Stem cells, tissue turnover and low doses

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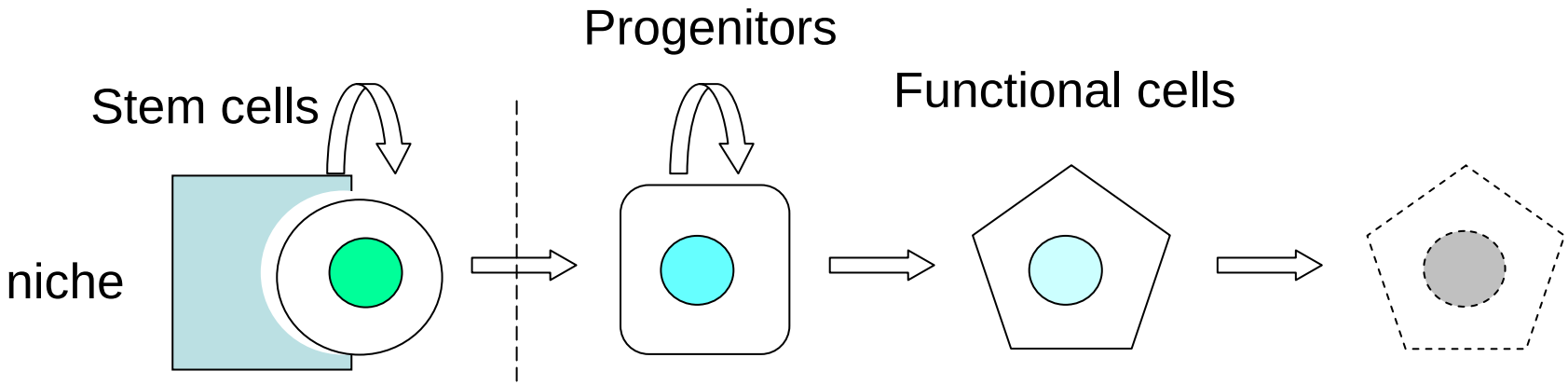
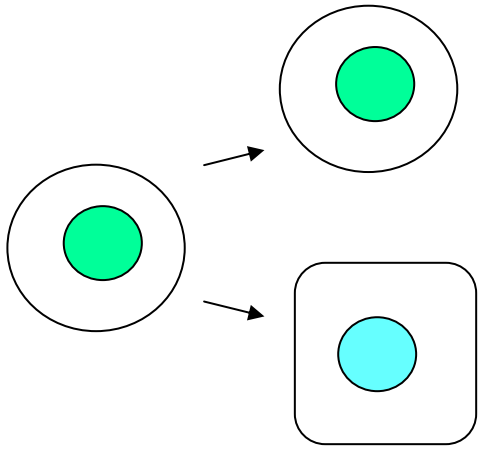
Stem cells and tissue turnover: two levels of the determinant for low dose/dose rate carcinogenesis risk

