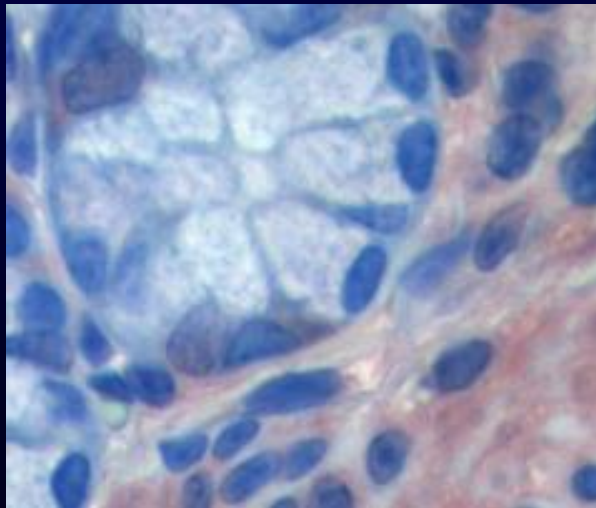
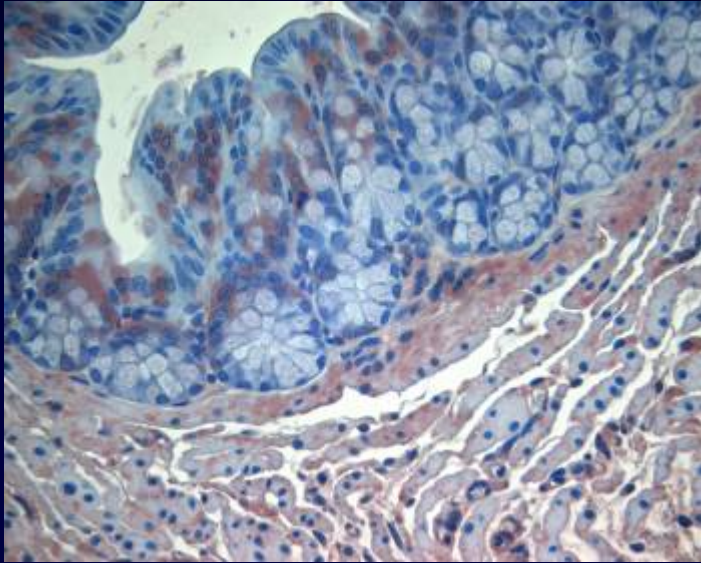


