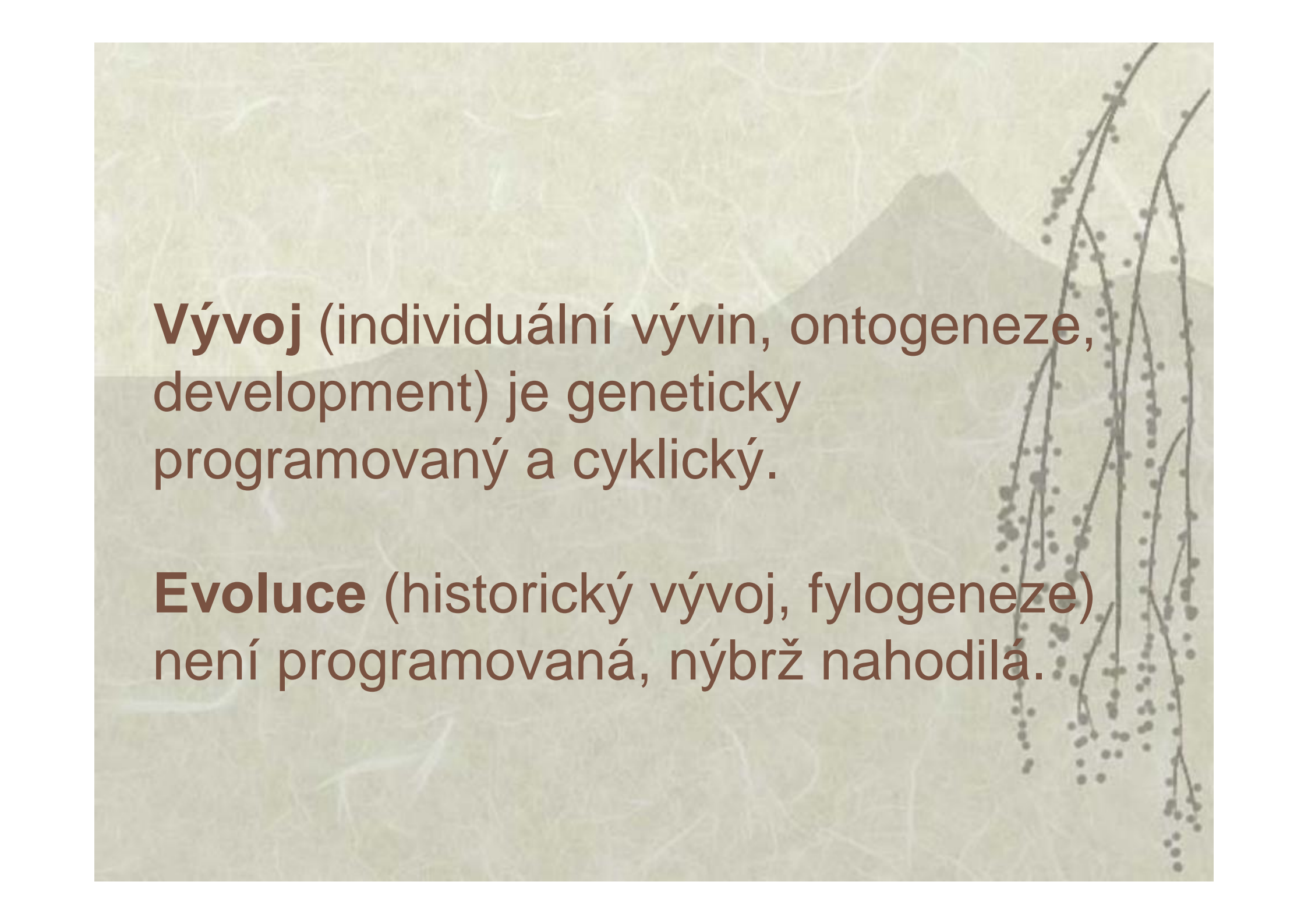
The background features a stylized, muted-toned illustration of a mountain range on the left and a willow tree with drooping branches on the right. The overall aesthetic is soft and naturalistic, with a light beige or tan color palette.

Vztah
evoluce a ontogeneze

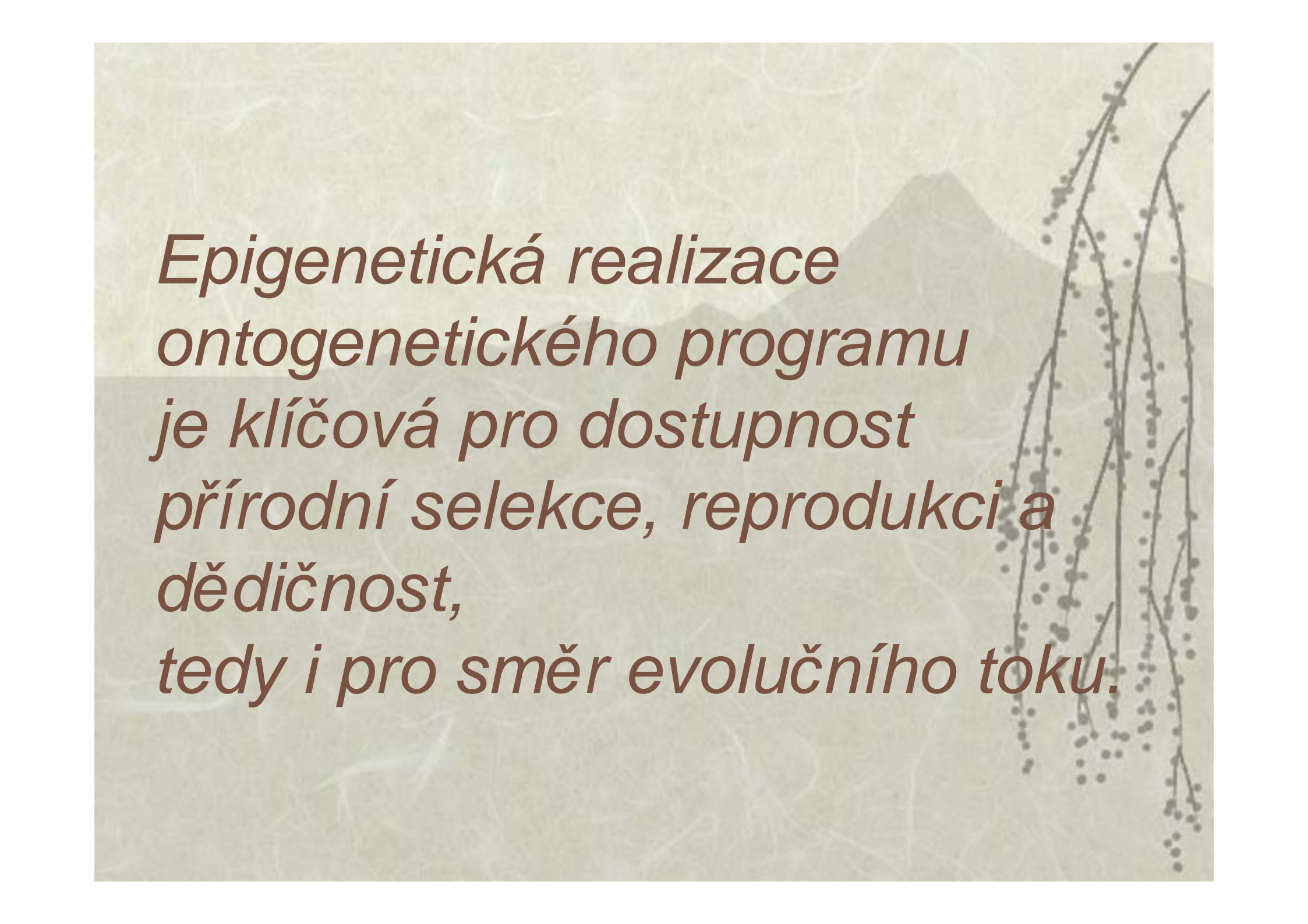
Evolution & Development
(Evo-Devo)

Prof. Boris Vyskot



Vývoj (individuální vývin, ontogeneze, development) je geneticky programovaný a cyklický.

Evoluce (historický vývoj, fylogeneze) není programovaná, nýbrž nahodilá.



*Epigenetická realizace
ontogenetického programu
je klíčová pro dostupnost
přírodní selekce, reprodukci a
dědičnost,
tedy i pro směr evolučního toku.*

Vývojové zákony

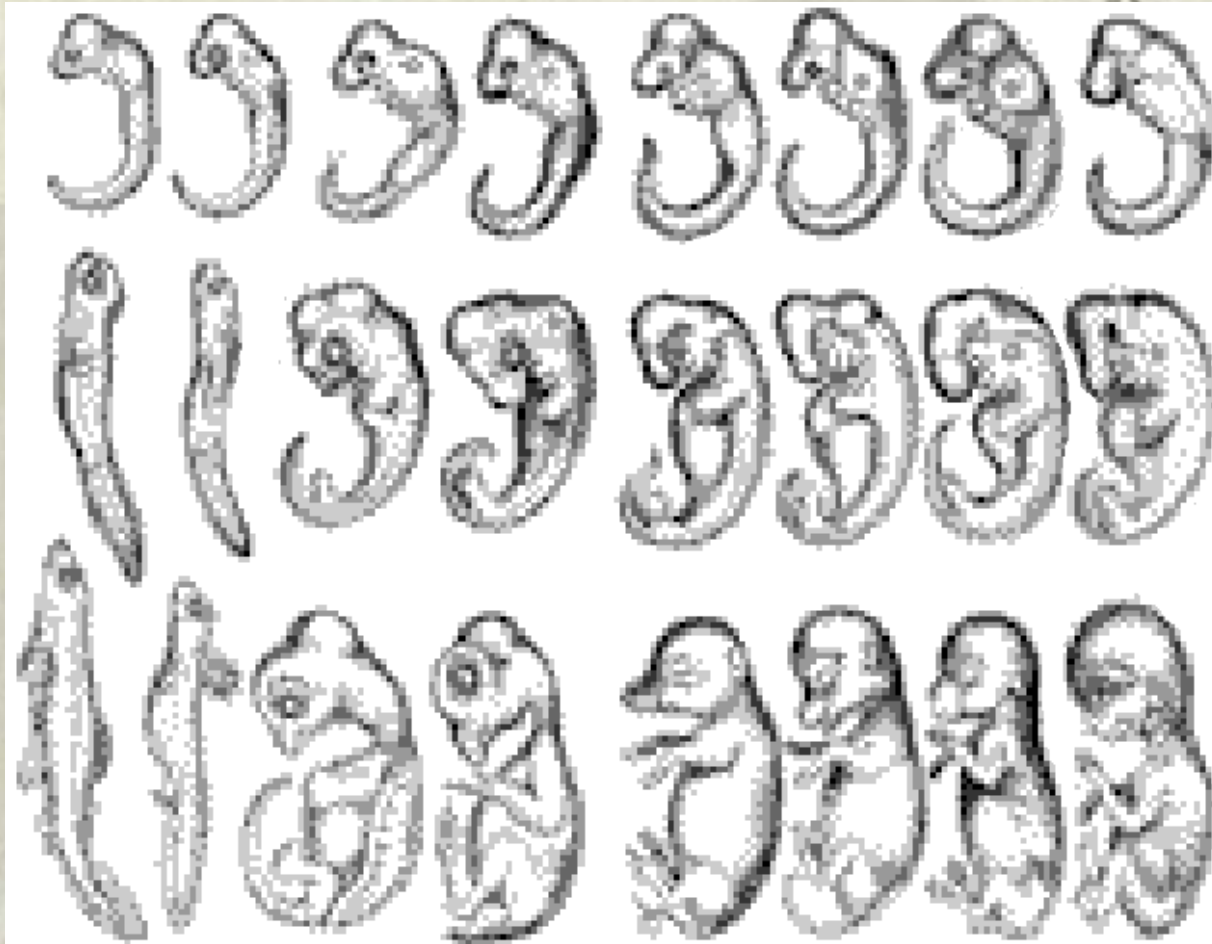
- ✓ Von Baerův zákon (1828):
“znaky vyskytující se u vyšší systematické skupiny se obvykle objeví ve vývinu dříve než znaky nižší skupiny”
- ✓ Haeckelův biogenetický zákon (1866):
“ontogeneze rekapituluje fylogenezu”

Evolve a ontogeneze :

EVOLution and DEVeLOpment



**Carl Ernst von Baer
(1792-1876)**



fylotypová stádia obratlovců

Baerovy zákony fylotypového stádia obratlovců

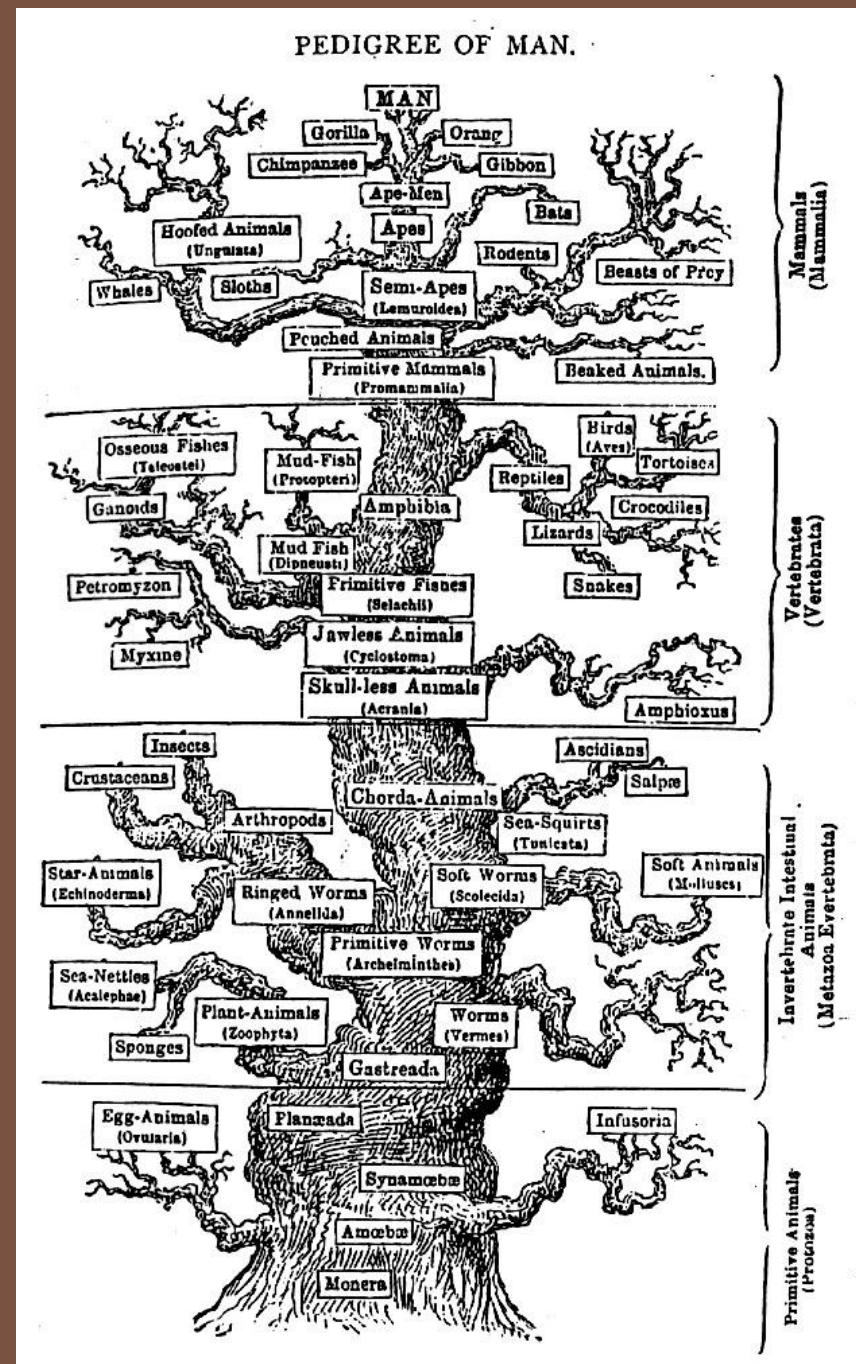
(1828)

- [1] Obecné znaky velké skupiny živočichů se v embryu vyskytují dříve než znaky specializované**
- [2] Méně obecné znaky se vyvíjejí ze znaků obecnějších, přičemž znaky velmi speciální se tvoří až ke konci embryogeneze**
- [3] Embrya odlišných druhů se od sebe v průběhu individuálního vývoje stále více a více odlišují**
- [4] Časně embryo evolučně vyššího živočišného druhu není podobné dospělci nižšího živočicha nýbrž jeho časnému embryu**



Ernst Haeckel
(1834 – 1919)

„ ONTOGENEZE
REKAPITULUJE
FYLOGENEZU „



Omezení biogenetického zákona

- ✓ Dospělé znaky předků jsou jen výjimečně časnými vývojovými stádii evolučních následovníků.
- ✓ Adaptace ve vývoji jsou stadium-specifické, odráží se ve výsledných fenotypech
- ✓ Ne všechny nové znaky vznikají prostřednictvím terminální adice

Richard B. Goldschmidt (~ 1935) :