Adult stem cells: the determinant of dose response

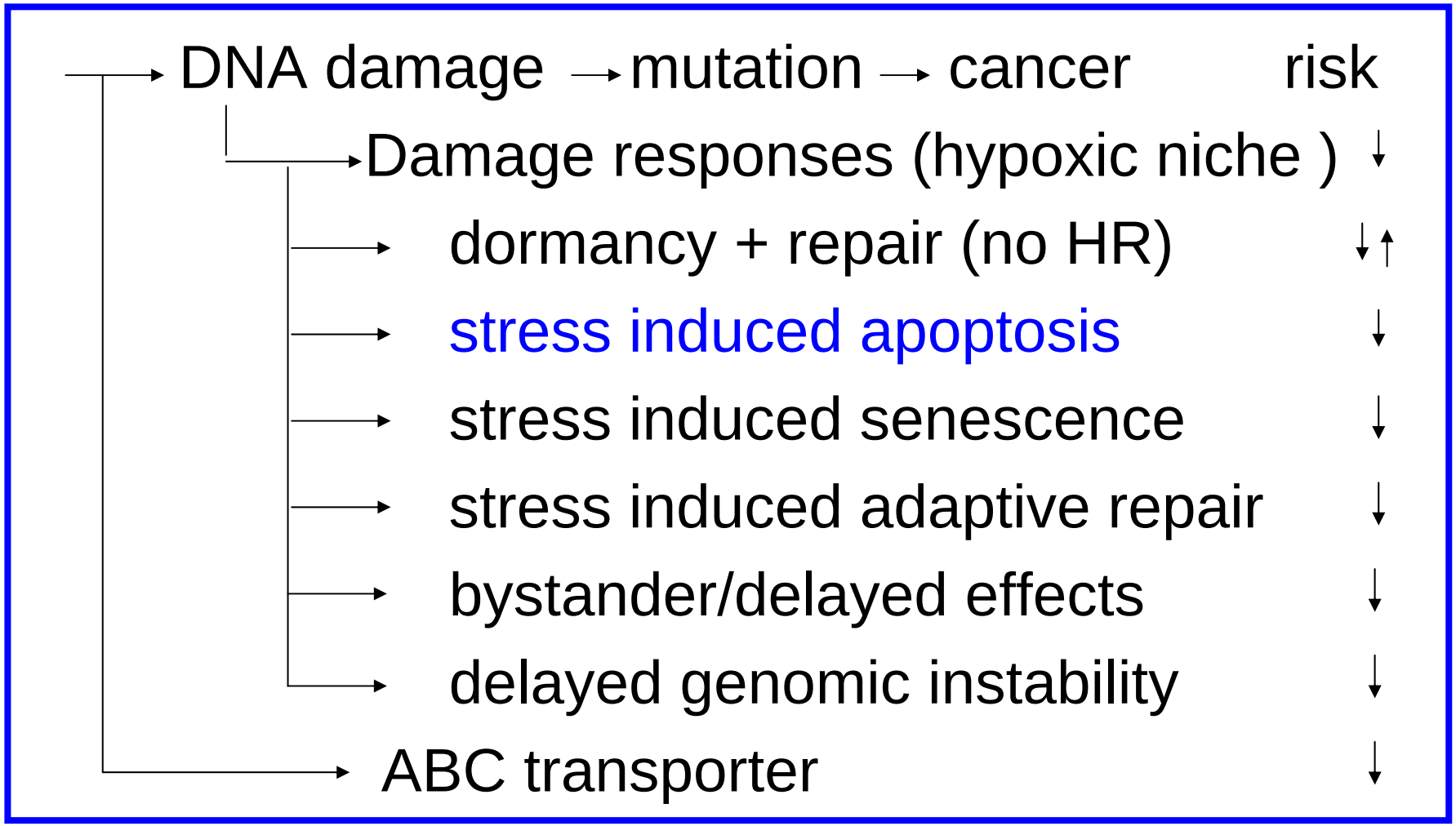




Characteristics of stem cells

- asymmetric division
- asymmetric segregation of DNA?
- mortal with limited division capacity
- reside in hypoxic niche
- dormant, sometime with high p21
- radioresistant or radiosensitive