cSHMT and One-Carbon Metabolism

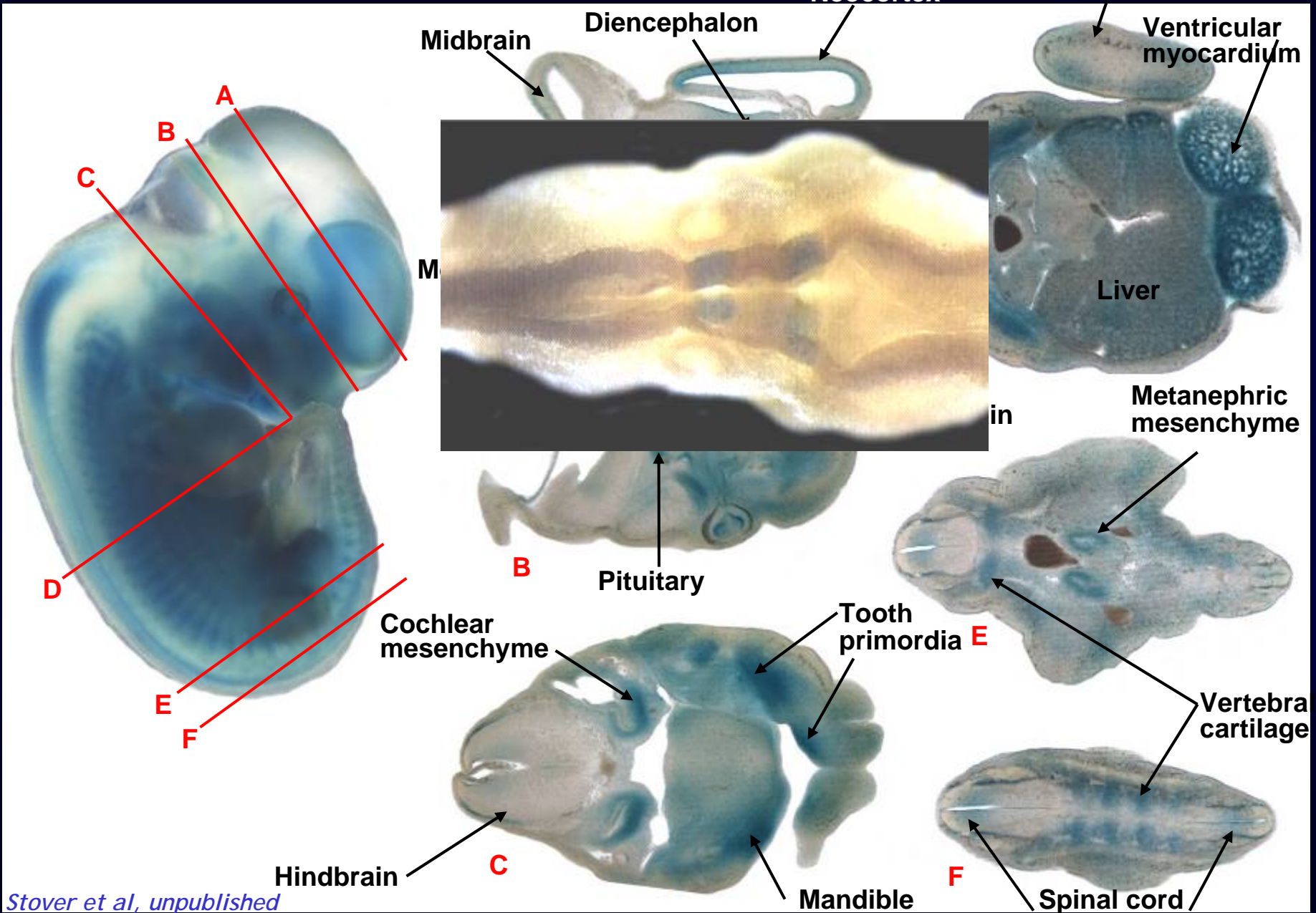


Nuclear & Cytoplasmic Localization of cSHMT

1:500 sheep anti-cSHMT 400X



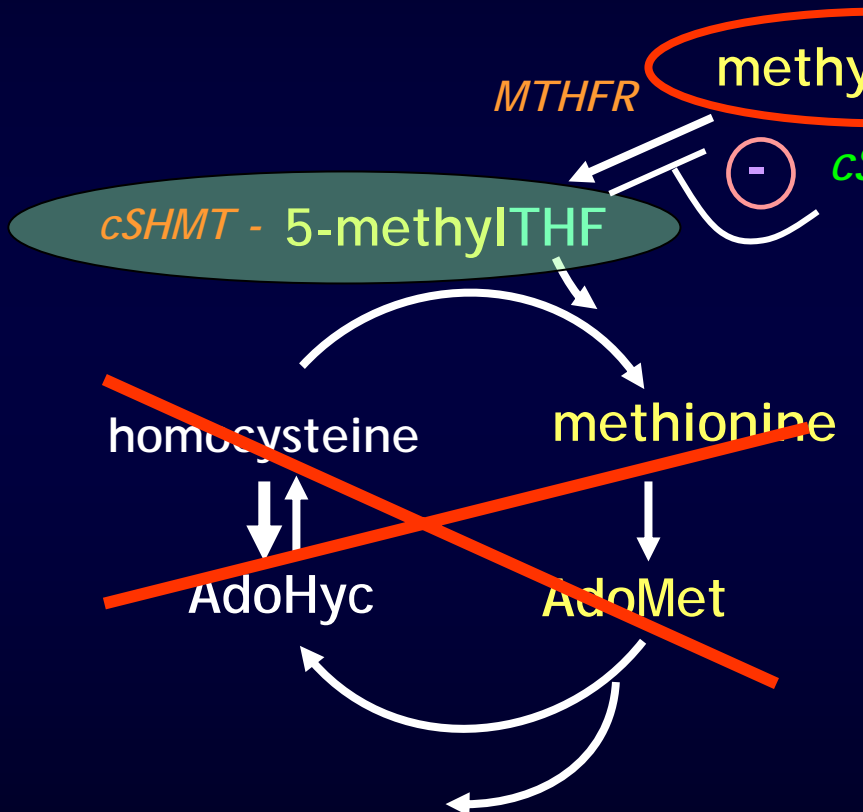
cSHMT Expression - 11.5 day embryo



- Regulates the Partitioning between Genome Synthesis and Methylation -
- Capacity to Buffer Methylation Potential-