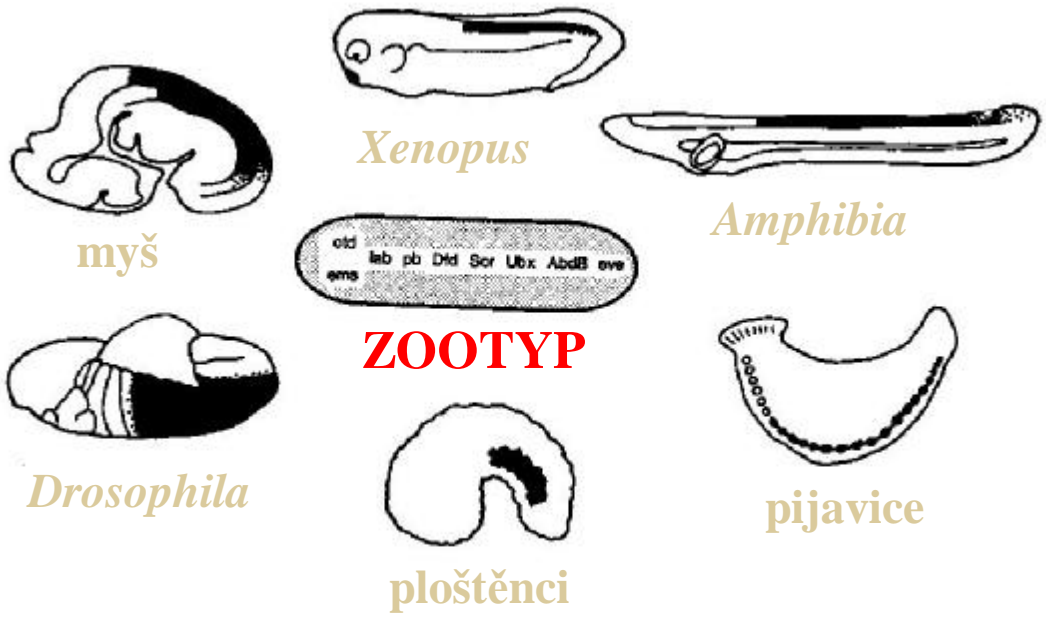
**“... Evoluce spočívá ve zdědění změn
individuálního vývoje ...”**

funkční biologie = anatomie, genová exprese

vývoj = změny funkční biologie / reálný čas

**evoluce = změny individuálního vývoje
/ historický čas**

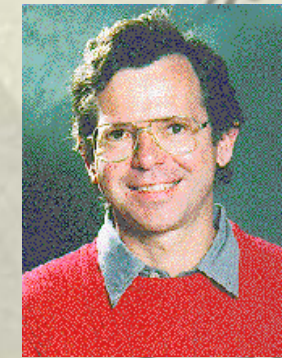




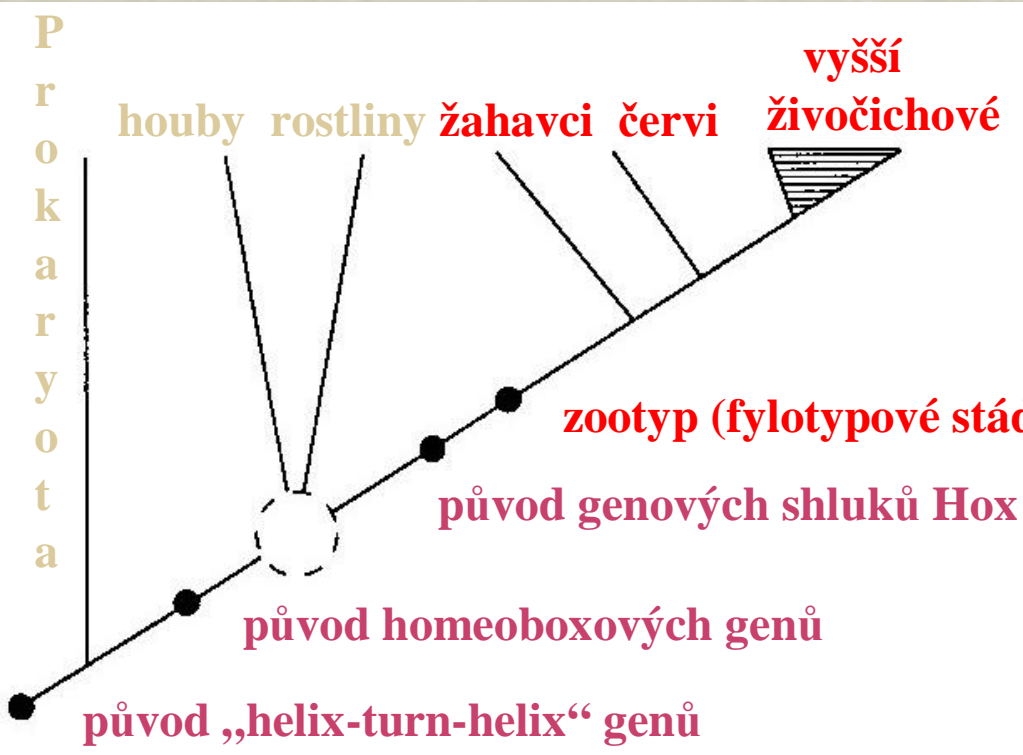
ZOOTYP



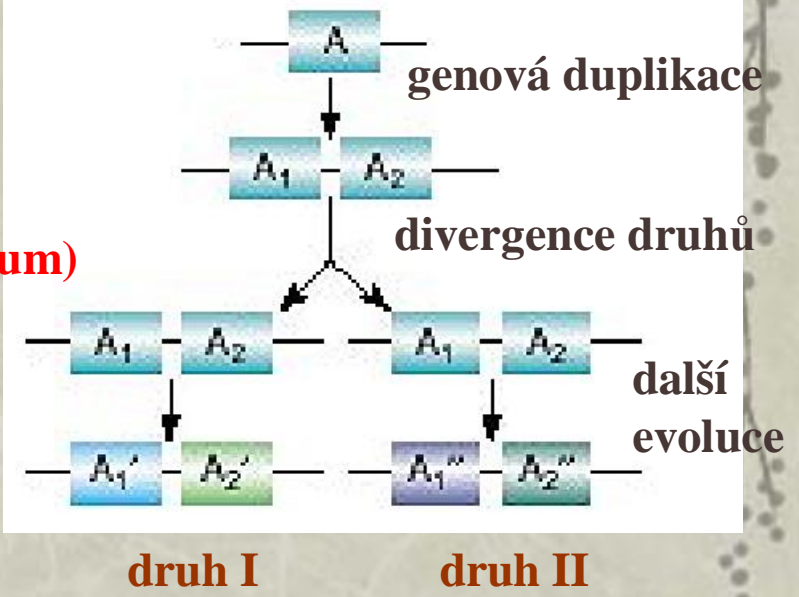
Étienne Geoffroy Saint-Hilaire (1772-1844, Paris)

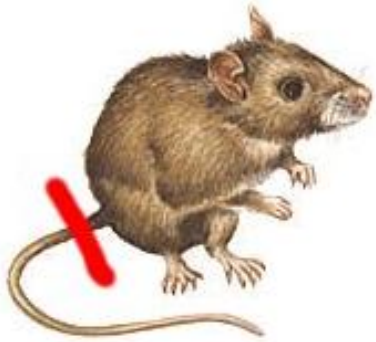


Jonathan Slack (*1949, Bath)



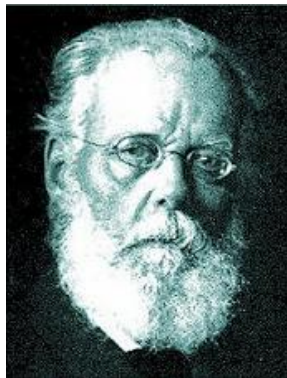
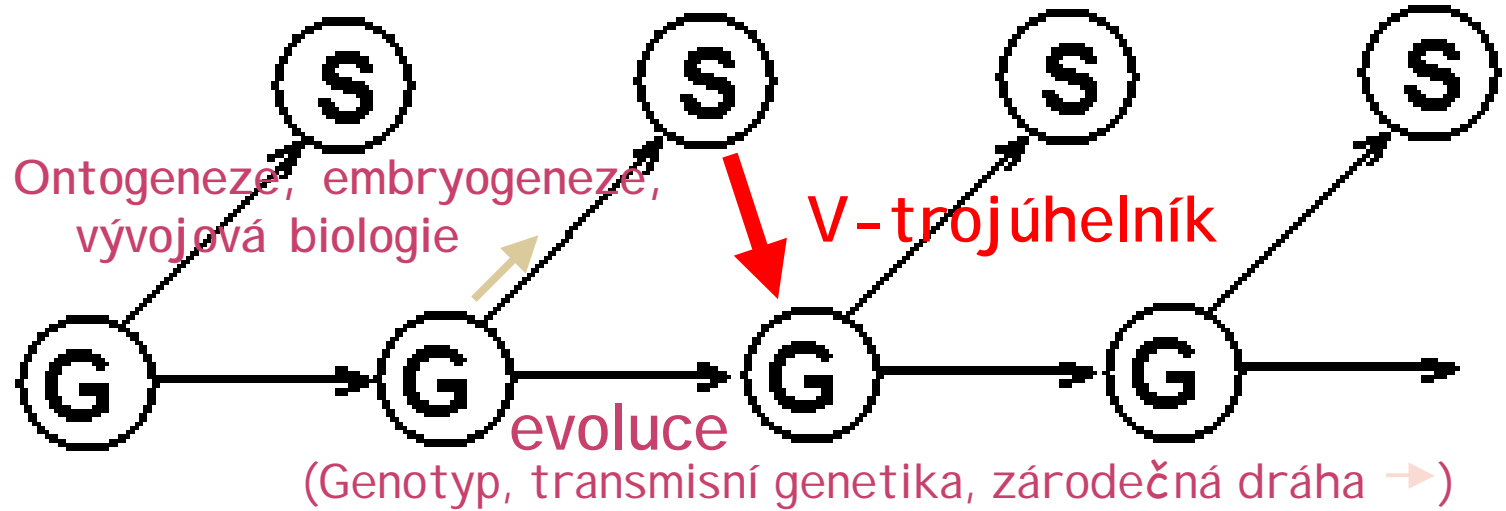
paralogní geny





Po selekci se dědí (přenáší) genotyp,
selekce se však realizuje na bázi fenotypu !

(Soma, fenotyp)



Weismann (1889): somatické změny získané v průběhu života vyšších živočichů neovlivňují reprodukční buňky či potomstvo (“Weismannova bariéra”).

Oocyte Generation in Adult Mammalian Ovaries by Putative Germ Cells in Bone Marrow and Peripheral Blood

Joshua Johnson,¹ Jessamyn Bagley,²
Malgorzata Skaznik-Wikiel,¹ Ho-Joon Lee,¹
Gregor B. Adams,³ Yuichi Niikura,¹
Katherine S. Tschudy,¹ Jacqueline Canning Tilly,¹
Maria L. Cortes,⁴ Randolph Forkert,³ Thomas Spitzer,⁵
John Iacomini,² David T. Scadden,³
and Jonathan L. Tilly^{1,*}

Boston, Massachusetts 02114

It has been suggested that germline stem cells maintain oogenesis in postnatal mouse ovaries. Here we show that adult mouse ovaries rapidly generate hundreds of oocytes, despite a small premeiotic germ cell pool. In considering the possibility of an extragonadal source of germ cells, we show expression of germline markers in bone marrow (BM). Further, BM transplantation restores oocyte production in wild-type mice sterilized by chemotherapy, as well as in ataxia telangiectasia-mutated gene-deficient mice, which are otherwise incapable of making oocytes. Donor-derived oocytes are also observed in female mice following peripheral blood transplantation. Although the fertilizability and developmental competency of the BM and peripheral blood-derived oocytes remain to be established, their morphology, enclosure within follicles, and expression of germ-cell- and oocyte-specific markers collectively support that these cells are bona fide oocytes. These results identify BM as a potential source of germ cells that could sustain oocyte production in adulthood.

Germline stem cells and follicular renewal in the postnatal mammalian ovary

NATURE | VOL 428 | 11 MARCH 2004 | www.nature.com/nature

Joshua Johnson*, **Jacqueline Canning***, **Tomoko Kaneko**, **James K. Pru** & **Jonathan L. Tilly**

Vincent Center for Reproductive Biology, Vincent Obstetrics and Gynecology Service, Massachusetts General Hospital, and Department of Obstetrics, Gynecology and Reproductive Biology, Harvard Medical School, Boston, Massachusetts 02114, USA

A basic doctrine of reproductive biology is that most mammalian females lose the capacity for germ-cell renewal during fetal life, such that a fixed reserve of germ cells (oocytes) enclosed within follicles is endowed at birth. Here we show that juvenile and adult mouse ovaries possess mitotically active germ cells that, based on rates of oocyte degeneration (atresia) and clearance, are needed to continuously replenish the follicle pool. Consistent with this, treatment of prepubertal female mice with the mitotic germ-cell toxicant busulphan eliminates the primordial follicle reserve by early adulthood without inducing atresia. Furthermore, we demonstrate cells expressing the meiotic entry marker synaptonemal complex protein 3 in juvenile and adult mouse ovaries. Wild-type ovaries grafted into transgenic female mice with ubiquitous expression of green fluorescent protein (GFP) become infiltrated with GFP-positive germ cells that form follicles. Collectively, these data establish the existence of proliferative germ cells that sustain oocyte and follicle production in the postnatal mammalian ovary.

R Pearl, WF Schoppe (1921), Zukerman (1951):

... *základní biologická doktrína* ... v průběhu života jedince nenastává zvýšení počtu primárních oocytů nad rámec těch, které byly vytvořeny při tvorbě vaječníku (končí narozením) ...

J Johnson et al. (2004):

... juvenilní i adultní vaječníky myši mají mitoticky aktivní zárodečné buňky ...

... chemoterapie eliminující zásoby folikulů může být překonána aktivací nových zárodečných buněk ...

... transplantace wt-ovarií do GFP-myši vede k infiltraci folikulů GFP-pozitivními zárodečnými buňkami ...

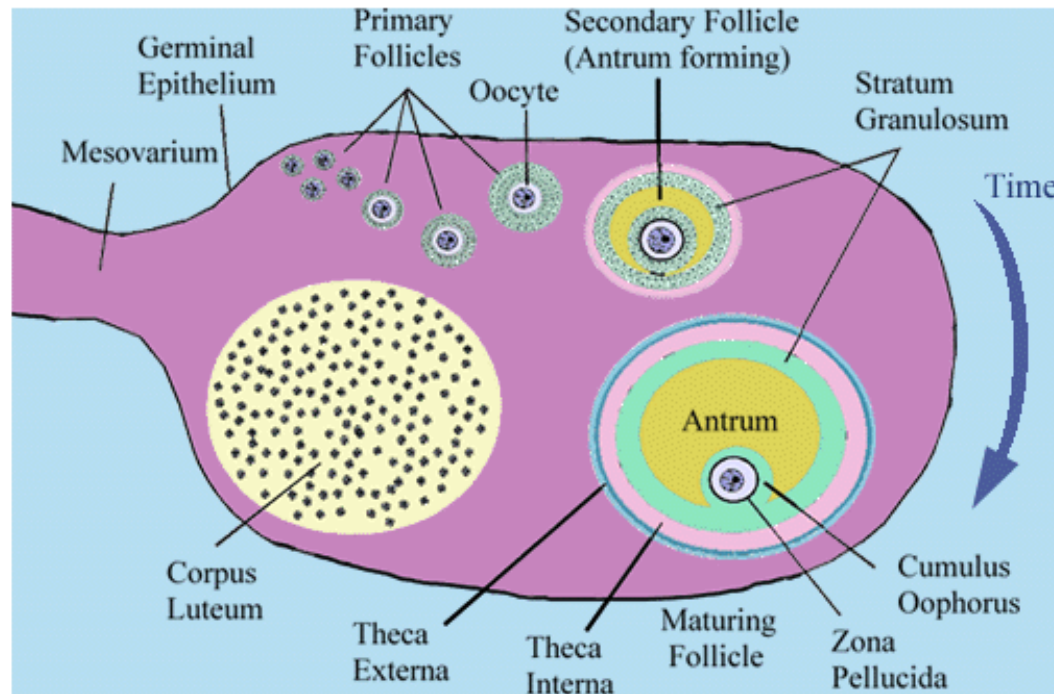
J Johnson et al. (2005):

... možnost extragonadálního zdroje zárodečných buněk – transplantace kostní dřeně nebo periferní krve (pluripotentní buňky) vedou ke vzniku oocytů donorového typu ...

... schopnost fertilizace a dalšího vývoje oocytů odvozených z kostní dřeně či krve však dosud nebyla prokázána ...

A Schematic Drawing of the Ovary

The blue arrow follows the the ovarian follicles from their maturation (from primary follicles) to as they mature. The schematic is merely drawn this way to show all the stages of matu



Povedou tyto výsledky ke zpochybnění Weismannovy bariéry a umožní vysvětlení epigenetického (Lamarckova) dědění získaných znaků ?!?

Pozor! U samečků-živočichů základní biologická doktrína (princip reprodukční biologie) neplatí vůbec: samčí zárodečné buňky (spermatogonie) se mitoticky množí a jejich meiotické deriváty (spermie) obvykle vznikají až v dospělosti.