Stem cell response determines risk development

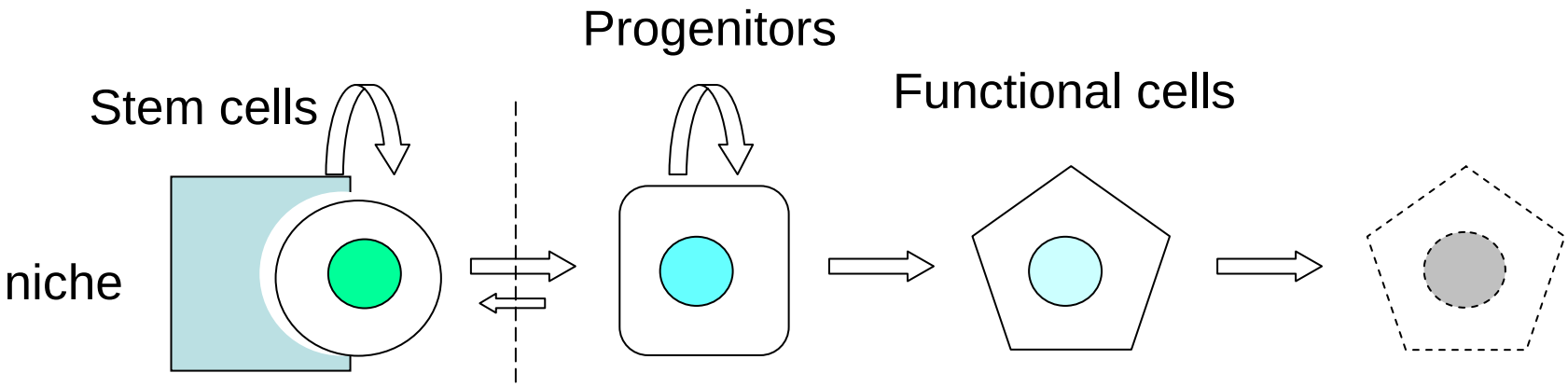


What dose response stem cells exhibit?

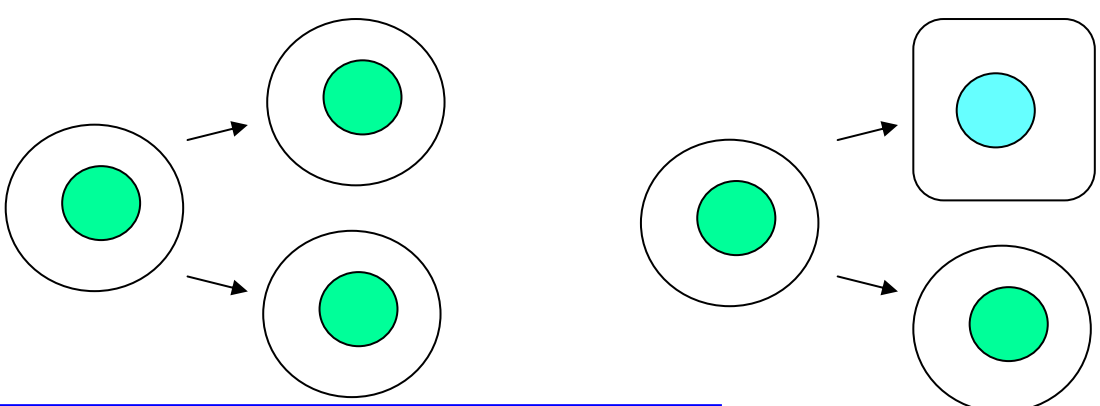
Conclusions from the chemical carcinogen field

- Xenobiotic-metabolizing EHs are α/β hydrolase fold enzymes working with a catalytic triad
- The first step of enzymatic epoxide hydrolysis is optimized for speed, allowing efficient detoxification with broad substrate specificity
- Experimental verification showed that this high speed detoxication introduces a practical threshold of genotoxicity, at least for the epoxides investigated

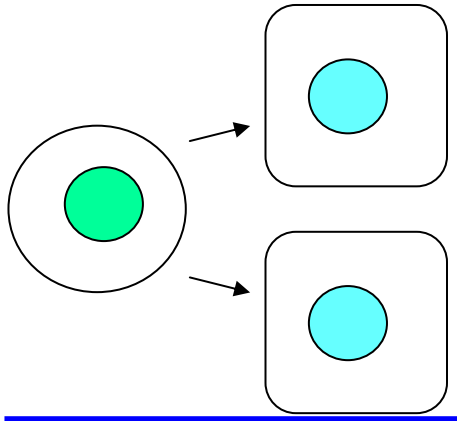
Tissue turnover: another level of dose response