5-methylTHF sequestration

Nuclear import



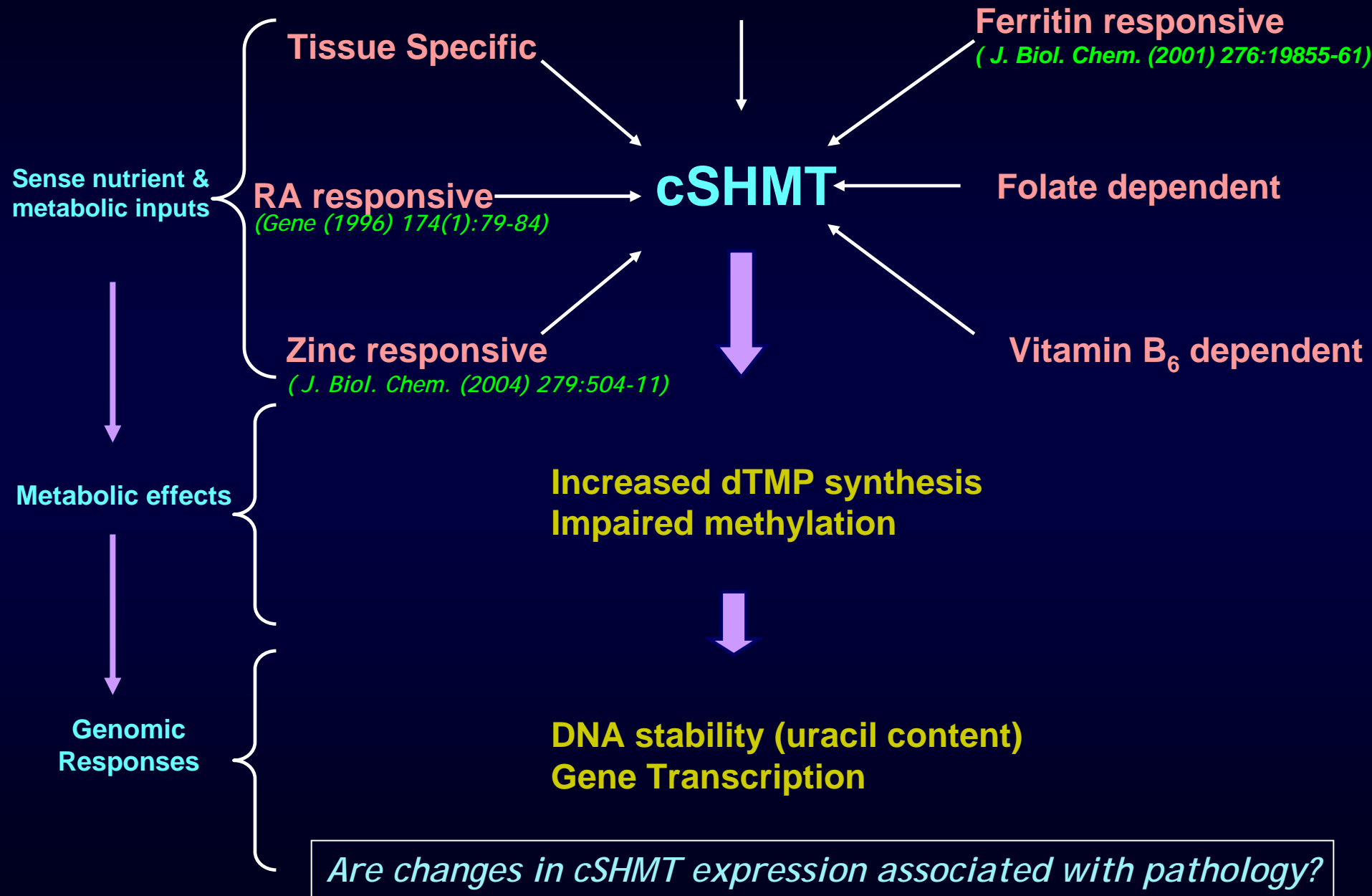
Strain	AdoMet (pmoles/u g protein)	AdoHyc	<u>AdoMet</u> / <u>AdoHyc</u>
Balb/c	0.6 +/- .16	2.9 +/- .9	0.22
129	0.4 +/- .17	3.3 +/- .8	0.11
SHMT -/-	3.4 +/- .30	2.1 +/- .8	1.6

METHYLATION

- DNA
- Proteins (histones)
- Lipids, etc.

Is SHMT a nutrient "sensor" and metabolic programmer?