Transplantace pólové cytoplasmy může indukovat tvorbu zárodečné linie

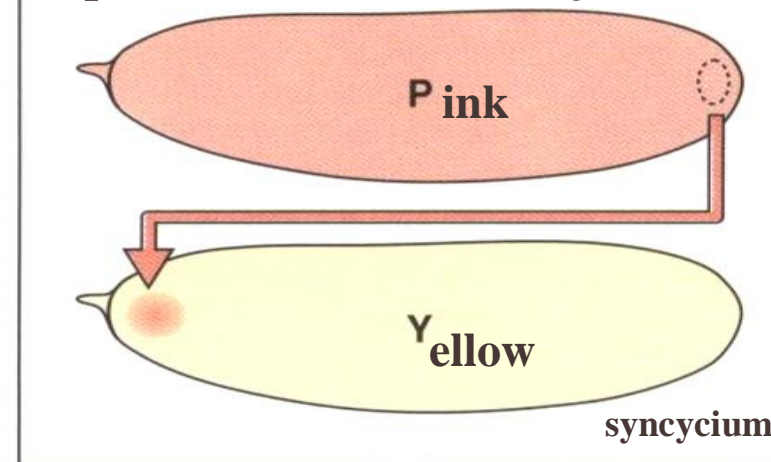
...

primordiální zárodečné buňky jsou prvními odlišnými, na posteriorním konci

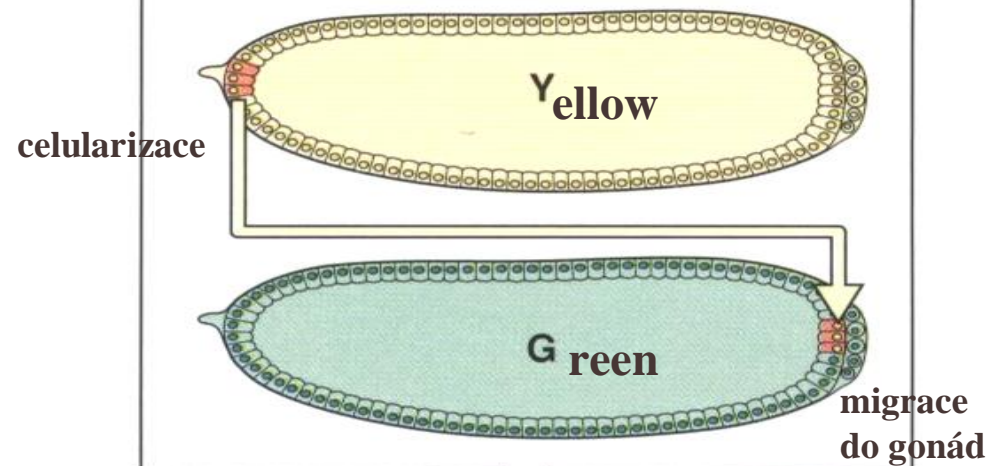
...

u drosofily, hlístice (granule P) a žab

cytoplasma posterioru oplozeného vajíčka přenesena do anterioru jiného

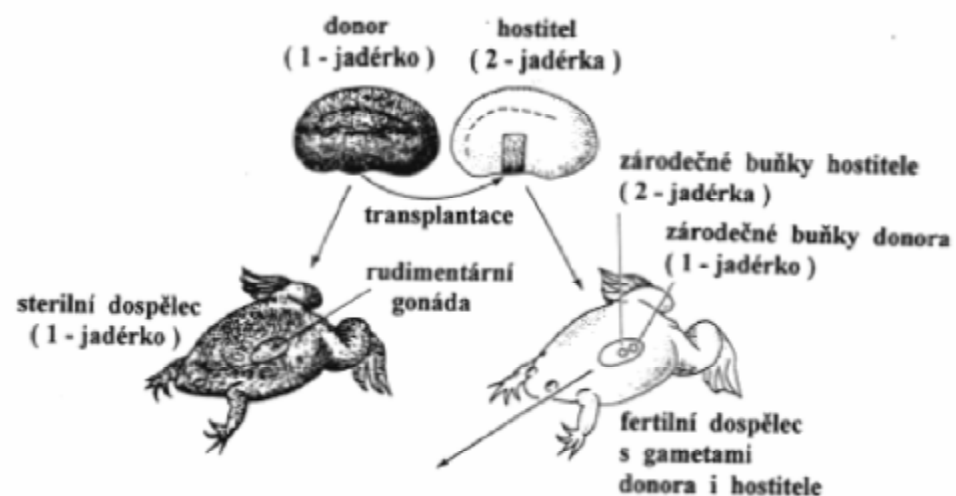


anteriorní buňky (s pólovou plasmou) přeneseny do jiného posterioru



moucha G vytváří zárodečné buňky s genotypem G a Y

Obr. 44. Demonstrace primordiálních zárodečných buněk v časném endodermu embrya žáby (podle Gilberta, 1988). Část ventrální tkáně neuruly, kde jsou přítomny prekuzory zárodečných buněk, mutantního donora (tvořícího ve svých jádrech pouze jediné jadérko) byla přenesena do recipienta divokého typu (se dvěma jadérky). Po operaci byly žáby donora sterilní, neboť zárodečné buňky byly odstraněny a neurula již není schopna si vytvořit nové. Hostitelská žába však byla fértilní a vytvářela meiózou gamety buď s žádným nebo jedním jadérkem (typ donora), nebo s jedním jadérkem (typ hostitele, tj. vlastní). Křížením této chimérické žáby s divokým typem vzniká potomstvo s jedním nebo dvěma jadérky (původní experimenty, Blackler 1966).



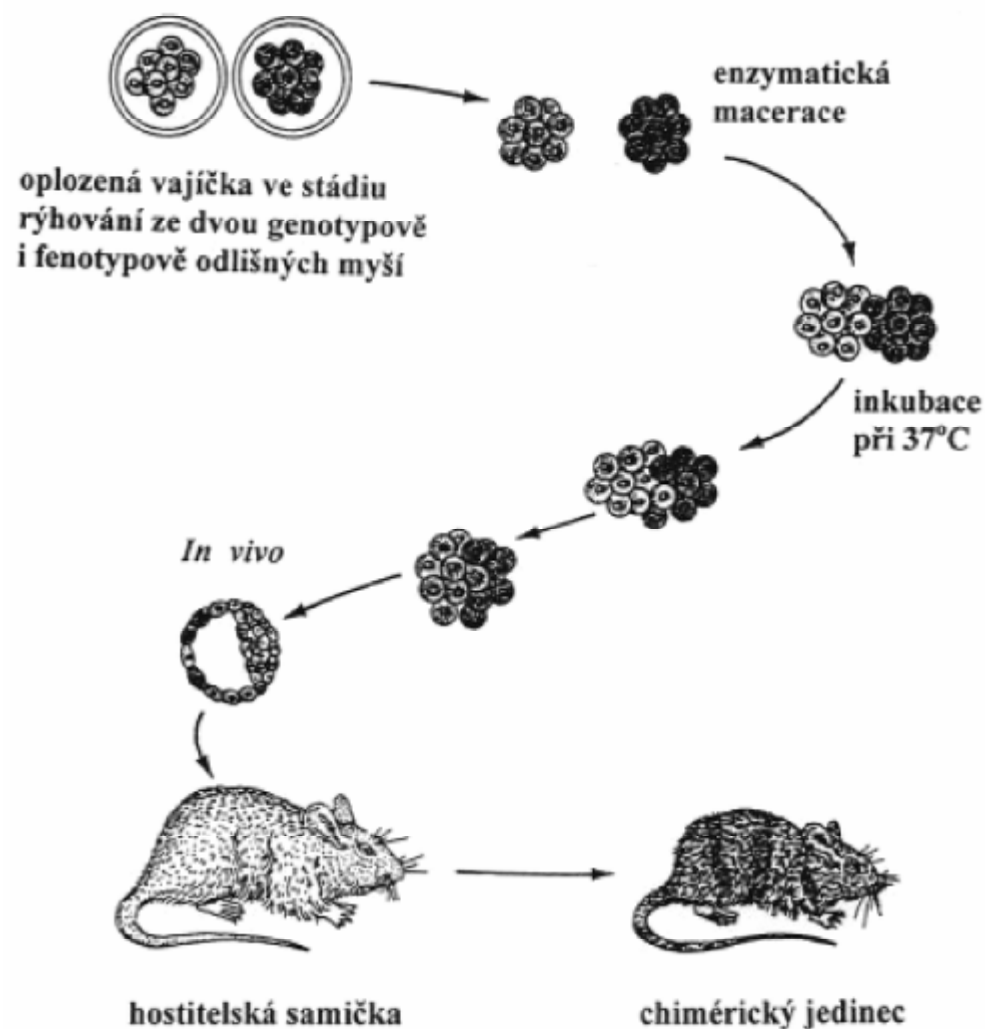
| | | |
|-------------------|---------------|------------------|
| chimérická žába - | tkáň donora : | tkáň hostitele : |
| | meióza ↓ | ↓ |
| | 1 - jádérko | 0 - jádérko |
| | | 1 - jádérko |

potomstvo:

wild-type

partner → 1 - jádérko : 2 - jádérka 1 - jádérko 2 - jádérka
gamety

Obr. 49. Konstrukce chimérické myši kombinací blastomer z odlišných jedinců (podle Müllera, 1997). Tento experiment vychází ze schopnosti regulace, tj. schopnosti části blastuly regenerovat po excizi zbývající části, a relativně pozdní diferenciace buněčných linií u savců. Blastocysty dvou odlišných myších linií byly zbaveny zony pellucidy, fúzovány a produkt byl vnesen do dělohy pseudopregnantní samičky. Výsledný jedinec je genetickou mozaikou buněk obou výchozích linií.



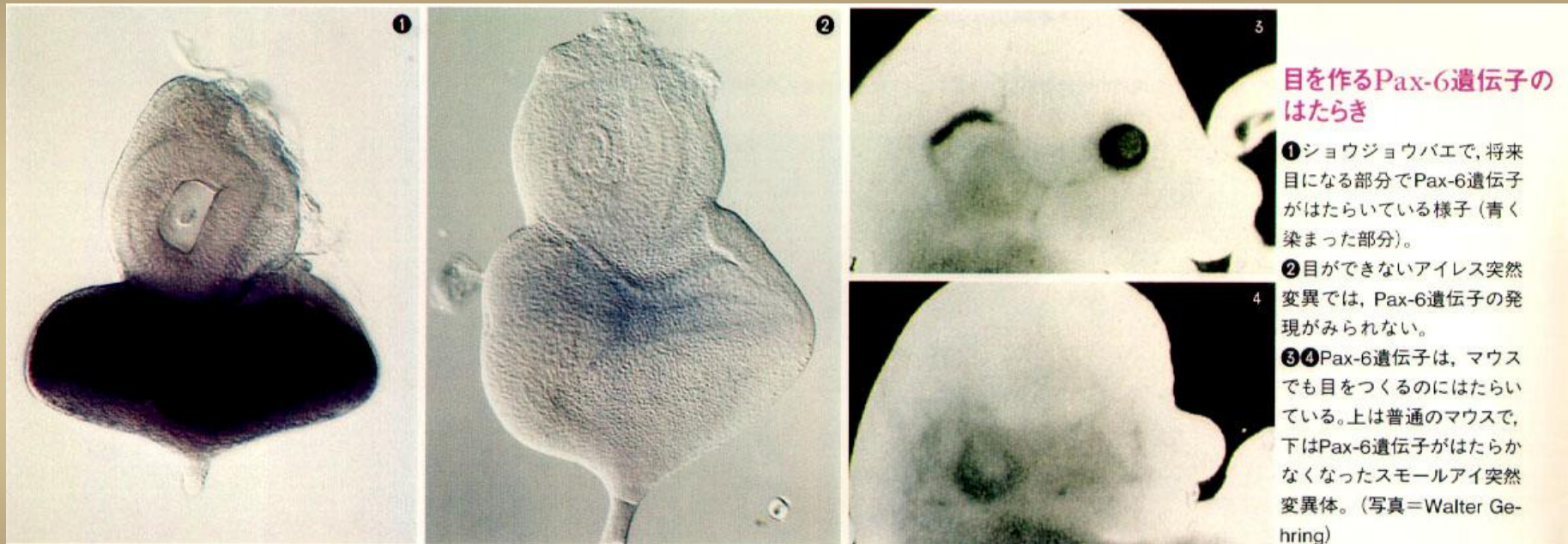
Redundance ve vývoji

- ✓ Mutace vývojových genů často vedou k neprůkaznému fenotypu.
- ✓ Toto je zřejmě způsobeno funkční redundancí genové exprese.
- ✓ Nejčastější typ redundance vzniká jako důsledek genové duplikace.

Heterotopní evoluce

- ✓ Změny pozice (topologie), ve které jsou znaky exprimovány v průběhu vývoje
- ✓ Heterotopie může vytvářet nové morfologie odlišné od drah, které vyvábí formy předků
- ✓ Heterotopie je zvýrazněna prostorem, nikoli časem
- ✓ Halder et al. (1995) indukovali extra-oči na křídlech, nohách a tykadlech *Drosophila* ektopickou expresí "eyeless" cDNA

PAX6/Eyeless exprese v muších a myších očních základech



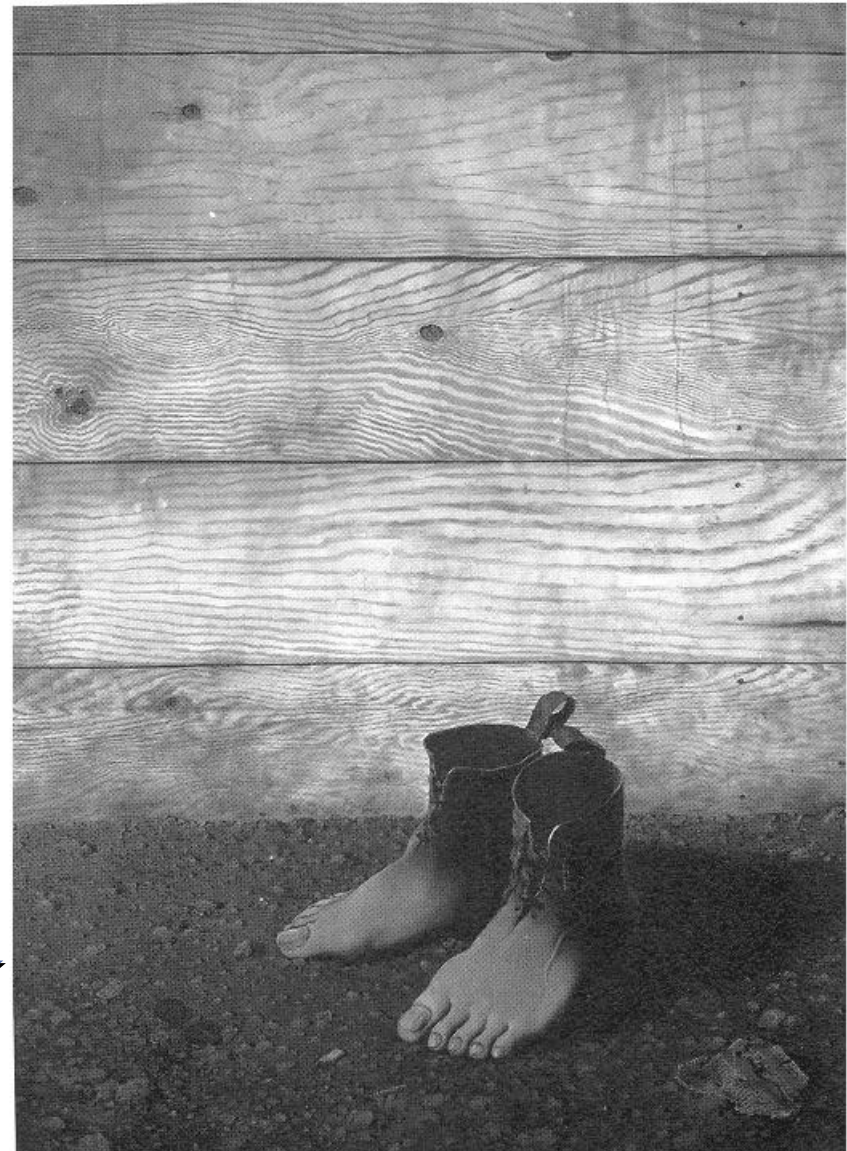


William Bateson

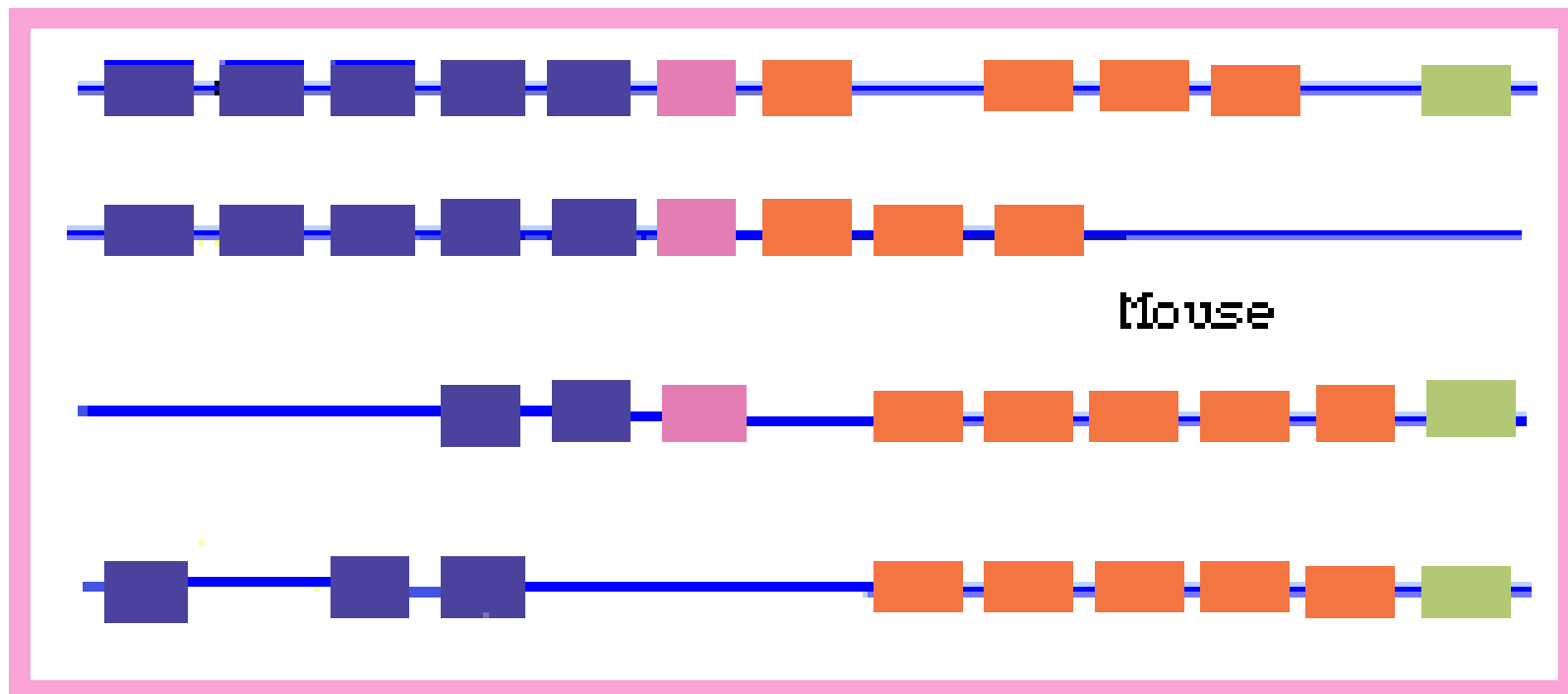
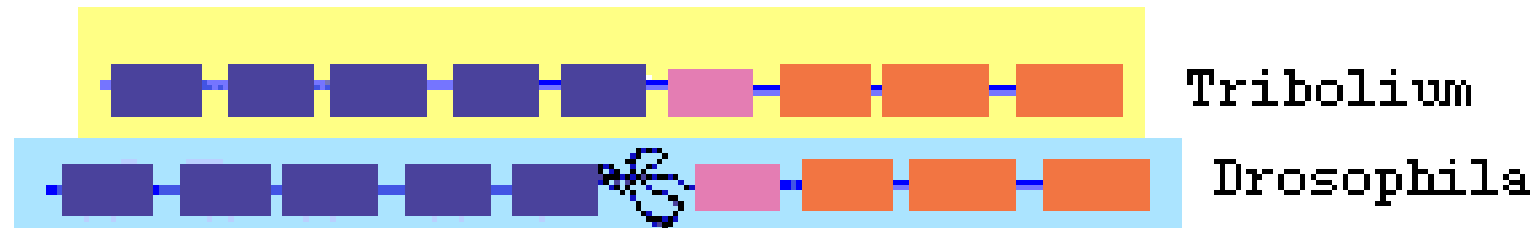
(1861-1926)