Three scenarios of stem cell divisions



Stem cell competition



Stem cell loss

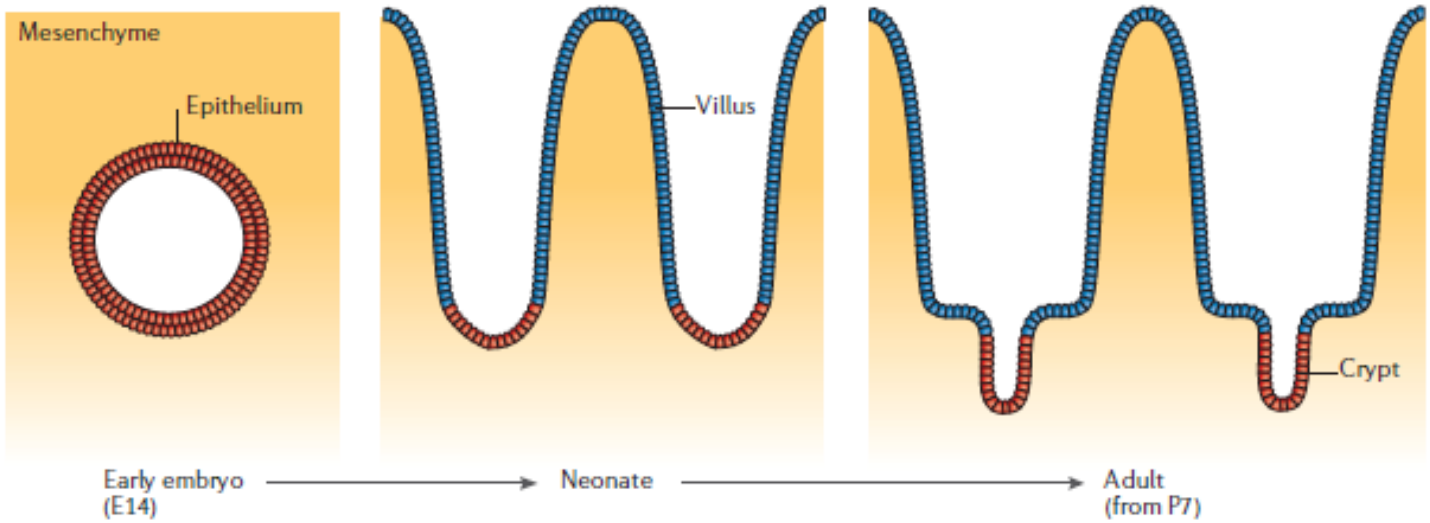
Tissue level system to eliminate damaged/mutated cells

Stem cell competition seems to be stronger during fetal to neonatal stages than in adult

A key to the radiation risk of fetal stage exposures?