Developmental Regulation



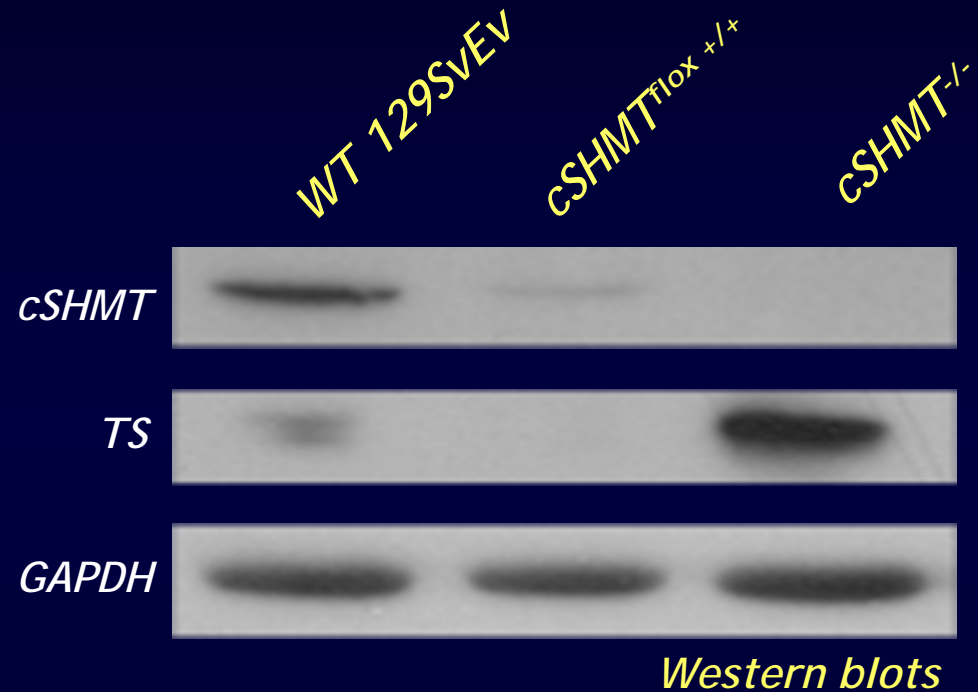
cSHMT Deletion Induces:

- NTDs
- Programming of thymidylate synthesis

10.5 d.p.c.



cSHMT +/-



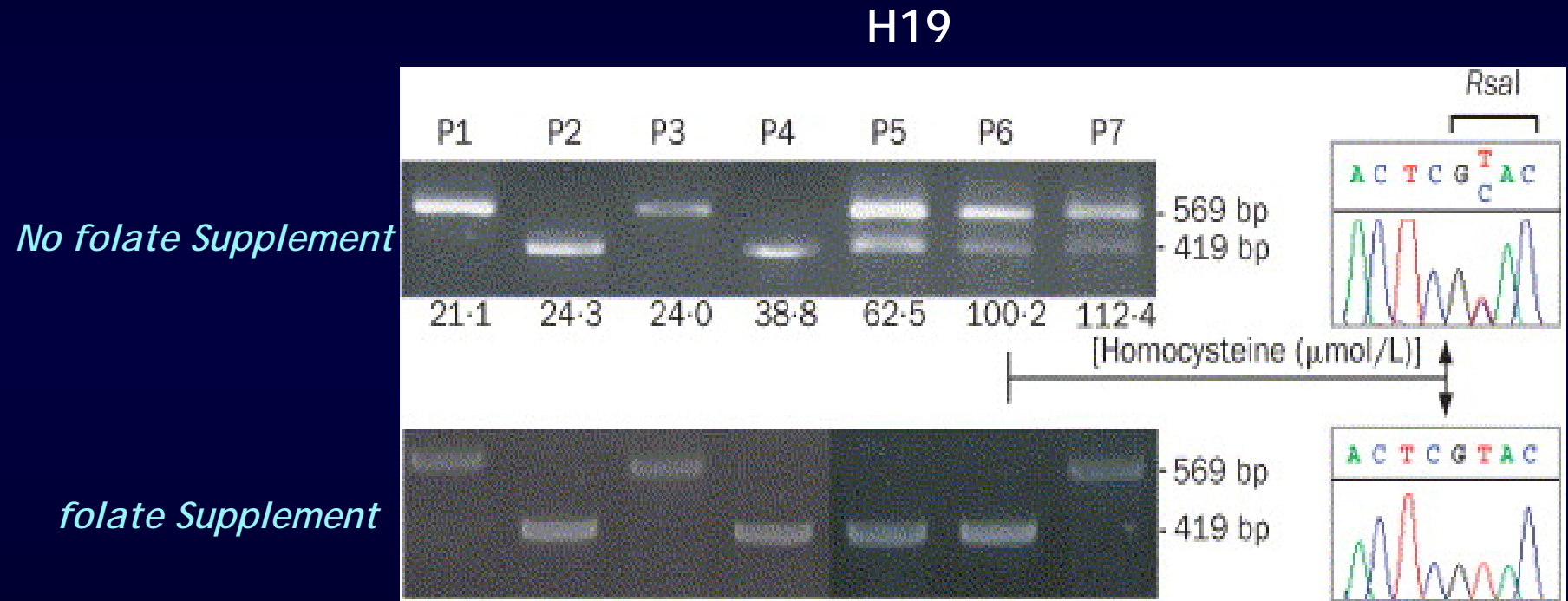
- Only *cSHMT +/-* exhibit NTDs
- *cSHMT -/-* display elevated *TS*
 - *TS Programming*