***Materials for the Study of
Variation (1894)***

***... HOMEÓZA je zvláštním
typem variability, kdy jeden
člen opakující se série přebírá
rysy, které se normálně vyvíjejí
u jiného člena série ...***



Homeotické geny dávají vznik sériově homologním strukturám

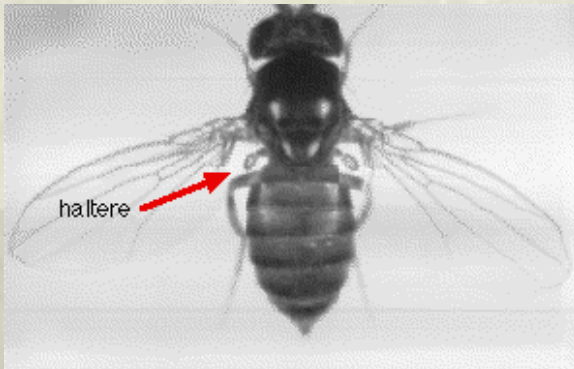


HOMEOTICKÉ GENY

jeden z klíčů specifikace a diferenciacce

embryo

dospělec



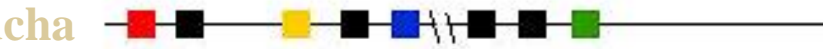
BITHORAX specifikuje třetí článek hrudi a zadeček: ztráta funkce – místo kyvadélek se tvoří druhý pár křídel (více anteriorní fenotyp)



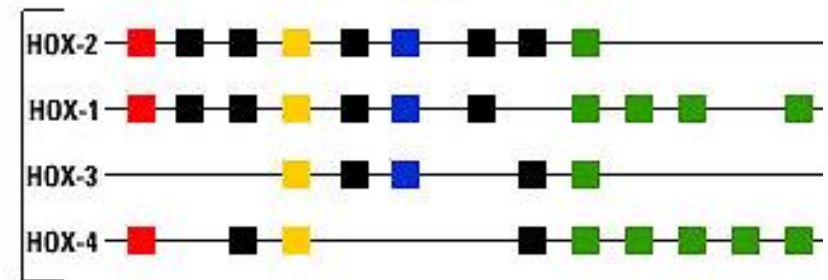
Antennapedia komplex (anterior)

Bithorax komplex (posterior)

moucha



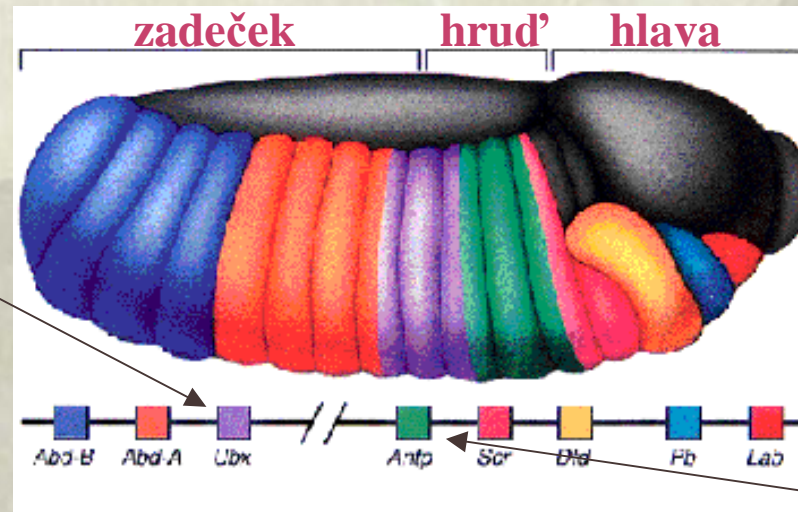
myš



Edward Lewis (1963) : pravidlo spacio-temporální kolinearity

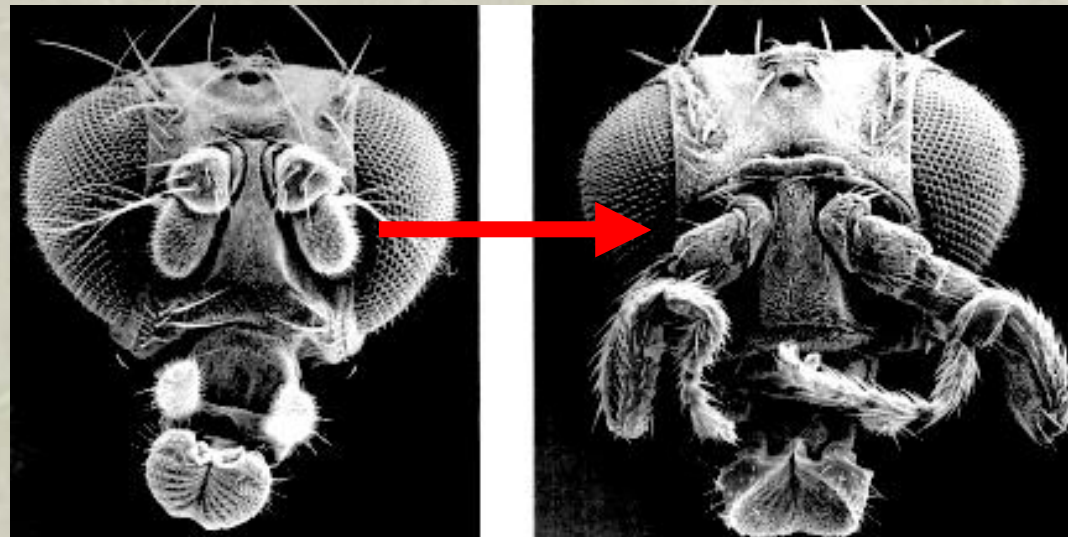
ANTENNAPEDIA specifikuje mesothorax:
jeho ektopická „dominantní“ exprese vyvolává tvorbu
nohou na hlavě (více posteriorní fenotyp)

Bithorax



Antennapedia

wt

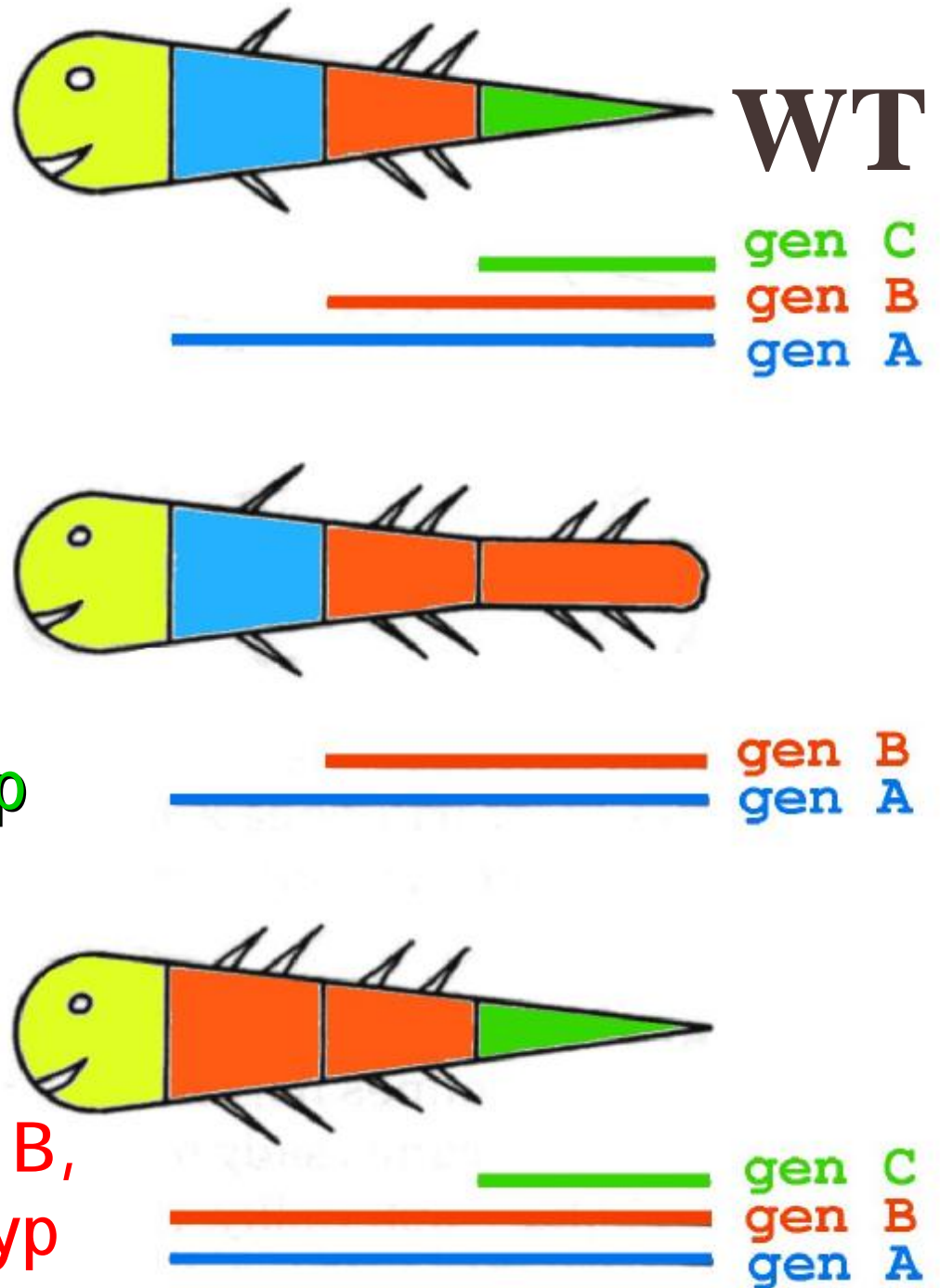


mutant

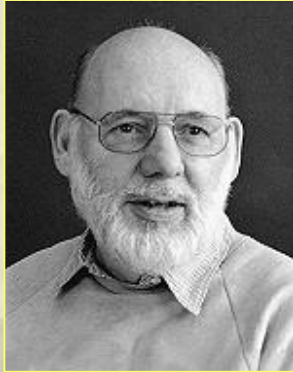
Homeotické geny
řídí anteriorně -
posteriorní
specifikaci těla

mutace :
ztráta funkce genu C,
„více anteriorní“ fenotyp

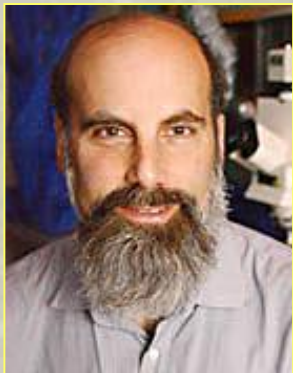
mutace :
ektopická exprese genu B,
„více posteriorní“ fenotyp



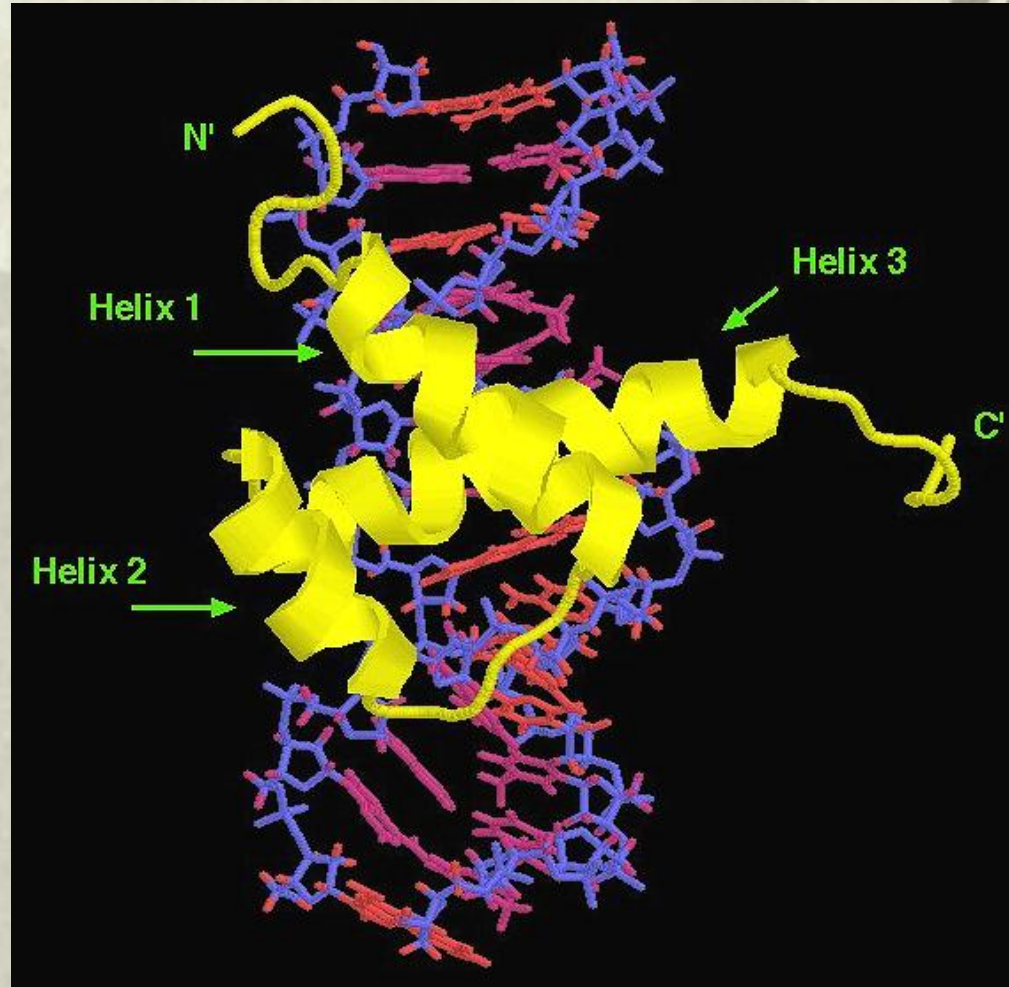
Objev homeoboxu (1982)



Walter Gehring
(Basel)

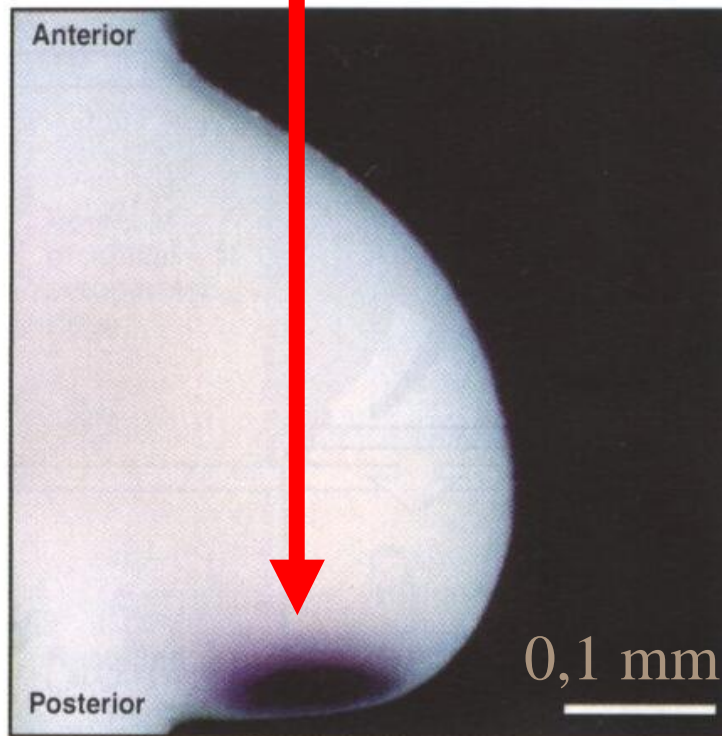


Matthew Scott
(Stanford)

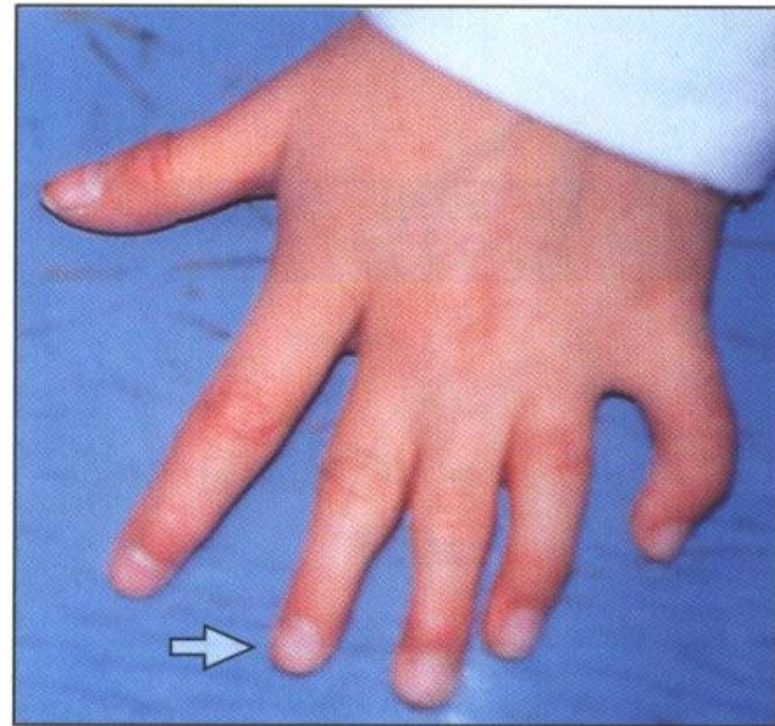


vazba homeodomény Antennapedia na DNA

Polarizační oblast pupene specifikuje končetinu podél antero-posteriorní osy
exprese genu *Sonic hedgehog* na posteriorním konci pupene poskytuje poziční signál podél A-P osy