Stem cell competition during neonate

Embryos/fetus → After birth



Stem cells compete for the niche

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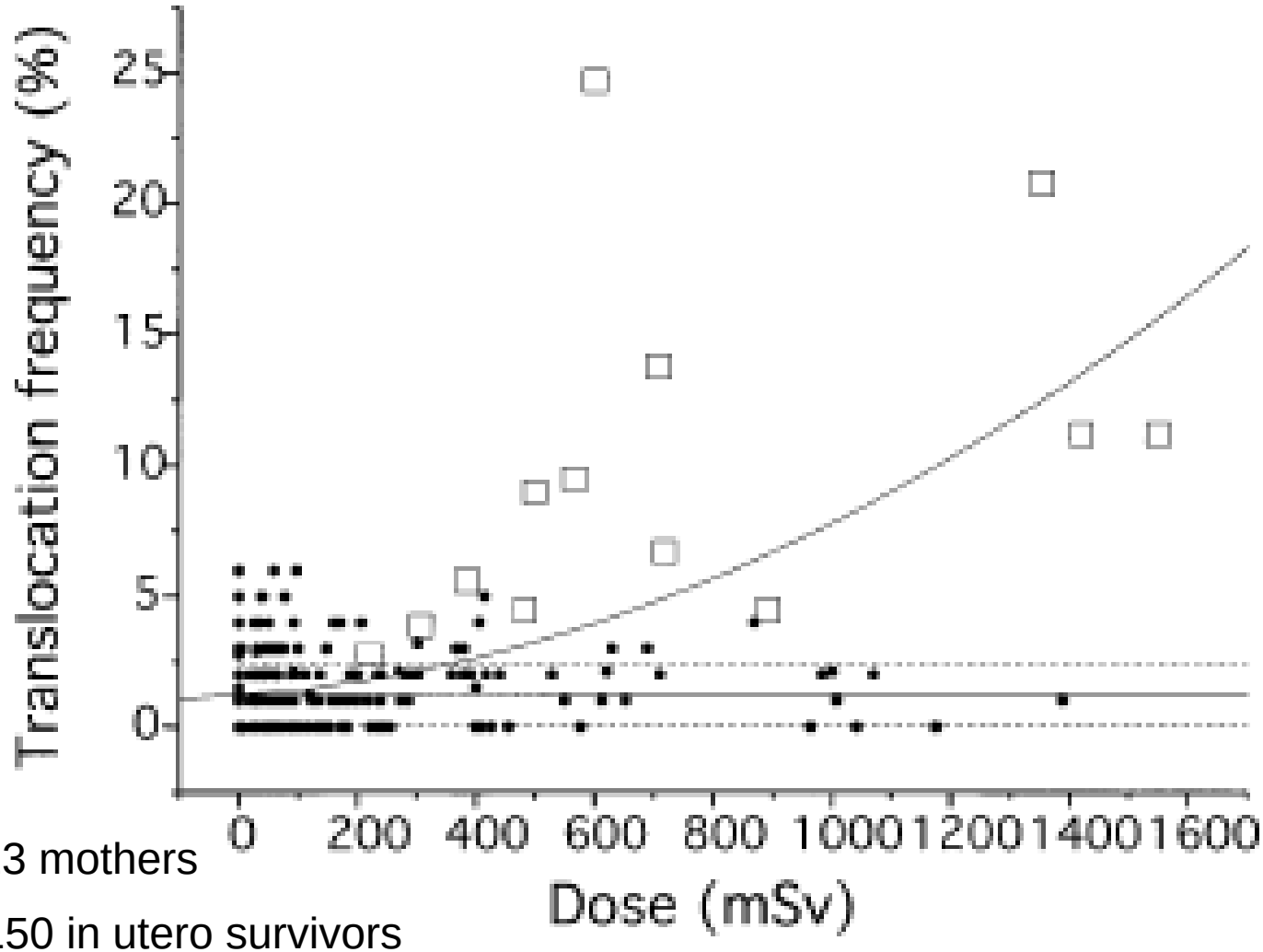
Elimination of damaged stem cells

Fetal exposure less risky than childhood exposure?

The loss of mutated cells does occur
Fetal exposures lack chromosome mutations



□ 13 mothers

● 150 in utero survivors

—— 181 survivors

Ohtaki et al. Rad. Res. 161, 373, 2004

From the discussion session
- seneral points -

1. Stem cells and tissue turnover as major determinants of low dose/dose rate radiation risk development.
2. Stem cells and tissue turnover differ between tissues.
3. Need to know more about radiobiology of stem cells before we share the understanding of their importance.

4. Need dialogues to share concepts
5. Need more sharing of resources and technologies, within the field, and between the fields.
6. Collaborations between groups strongly recommended.
7. To these ends, implementation of systems to exchange information are helpful.
8. For the above needs, selecting a key personnel/institution would facilitate the progress of this new field.

From the discussion session- specific points -

1. Consideration be given to research on tissue response as opposed to cell response.
2. Consider the relevance/importance tissue turnover and hierarchy, especially for their roles in elimination of irradiated stem cells.
3. Generalization must not be made: stem cells of specific tissue, blood stem to be hyper sensitive vs skin stem cells to be hyper resistant
4. Need to understand varying radiosensitivity of different tissue stem cells.
5. Consideration on apparent lower detrimental effects exhibited in fetus than mother.
6. Development of stem cells and stem cell niche need to be elucidated.
7. Should have parallel stem cell research models for mouse and human.
8. Importance of establishing iPS bank of genetically predisposed/ diseased individuals, and importance of sharing specific mouse strains.
9. Need of a tracking system of initial damaged cells all the way to cancer formation to confirm causal relation of radiation carcinogenesis.