Nutrition, Metabolism Methylation & Epigenetic Modifications

- Does the genome *sense* metabolism/nutrition and *buffer* networks through chromatin modifications?
- Does genetic variation at the level of “nutrient sensing” influence epigenetic responses?
Is there a genetic component to the epigenetic response?
- Can diet affect epigenetic buffering and/or programming responses within the physiological or pharmacological range?

Can folate affect imprinted (programmed) gene expression?

Uremia and Hyperhomocysteinemia *Loss of H19 and SYBL1 Imprinting*



Lancet. 2003 May 17;361(9370):1693-9.

Can folate (program) gene expression?

Conclusions:

- Nutrition can program gene expression within critical developmental windows
- Programming persists into adulthood in the absence of dietary intervention; may be heritable



gestation leads to increased embryonic IAP methylation and the pseudoagouti phenotype

Nat Genet. 1999 23:314

J Nutr. 2002 132:2393S

Mol Cell Biol 2003 23:5293

Envir Health Perspect. 2006 114:567

Can folate-induced epigenetic changes compensate for genetic lesions?

“Nutritional Embryo Rescue”

“Good Diet Hides Genetic Mutations”

- Validated in mouse models

Humans?

MTHFR, TCII, MTHFD1 SNPs are not in HW Equilibrium and/or are risk factors for miscarriage

The use of supplemental folate has been suggested to reduce rates of human spontaneous abortion.

(Reprod. Biol. Endocrin. (2004) 2:7)

Consequences?

Dependency?

Good Diet Hides Genetic Mutations

After Claudia Kappen moved from the University of Arizona in Tucson to the University of Nebraska Medical Center in Omaha 2 years ago, she couldn't figure out why the mice she was studying were suddenly

chloroplast genes in multicellular animals and dinoflagellates.” If so, that would be a real eye-opener.

the mice she was studying were suddenly much healthier. A developmental biologist, she was interested in skeletal diseases and had bred a strain of transgenic mice whose bones were so fragile that the rib cage couldn't withstand breathing and the animals died soon after birth. But in Nebraska, their skeletons were much stronger.

In her quest to understand the animals' newfound vigor, Kappen and her colleagues have demonstrated again that diet can protect against some genetic diseases: She reported at the meeting that folate, part of the vitamin B complex, compensates for an overactive gene involved in cartilage formation.

The study suggests a way that mutations could build up in a population, says Nipam Patel, an evo-devo researcher at the University of Chicago. If good nutrition can mask harmful genetic changes, mutations might accumulate un-

gist at the University of Texas Cancer Center in Houston have shown that folate can correct tube defects such as the spina bifida in humans, but it

Kappen and her colleagues the mice were chewing on the corn cobs—a nutrient source in the Arizona lab. On a hunch, she decided to see if folate was the



Science vol 296 page 1011

Gehring wants to isolate... changing the animals'... Mutation masks: folate can help mu... the mo

Nutrition and Epigenetic Programming

Opportunities for Research:

- Emerging area - Lots of descriptive work, mechanistic work is emerging
- Interactions among genes, gene variants and nutrition are dynamic and not yet predictable.
 - Nutrient modulation of epigenetics/genome programming
 - Critical windows, nutrient levels, long-term risks & benefits associated with nutritional intervention



Graduate Field of Nutritional Sciences
Graduate Field of Biochemistry, Molecular and Cellular Biology

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NIH/NICHD R01-HD35687

NIH/NIDDK R01-DK58144

NIH/NCI R01-CA105440