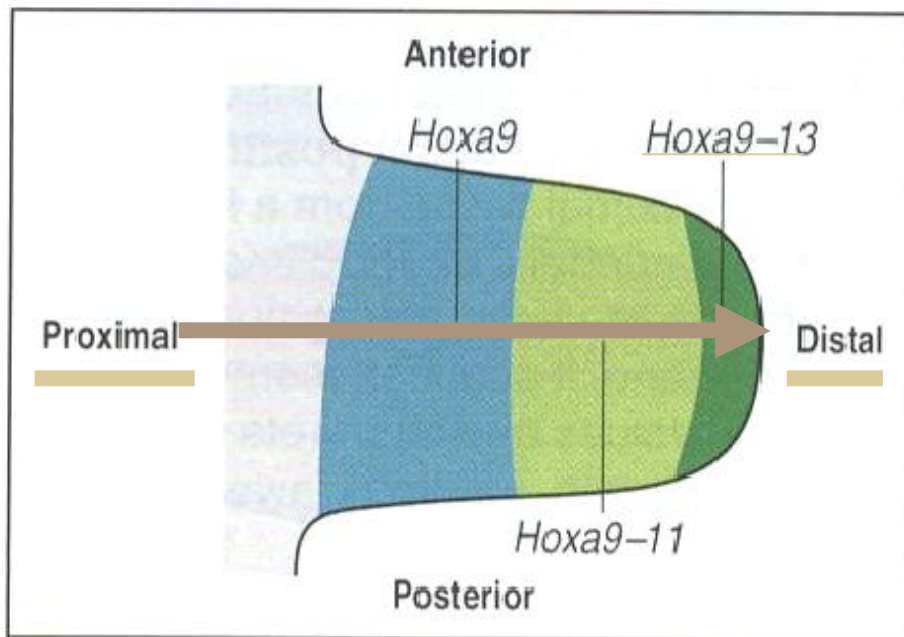
pupen kuřecí končetiny



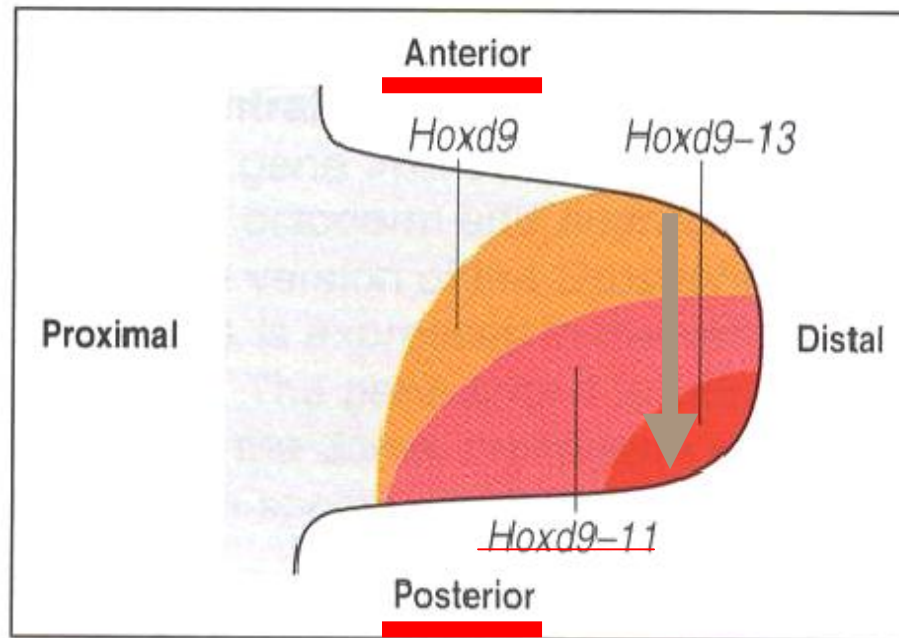
polydaktylie u člověka

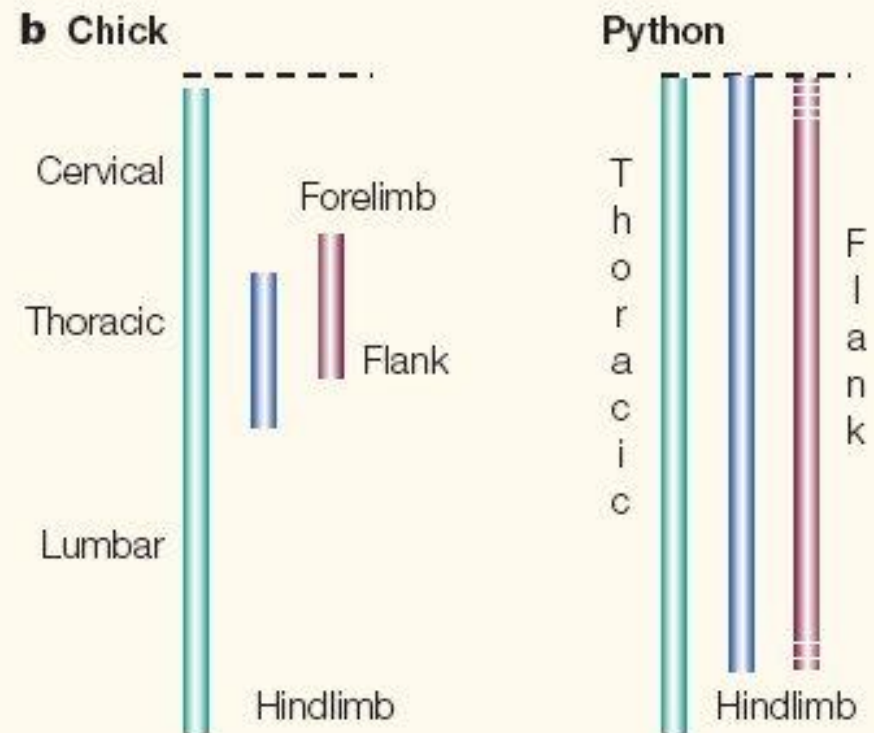
Exprese homeotických genů v pupenu křídla kuřete

Hox-a geny jsou exprimovány
podél proximo-distální osy :
Hox-a 13 je nejdistanější



Hox-d geny jsou exprimovány
podél antero-posteriorní osy :
Hox-d 13 je nezadnější





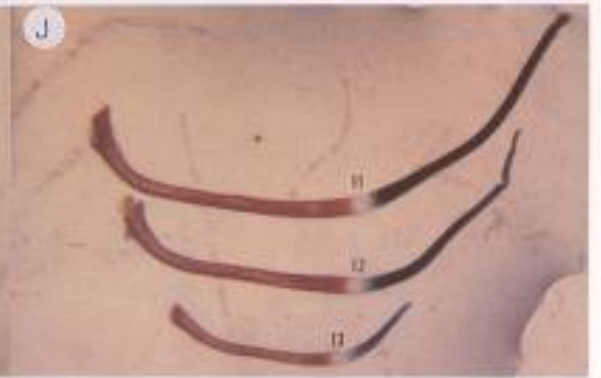
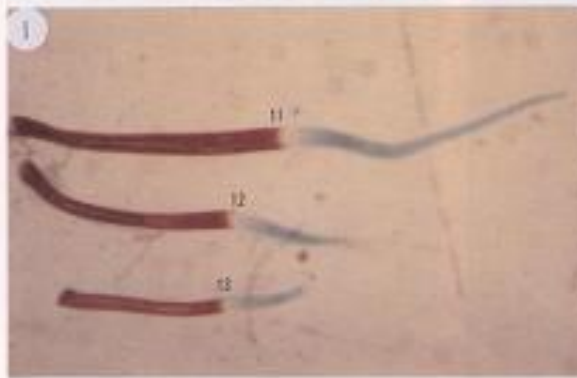
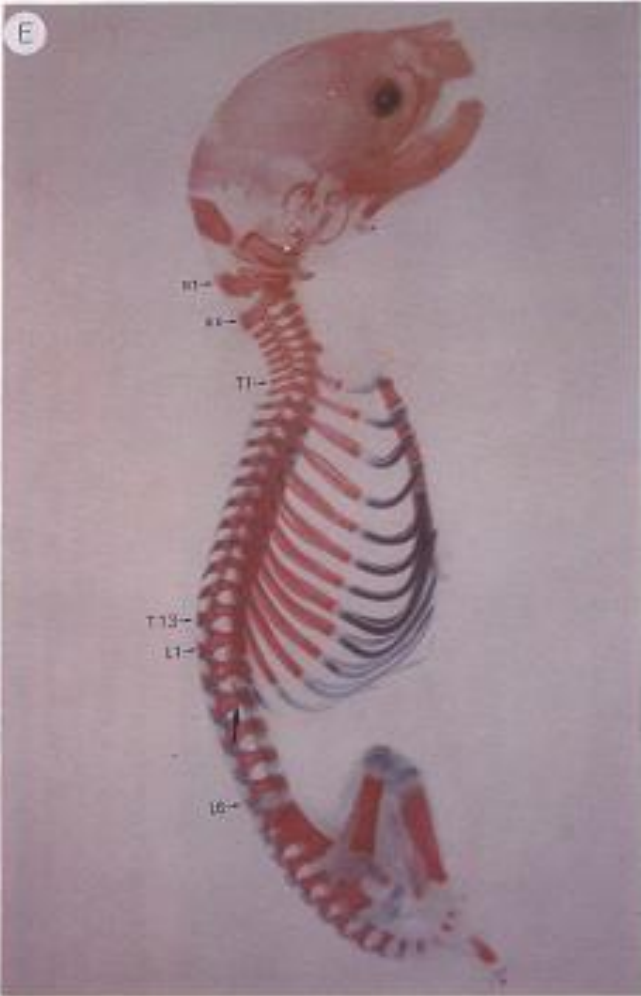
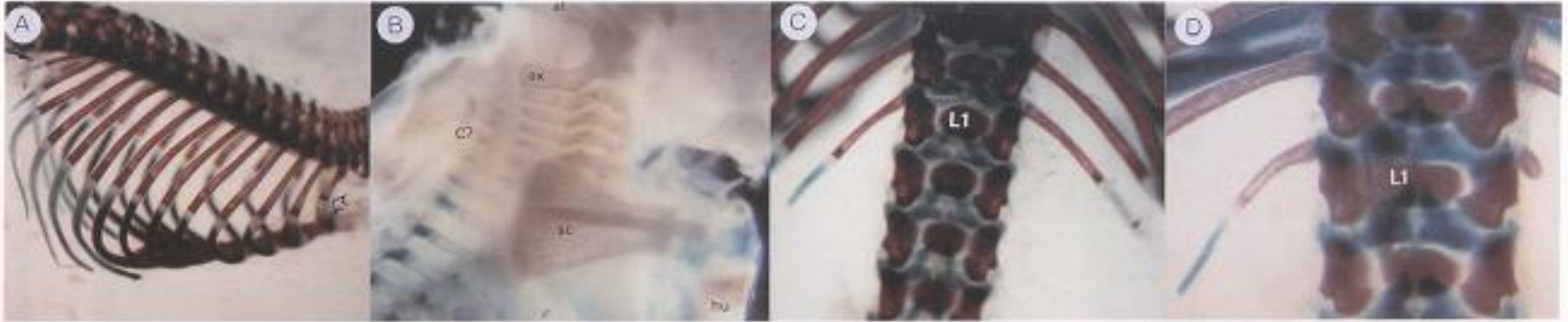
Hox gene expression in the evolution of snakes — a dramatic modification of the vertebrate body axis. **a** | The skeleton of a python embryo stained with Alcian blue (cartilage) and Alizarin red (bone). **b** | Schematic diagram comparing domains of *Hox* gene expression in chick and snake embryos: *HoxB5*, green; *HoxC8*, blue; *HoxC6*, red. *Hox* genes are involved in the regionalization of the lateral plate mesoderm into forelimb, flank and hindlimb, to specify limb position. The expansion of *HoxC8* and *HoxC6* domains in python correlates with the expansion of thoracic identity and can account for the absence of forelimbs

Evolve homeotických (selektorových) genů

- ✓ vysoký stupeň podobnosti mezi geny skupin *Antennapedia* a *Bithorax*, duplikace
- ✓ všechny obsahují homeobox, 180 bp
- ✓ kódují 60-amino-kyselinovou homeodoménu, která se váže k DNA
- ✓ příbuzné geny nalezeny i u všech jiných živočichů, člověka i rostlin

Mouellic et al.: Homeosis in the mouse induced by a null mutation in the *Hox-3.1* gene. – Cell 69, 251, 1992

- nahrazení kódující sekvence genu *Hox3.1* signálním genem *lacZ* homologní rekombinací v kultivovaných embryonálních kmenových buňkách
- gen rezistence k neomycinu zajišťuje selekci homologních rekombinantů
- *lacZ* gen je reportérový – detekuje místa exprese *Hox3.1* v heterozygotních myších *Hox3.1* +/- (... hybridizace s mRNA či imunobarvení)
- homozygotní stav *Hox3.1* -/- je semiletální, několik segmentů kostry je transformováno jako více-anteriorní (podobně u drosofily loss-of-function, mutace Bithorax)
- 8. pár žeber je spojen s hrudní kostí a tvorba 14. páru na bederním obratli





Forelimb Phenotype in *Hox-3.1* Mutant Mice

The mouse on the left has a *Hox-3.1*^{+/-} genotype. The mouse on the right, whose fingers are clenched, has a *Hox-3.1*^{-/-} genotype.

Chicken hindlimb



Duck hindlimb



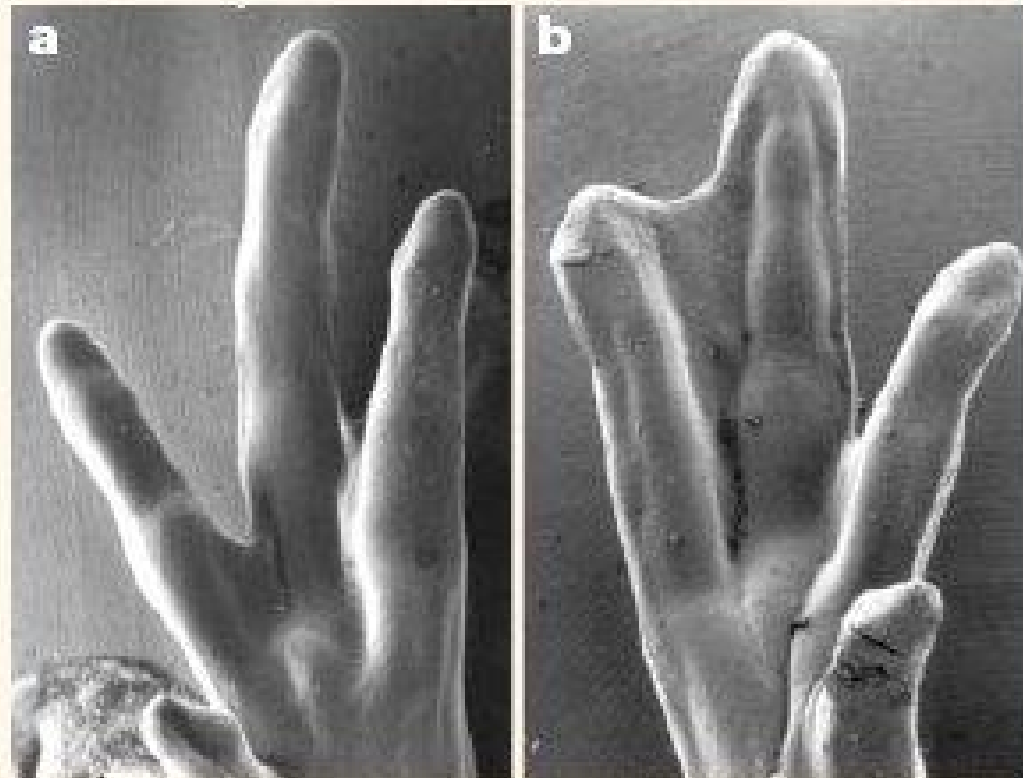
BMP

Gremlin

Apoptosis

Newborn

Regulation of chicken limb apoptosis by BMPs. Autopods of chicken feet (top) and duck feet (bottom) at similar stages. The *in situ* hybridizations show that while bone morphogenetic proteins (BMPs) are expressed in both the chicken and duck hindlimb webbing, the duck hindlimb also shows expression of *gremlin* in the webbing (arrows). Gremlin is an inhibitor of BMPs. The pattern of cell death (shown by neutral red dye accumulation) becomes distinctly different in the two types of webbing.



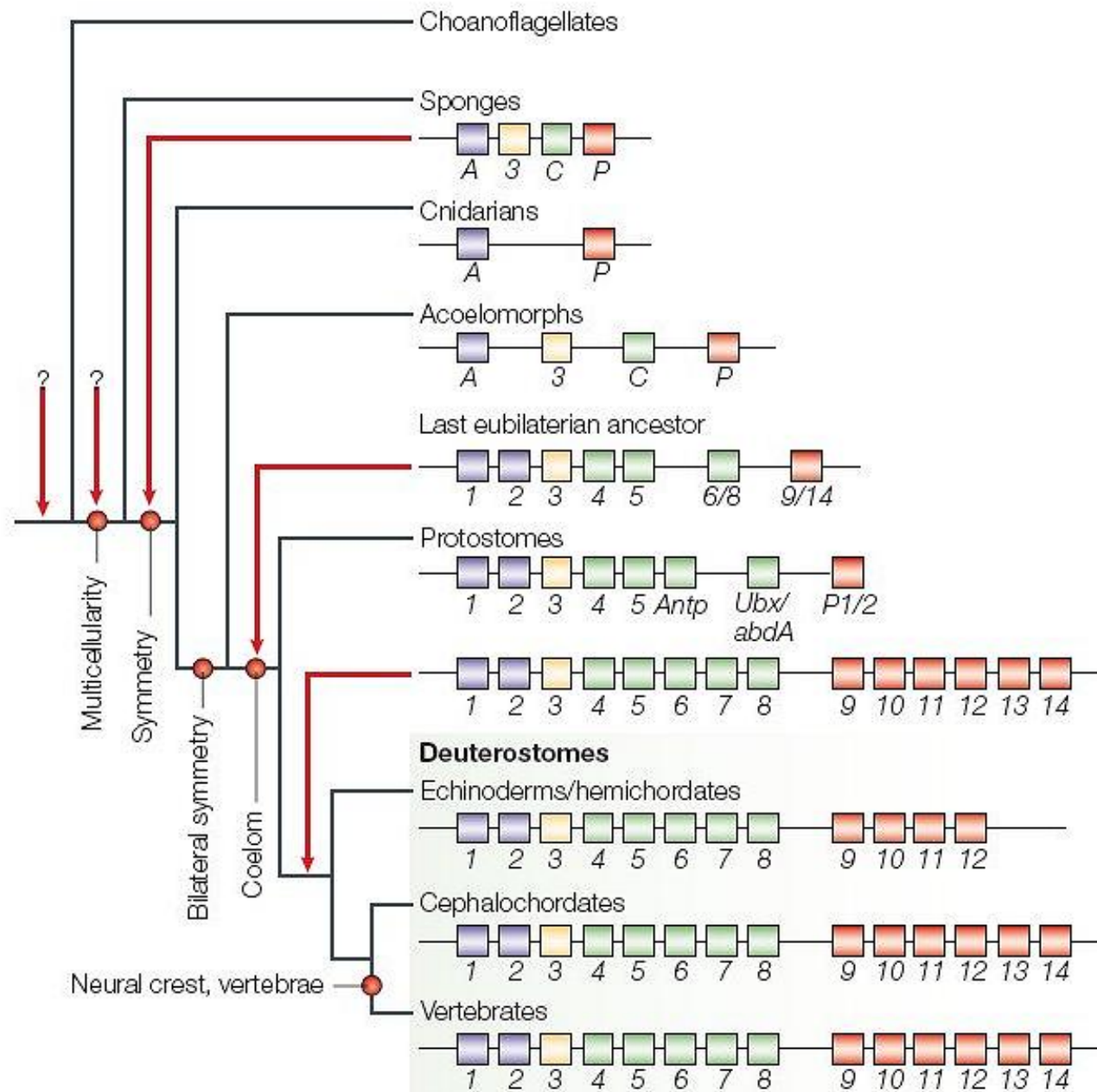
Inhibition of cell death by inhibiting BMP.

a) Control chicken hindlimbs have extensive apoptosis in the space between the digits, leading to the absence of webbing. **b)** When beads soaked with Gremlin protein, an inhibitor of bone morphogenetic protein (BMP), are placed into the interdigital mesoderm, the webbing persists and generates a duck-like foot.



Box 1 | Evolution of the Hox cluster during metazoan evolution

During evolution, large MACRO EVOLUTIONARY EVENTS markedly altered the metazoan body plan and gave rise to the morphological diversity and complexity of current phyla⁷⁸. The cladogram shows the main metazoan groups and the associated body-plan transitions (indicated by red circles). The closest unicellular relatives of metazoans were the choanoflagellates⁶¹; the question marks indicate uncertainty about the Hox gene complement in these evolutionary positions. The first body-plan transition in metazoans was the origin of radial symmetry, which gave rise, in the first instance, to cnidarians. The origin of bilaterality involved the generation of two body axes (anteroposterior and dorsoventral), the endomesoderm, and a nervous system that was



Homeoboxové genové shluky u metazoí

jsou staré asi 1 miliardu let, prostorová/časová kolinearita částečně zachována, poprvé se vyskytují na evolučním přechodu Cnidaria/Bilateria, souvislost se vznikem tří zárodečných listů

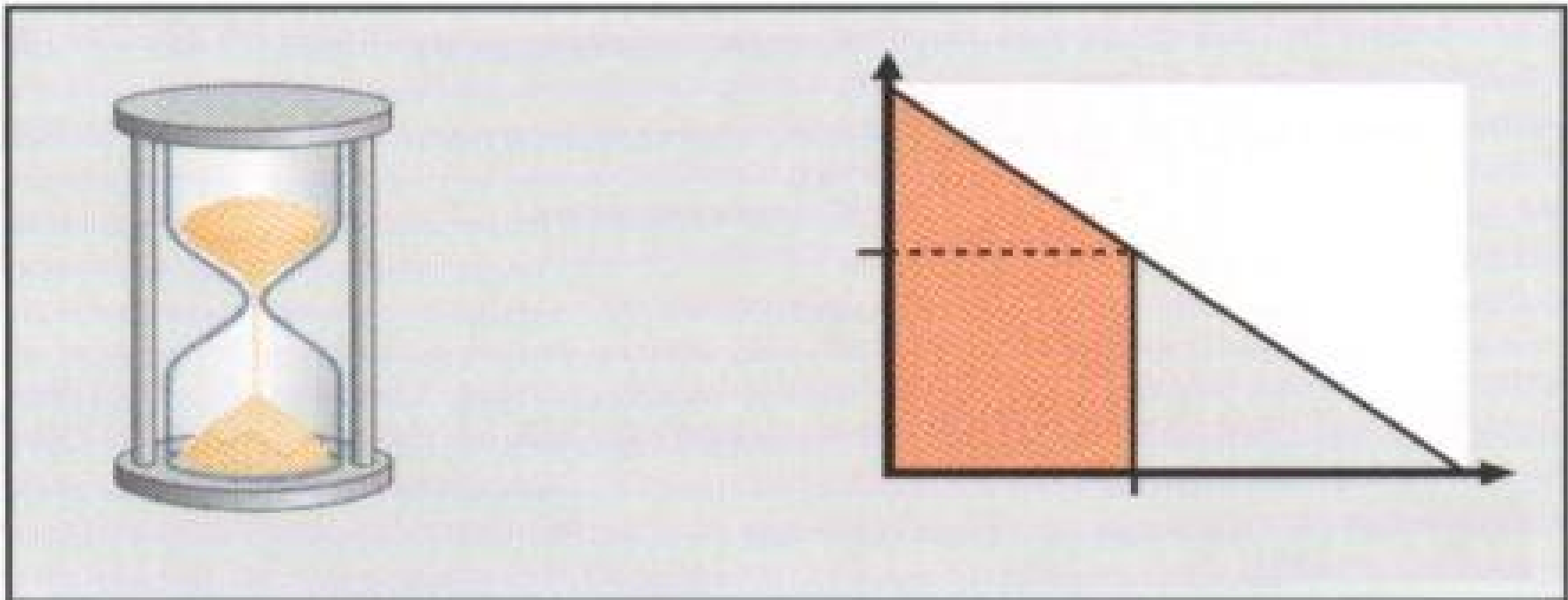
MEGACLUSTER (ancestrální ProtoHox)

se postupně amplifikoval a divergoval ve tři skupiny genů

- (a) **Hox-shluk**: Lewis 1978; 5+3 geny u drosofily, 39 genů ve 4 shlucích u savců), působí především v **ektodermu**
- (b) **ParaHox-shluk**: Brooke, Garcia, Holland 1998; je pouze u obratlovců, blízký Hox-shluku, řídí vývin **endodermu**
- (c) **NK-shluk**: Kim-Niremberg 1989; 4 geny u drosofily, též u obratlovců, řídí hlavně vývin **mesodermu**

Časování vývojových procesů,
zapínání a vypínání genů v závislosti
na koncentraci a čase, prahové hodnoty

HETEROCHRONNÍ GENY



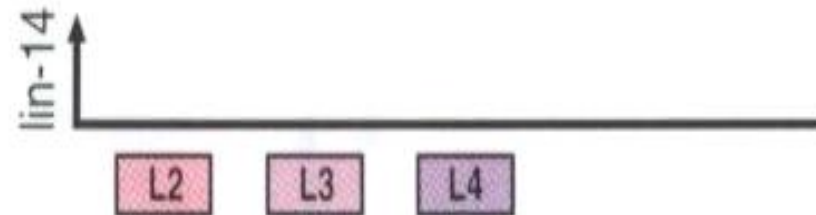
HETEROCHRONNÍ MUTACE

model řízení časového vývoje larvy hlístice C-elegans

specifická stádia larválního vývoje jsou určována hladinou proteinu lin-14

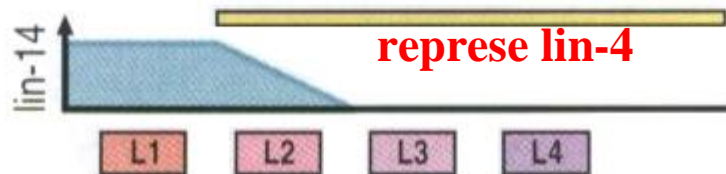


lin-14 mutace, „ztráta“ funkce

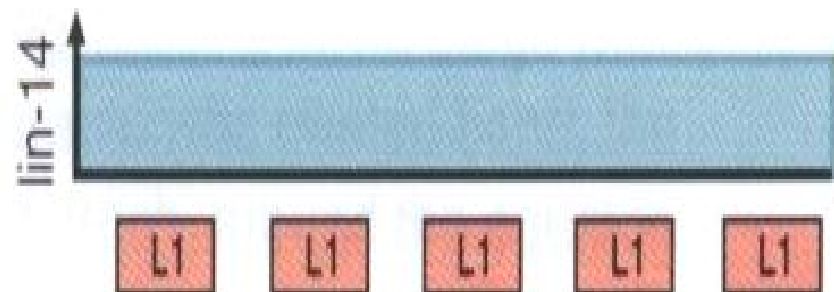


časový gradient lin-14 je výsledkem transkripční represe lin-14 proteinem lin-4, začínající při časném vývoji larvy

standardní typ



lin-14 mutace, „získání“ funkce, nebo „ztráta“ lin-4 funkce



Heterochonie

- ✓ Evoluční změny v rychlosti nebo časování vývojových událostí dávají vznik novým adultním fenotypům
- ✓ Odlišné rychlosti růstu různých částí těla během vývoje organismu jsou podstatou allometrických vztahů
- ✓ Heterochonie tvoří zjevnou asociaci mezi ontogenezou a fylogenezou

Heterochronická evoluce

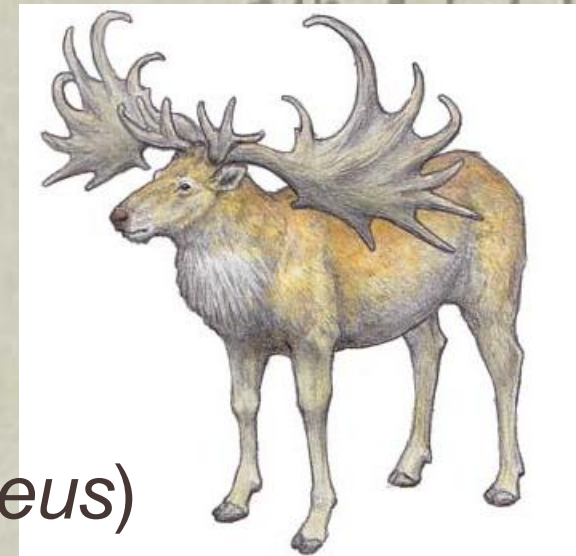
- ✓ Pedomorfie: je způsobena redukcí rychlosti vývoje znaku, což vede k juvenilním charakteristikám adultního potomstva jedince (vývin nastává časně = progeneze, nebo relativní redukce rychlosti nástupu jednoho znaku relativně k jinému = neotenie)
- ✓ Peramorfie: je způsobena zvýšením rychlosti vývoje znaku vedoucího ke zvýrazněnému znaku adultního potomstva (prodloužení růstové fáze = hypermorfóza)

Heterochronní evoluce

- ▼ Pedomorfie: neotenie u axolotla (*Ambystoma mexicanum*), kde juvenilní žábra jsou zachovány až do dospělosti



- ▼ Peramorfie: vzrůst velikosti paroží u irského losa (*Megaloceros giganteus*)





Polymorphism in the development of horns in the male dung beetle, *Onthophagus taurus*.
a | Small horns, produced by males below threshold size. **b** | Fully developed horns in a male over threshold size.

PROGERIE (progeneze) předčasné stárnutí u člověka

Obvykle single-genové mutace jsou odpovědné za senescentní fenotypy, které imitují normativní stárnutí

- impakt na určitý (jediný) orgán či tkáň (unimodální progeroidní syndromy), př. Alzheimer**
- impakt na mnohé orgány a tkáně (segmentační progeroidní syndromy), př. Hutchinson-Gilford, Werner**



NIH SeniorHealth

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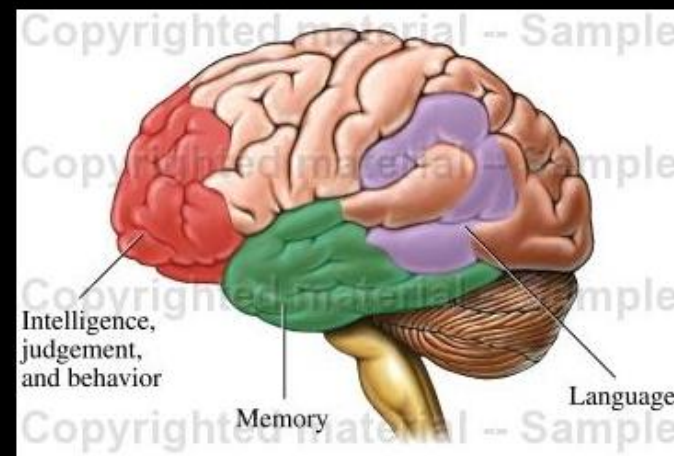
Dr. Alois Alzheimer
(1864-1915, Mnichov)

Alzheimer's Disease

Alzheimer's Disease Defined

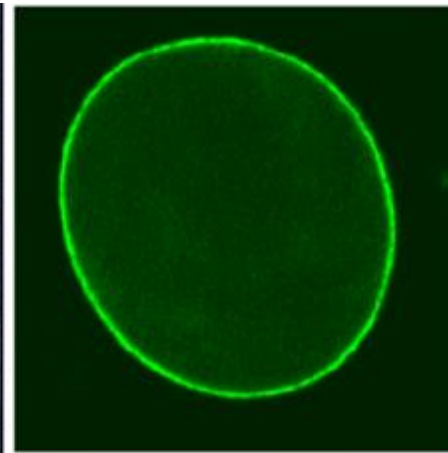
Dementia is a brain disorder that seriously affects a person's ability to carry out daily activities. Alzheimer's disease is the most common form of dementia among older people. It involves the parts of the brain that control thought, memory, and language. Every day scientists learn more, but right now the causes of Alzheimer's disease are still unknown, and there is no cure.

← Areas of the Brain Affected by Alzheimer's Disease

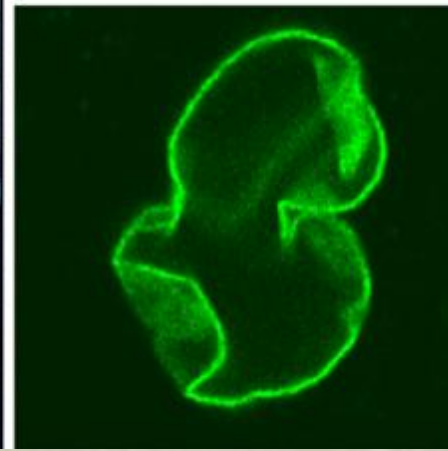


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wt



HGPS



Hutchinson-Gilfordův progeria-syndrom

je onemocnění dětí způsobené mutací proteinu významného pro architekturu jádra: aberantní morfologie.

Filamenty u periferie jádra odpovídají za udržování struktury a stability jádra, ochrana před mechanickým stresem. Lamina též udržují genomové domény, regulační funkce v expresi.

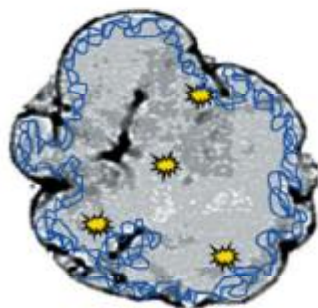
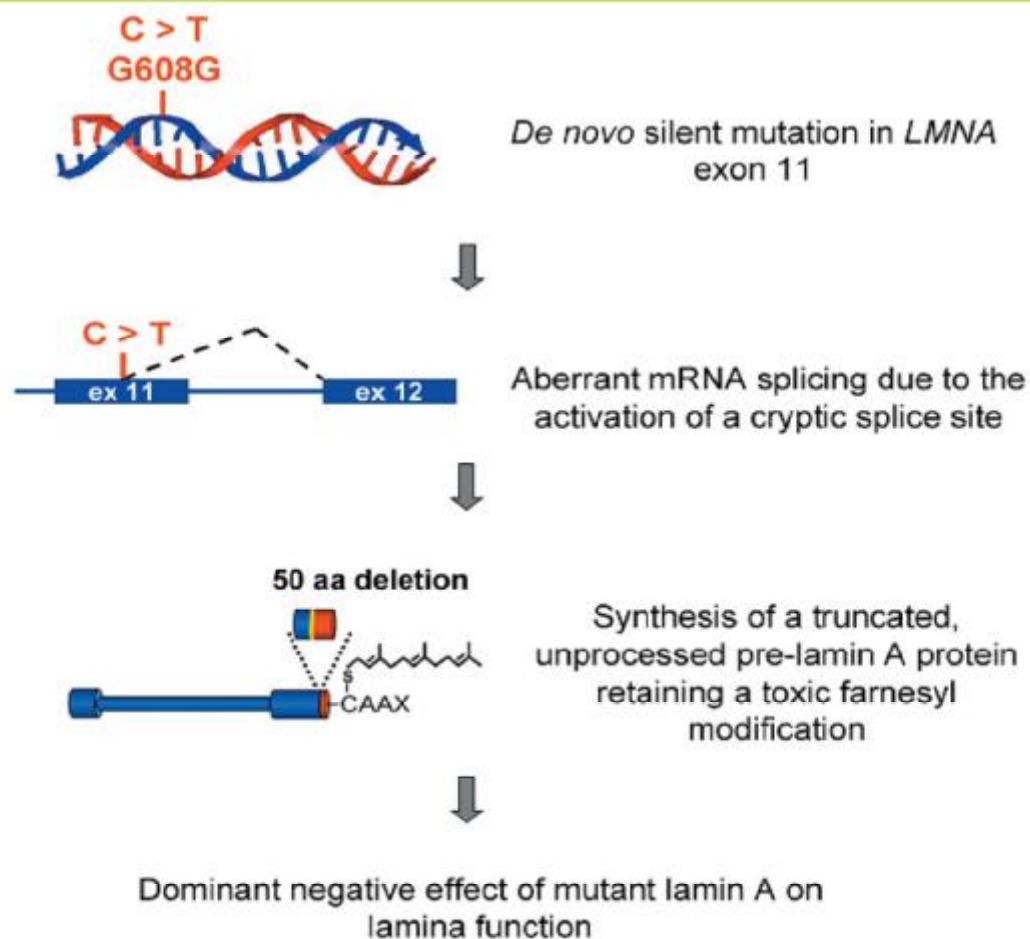
Spontánní bodová mutace
v kodonu 608 genu kódu-
jícího protein lamin A

Silentní aa-mutace aktivuje
kryptické místo sestřihu RNA

Mutantní protein progerin
postrádá 50aa na C-konci

Mění se jeho post-translační
modifikace

Progerie u člověka i myši,
scvrklá jádra,
defektní reparace DNA,
genomová nestabilita



- Nuclear morphological abnormalities
- Disorganization of heterochromatin
- Defective repair of DNA damage and increased genomic instability

DOI: 10.1371/journal.pbio.0030395.g001

The Molecular Basis of Nuclear Defects in HGPS



Figure 1. Photographs of a Female Patient with the Werner Syndrome, the Prototypic Segmental Progeroid Syndrome

The patient had multiple cardinal signs of the classical form of the disease, including bilateral cataracts, characteristic dermatological pathology, short stature, premature graying and thinning of scalp hair, and parental consanguinity (she was the product of a second cousin marriage). She also had type 2 diabetes mellitus, hypogonadism (with menopause at age 35 years), osteoporosis, flat feet, and a characteristic high-pitched, squeaky voice. Cytogenetic studies revealed minor mosaicisms for autosomal translocations, deletions, and aneuploidy involving the X chromosome, initially raising the question of a mosaic Turner syndrome (Jaramillo et al., 1985), but consistent with the more general cytogenetic instability and cell selection reported in such patients (Salk et al., 1981a, 1981b). The patient died at the age of 61 of unreported causes. The International Registry of Werner Syndrome (<http://www.pathology.washington.edu/research/werner/registry/frame2.html>) determined that this patient was homozygous for a previously described large genomic deletion involving exons 19–23 of the *WRN* gene. (A) Age ~13 (growth had ceased at age 12); (B) Age 21; (C) Age 56. Photographs are courtesy of the patient's spouse, with informed consent of the patient.

Wernerův syndrom – autosomální recesivní choroba, ztráta funkce DNA helikázy, onset v dospělém věku.

Helikáza hraje úlohu v DNA replikaci a rekombinaci, replikační vidlička.

Pacienti trpí defektní replikací DNA, problémy s reparací, restrukturalizace chromatinu.

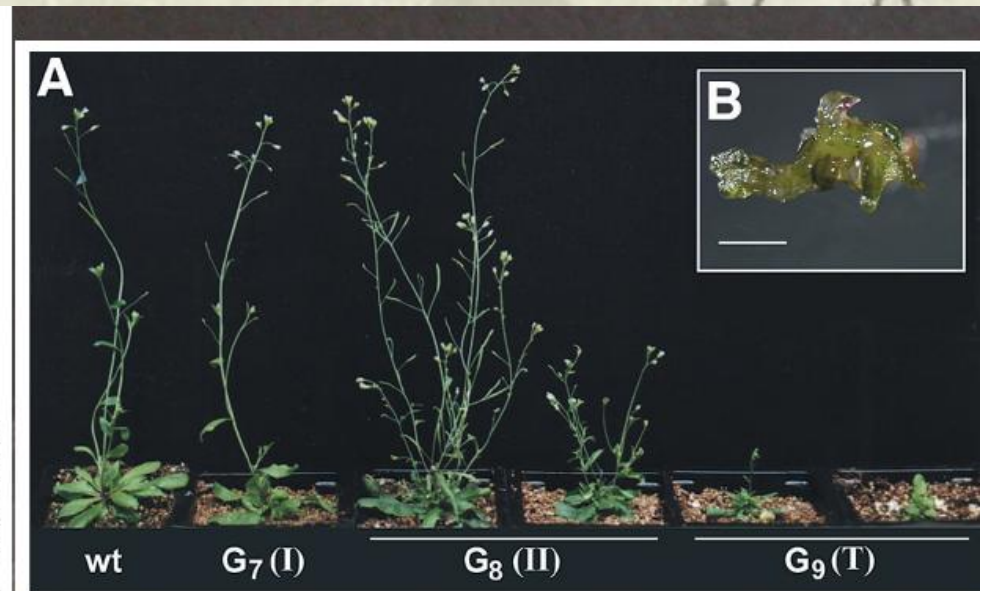
Senescence – permanentní zástava buněčného dělení, dysfunkce telomer.

Kuriozní antagonismus mezi stárnutím a rakovinou: buněčná senescence – zástava dělení – je obranným mechanismem k účinnému zastavení proliferace nádorových buněk.

Living with Genome Instability: Plant Responses to Telomere Dysfunction

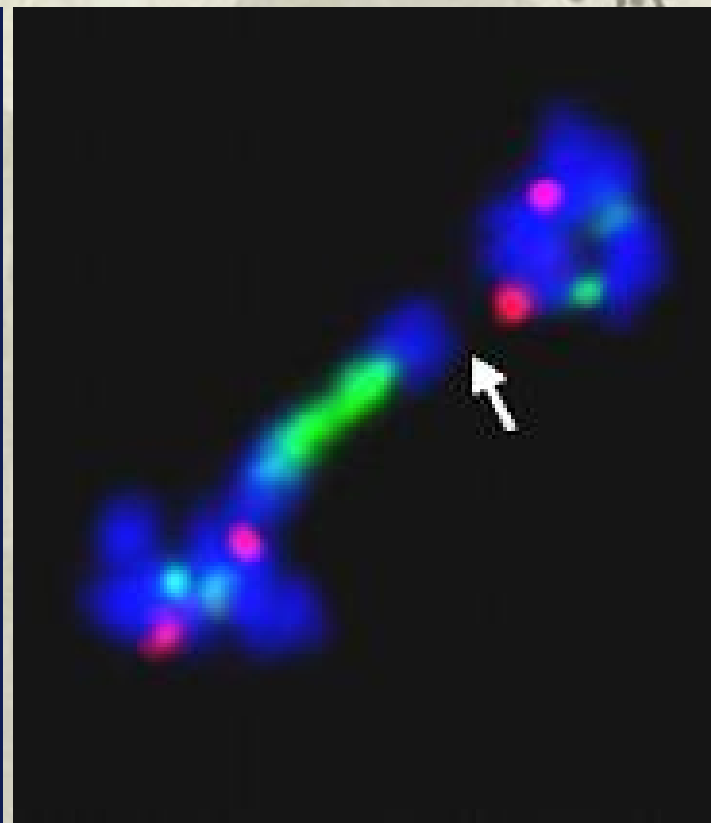
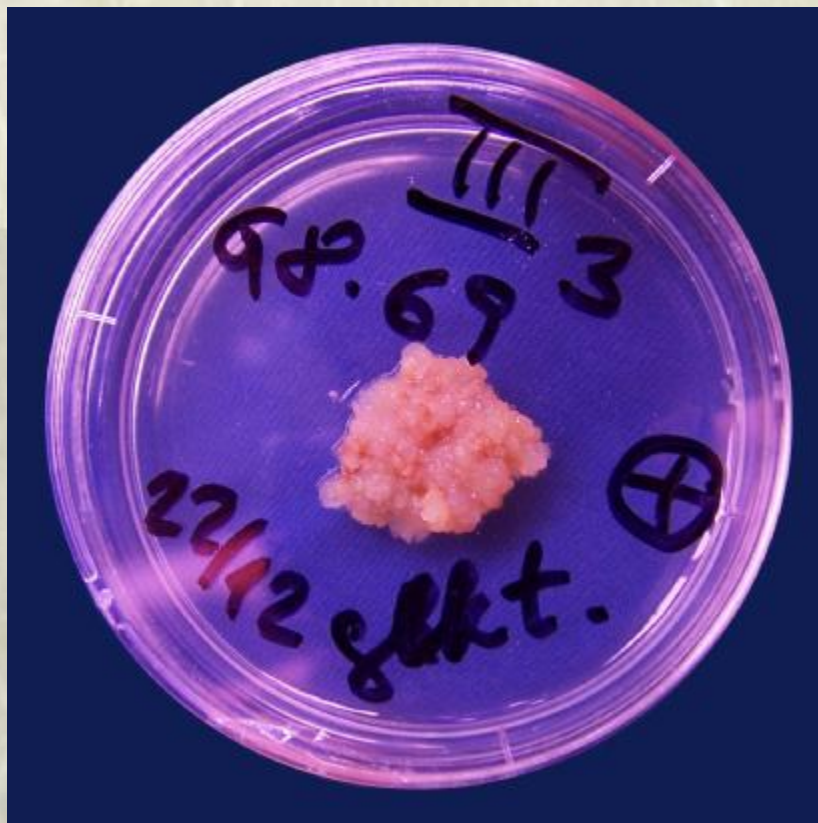
Karel Riha,¹ Thomas D. McKnight,² Lawrence R. Griffing,²
Dorothy E. Shippen^{1*}

Loss of telomere function in metazoans results in catastrophic damage to the genome, cell cycle arrest, and apoptosis. Here we show that the mustard weed *Arabidopsis thaliana* can survive up to 10 generations without telomerase. The last five generations of telomerase-deficient plants endured increasing levels of cytogenetic damage, which was correlated with developmental anomalies in both vegetative and reproductive organs. Mutants ultimately arrested at a terminal vegetative state harboring shoot meristems that were grossly enlarged, disorganized, and in some cases, dedifferentiated into a callusoid mass. Unexpectedly, late-generation mutants had an extended life-span and remained metabolically active. The differences in plant and animal responses to dysfunctional telomeres may reflect the more plastic nature of plant development and genome organization.



www.sciencemag.org SCIENCE VOL 291 2 MARCH 2001

Nesmrtelnost telomerázově-deficientních buněk kultivovaných *in vitro*





Eric J. Richards
Associate Professor of Biology

Office: Monsanto 511 Phone: (314) 935-7196

PERSPECTIVES

OPINION

Inherited epigenetic variation — revisiting soft inheritance

Eric J. Richards

Abstract | Phenotypic variation is traditionally parsed into components that are directed by genetic and environmental variation. The line between these two components is blurred by inherited epigenetic variation, which is potentially sensitive to environmental inputs. Chromatin and DNA methylation-based mechanisms mediate a semi-independent epigenetic inheritance system at the interface between genetic control and the environment. Should the existence of inherited epigenetic variation alter our thinking about evolutionary change?

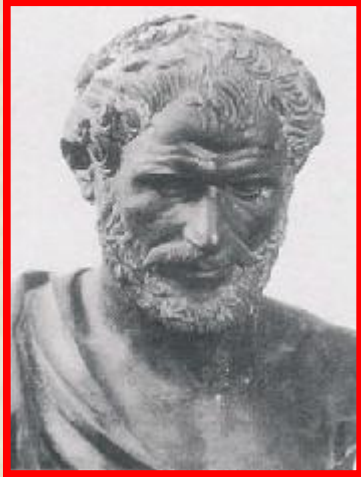
A unifying theme in biology is that the characteristics displayed by organisms are controlled — ultimately — by the nucleotide sequence of their genome. Another cornerstone of modern biology is that inherited information that is transmitted on the chro-

position of cytosine (5mC), the most common DNA modification used in eukaryotes. Curiously, although 5mC is not present in all eukaryotic species, cytosine methylation is an ancient mechanism that has been lost relatively recently in some eukaryotic

of epigenetic modifications from their genotypic context. This autonomy, coupled with the stability and persistence of epigenetic marks, provides an alternative inheritance system, operating at the interface of the familiar stable genetic system that is encoded in primary nucleotide sequence and the transient protein–DNA interactions that mediate gene-expression changes in response to developmental signals and environmental stimuli.

Epigenetic inheritance

The molecular pathways that initiate different epigenetic states on identical DNA sequences are now coming into focus through recent studies demonstrating that small RNA molecules, generated by the RNA interference machinery (BOX 3), can direct cytosine methylation and histone modification marks that are associated with transcriptional quiescence to particular genomic regions (reviewed in REFS 4–6). In addition, epigenetic silencing machinery can be recruited to specific genomic



Aristoteles
(384-322 př.Kr.)

EPIGENEZE

**individuální vývoj organismů spočívá
v postupném vzrůstu jejich komplexity**

EPIGENETIKA

kombinuje ...

preformistickou GENETIKU

**(studium dědičného materiálu
nacházejícího se v zygotě)**

a vývojovou biologii

**(studium změn, ke kterým dochází
v post-zygotickém období - EPIgeneze)**



Conrad Waddington
(1905-75)

Box 2 | Epigenetic phenomena

The fundamental characteristic of epigenetic phenomena is that one genotype can show alternative phenotypes, which are based on the epigenetic state of one or more loci within the genome. Many of the classic epigenetic experimental systems were discovered because of apparent genetic instability or deviations from expected Mendelian inheritance patterns. Some of the best-studied epigenetic phenomena are listed below:

Transposon activity 'changes in phase'. Originally defined and articulated by McClintock; an alteration in transposition rate or the expression of a nearby gene correlated with a change in the epigenetic state of the transposon

Position-effect variegation. Caused by the reversible inactivation of a gene that is due to a change in genomic environment, usually because of moving a euchromatic gene close to a domain of heterochromatin

X-chromosome inactivation. A sex-chromosome dosage-compensation mechanism in mammals that leads to the transcriptional silencing of a large percentage of genes on one X-chromosome in XX females

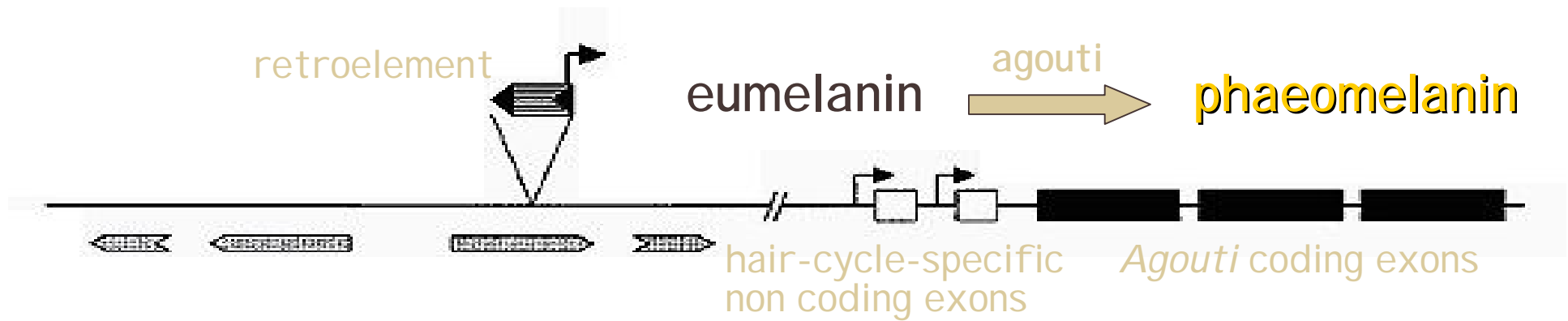
Paramutation. An allelic interaction that leads to heritable changes in one allele's gene-expression state

Parental imprinting. Parent-of-origin specific gene expression, whereby a single allele is differentially expressed depending on the sex of the parent transmitting the allele

Transgene silencing. Can occur at the transcriptional or post-transcriptional level; post-transcriptional gene silencing was discovered in early plant transgenesis experiments and was later found to be mediated by RNA interference pathways.

Table 1 | Examples of meiotically transmitted epialleles

| Locus/epiallele | Organism | Mechanism | Stability | Phenotype |
|--------------------------|------------------------------------|--|------------|---------------------------------------|
| <i>a-m2-7991A1</i> | Maize | Transposon-associated; the <i>Spm</i> element is inserted upstream of the <i>a</i> pigmentation gene; the epigenetic state of the transposon is associated with DNA methylation | Metastable | Pigmentation and transposition |
| <i>A^y</i> | Mouse | Transposon-associated; the IAP element is inserted upstream; loss of the silent epigenetic state is associated with overexpression | Metastable | Yellow coat colour; obesity |
| <i>Axin^{Fu}</i> | Mouse | Transposon-associated; intronic IAP element; loss of the silent epigenetic state of the transposon is associated with overexpression of a partial <i>Axin</i> coding sequence | Metastable | Kinked tail |
| <i>B'</i> | Maize | The epigenetic state of the short tandem repeat block 100 kb upstream of the coding sequencing is associated with transcriptional inactivity; generated by paramutation | Stable | Reduced pigmentation |
| <i>b2</i> | <i>Ascobolus immersus</i> | Induced by gene duplication (methylation is induced premeiotically); DNA hypermethylation is associated with gene silencing | Metastable | Reduced pigmentation |
| <i>bal</i> | <i>Arabidopsis thaliana</i> | Loss of gene silencing of an array of pathogen resistance genes leads to overexpression | Metastable | Dwarfism; elevated disease resistance |
| <i>fwa</i> | <i>Arabidopsis thaliana</i> | Transposon-associated; the SINE element is upstream of the coding sequence; loss of the silent epigenetic state on SINE-associated repeats is associated with ectopic expression | Stable | Delayed flowering |
| <i>Lcyc</i> | <i>Linaria vulgaris</i> (toadflax) | DNA hypermethylation of coding sequence is associated with gene silencing | Metastable | Radially symmetrical flowers |
| <i>MLH1</i> | Human | DNA hypermethylation of upstream region is associated with gene silencing | Metastable | Predisposition to tumour formation |
| <i>P-pr</i> | Maize | Elevated cytosine methylation of coding sequence is associated with gene silencing | Stable | Reduced pigmentation |
| <i>pai2</i> | <i>Arabidopsis thaliana</i> | Repeat-associated; RNA-directed DNA hypermethylation of coding sequence is associated with gene silencing | Metastable | Metabolic |
| <i>sup</i> | <i>Arabidopsis thaliana</i> | DNA hypermethylation of coding sequence is associated with gene silencing | Metastable | Abnormal floral organ number |



Agouti Viable Yellow - epigenetický mozaicismus :

metylace retroelementu vede k inaktivaci ektopické exprese



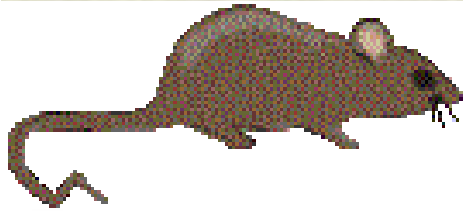
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**Případ metastabilní epialely *Axin Fused* :
paternální exprese, lokus *kinked tail* je však epigeneticky
labilní, expresivita variabilní**



Případ metastabilní epialely *Axin Fused* :



paternální exprese, lokus *kinked tail* je však epigeneticky labilní, expresivita variabilní

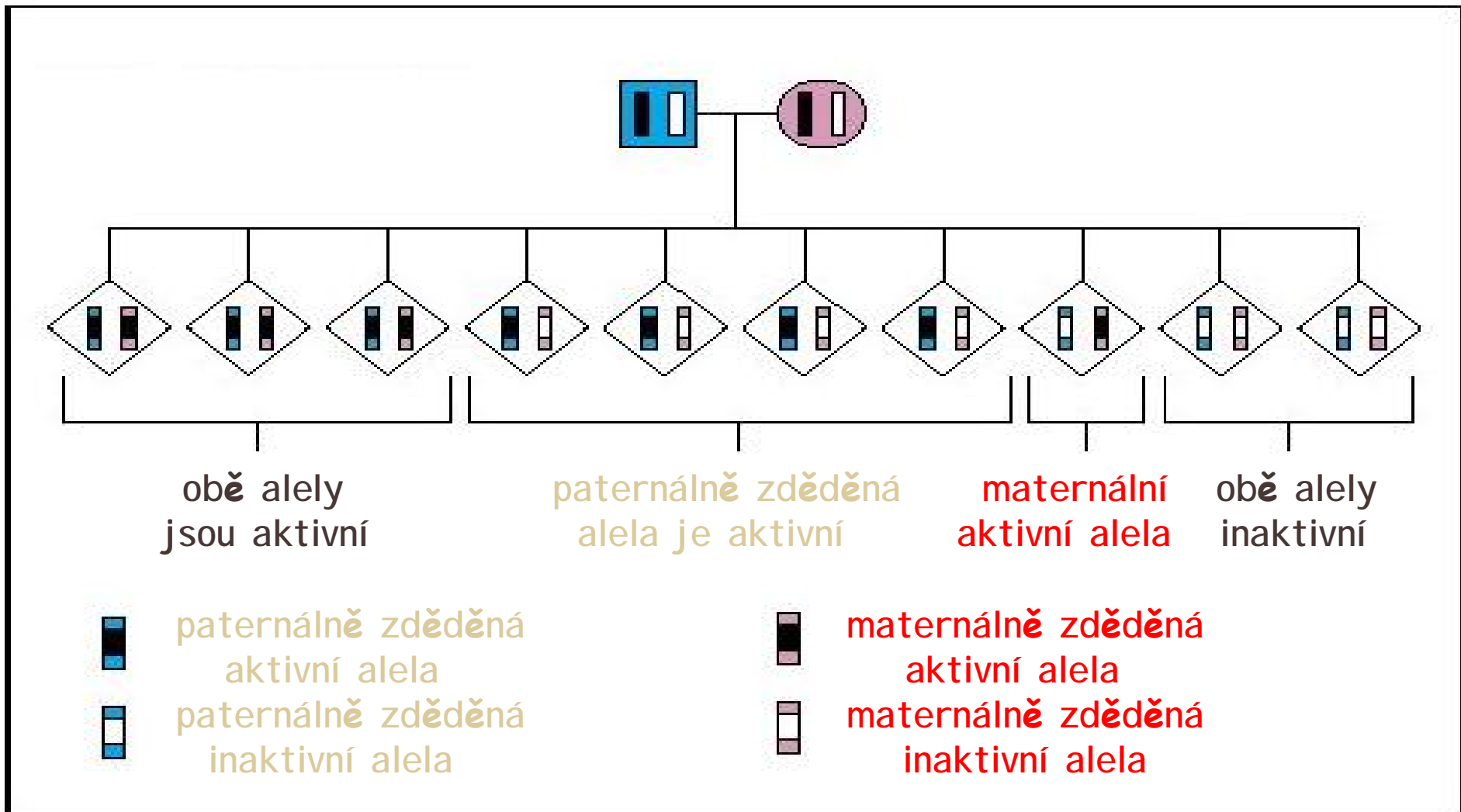


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Vznik a dědičnost rostlinných monster: (epi)mutace



Carl Linnaeus
(1707–1778)



Charles Darwin
(1809–1882)



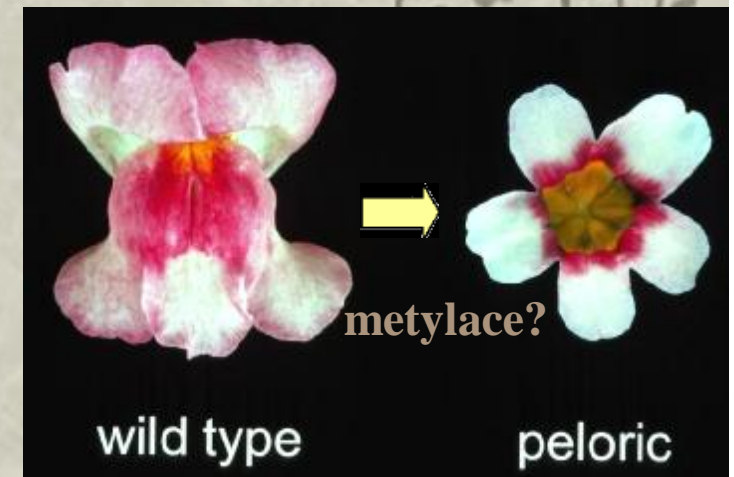
Enrico Coen
(1999)



Linnaeus ... pelorie u Inice, historicky první doložená mutace? (1744)

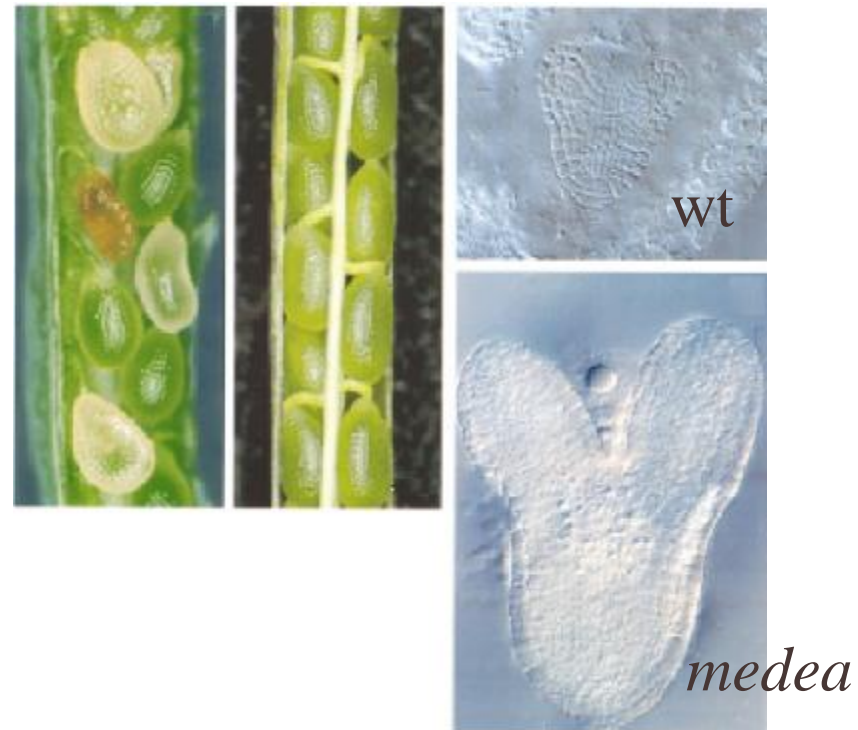
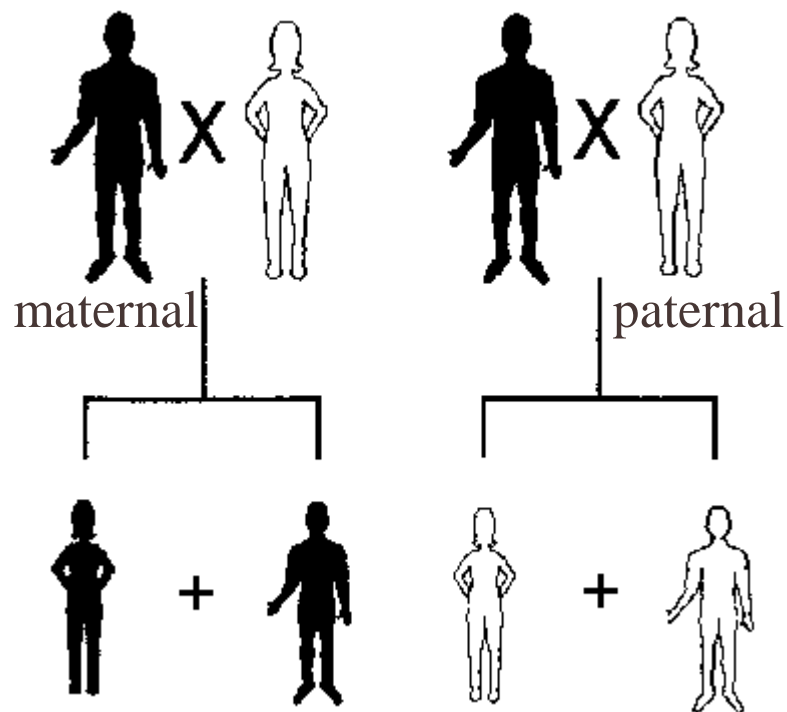
Darwin ... křížení normálních a pelorických forem v F2 127:37 (*Variation of Animals and Plants under Domestication* 1868)

Coen ... hypermetylace homologu genu *cycloidea*



Tři třídy dědičné epigenetické variability

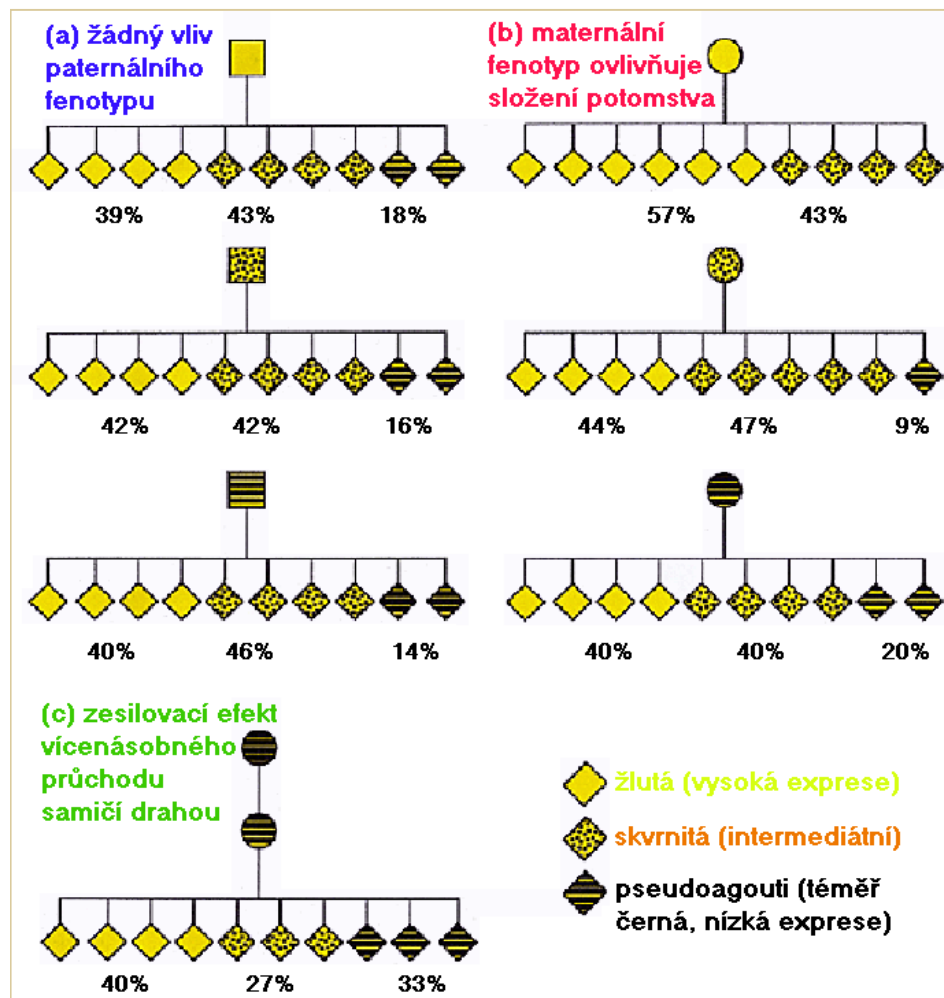
- (A) Epigenotyp lokusu je striktně determinován genotypem; epigenotyp je obligatorním fenotypem alternujících genotypů. Penetrance and expresivita jsou vysoké.
Příklad: sex-specifický parentální imprinting u savců, maternální exprese MEDEA u rostlin



Tři třídy dědičné epigenetické variability

(B) „Usnadněná“ epigenetická variabilita, která funguje v „pravděpodobnostním“ režimu, obvykle v kontextu s genotypem.

Penetrance a expresivita jsou variabilní.



Příklad: lokus Agouti viable yellow u myši, lokus Superman v DNA metylačních mutantech u Arabidopsis

Tři třídy dědičné epigenetické variability

- (C) Stochastické případy dávají vznik alternativním epi-alelám v omezené četnosti, bez ohledu na genotyp.
Penetrance and expresivita jsou nízké.
Příklad: divergence epigenotype v průběhu stárnutí v somatických liniích buněk, pelorické mutanty u rostlin

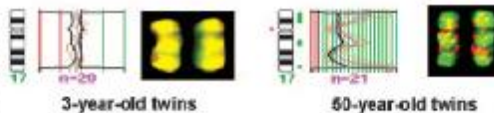
Epigenetic differences arise during the lifetime of monozygotic twins

PNAS | July 26, 2005 | vol. 102 | no. 30

Mario F. Fraga^{*}, Esteban Ballestar^{*}, Maria F. Paz^{*}, Santiago Ropero^{*}, Fernando Setien^{*}, Maria L. Ballestar^{*}, Damia Heine-Suñer[†], Juan C. Cigudosa[‡], Miguel Urioste[§], Javier Benitez[§], Manuel Boix-Chornet[§], Abel Sanchez-Aguilera[¶], Charlotte Ling[¶], Emma Carlsson[¶], Pernille Poulsen^{**}, Allan Vaag^{**}, Zarko Stephan^{††}, Tim D. Spector^{††}, Yue-Zhong Wu^{‡‡}, Christoph Plass^{‡‡}, and Manel Esteller^{*§§}

^{*}Epigenetics, [†]Cytogenetics, and [‡]Genetic Laboratories, Spanish National Cancer Centre (CNIO), Melchor Fernandez Almagro 3, 28029 Madrid, Spain; [§]Department of Behavioral Science, University of Valencia, 4610 Valencia, Spain; [¶]Molecular Genetics Laboratory, Genetics Department, Son Dureta Hospital, 07014 Palma de Mallorca, Spain; ^{‡‡}Department of Clinical Sciences, University Hospital Malmö, Lund University, S-205 02 Malmö, Sweden; ^{**}Steno Diabetes Center, 2820 Gentofte, Denmark; ^{††}Twin Research and Genetic Epidemiology Unit, St. Thomas' Hospital, London SE1 7EH, United Kingdom; and ^{§§}Human Cancer Genetics Program, Department of Molecular Virology, Immunology, and Medical Genetics, Ohio State University, Columbus, OH 43210

Monozygous twins share a common genotype. However, most monozygotic twin pairs are not identical; several types of phenotypic discordance may be observed, such as differences in susceptibilities to disease and a wide range of anthropomorphic features. There are several possible explanations for these observations, but one is the existence of epigenetic differences. To address this issue, we examined the global and locus-specific differences in DNA methylation and histone acetylation of a large cohort of monozygotic twins. We found that, although twins are epigenetically indistinguishable during the early years of life, older monozygous twins exhibited remarkable differences in their overall content and genomic distribution of 5-methylcytosine DNA and histone acetylation, affecting their gene-expression portrait. These findings indicate how an appreciation of epigenetics is missing from our understanding of how different phenotypes can be originated from the same genotype.



Meioticky NEpřenášené epigenetické stavy ovlivněné prostředím

The neo-Darwinian concept of inheritance posits that the hereditary material is 'hard' and impervious to environmental influences. If the formation of epialleles is random and not initiated or guided by the environment, the generation of epigenetic variation could be equated with random genetic mutation without otherwise altering our current view of evolutionary mechanisms. On the other hand, if the physical or behavioural environment of the cell or organism influences epiallele formation, a mechanistic foundation for soft inheritance exists

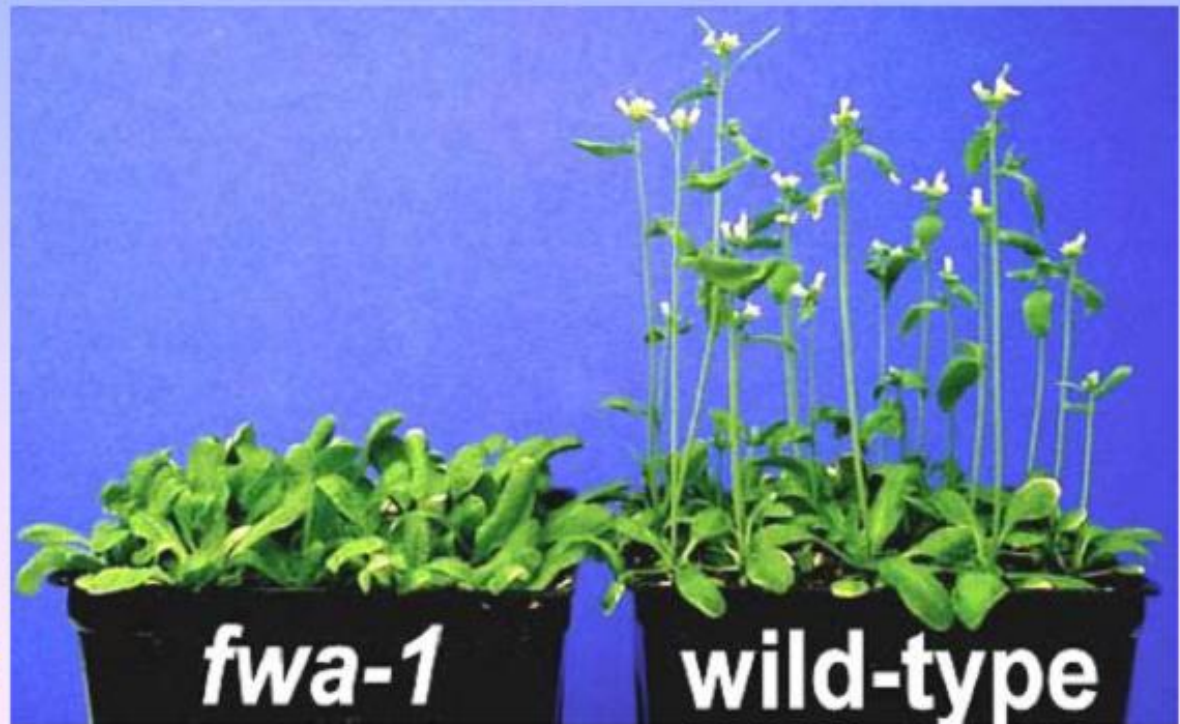
Recentní výsledky ukazují, že epigenetické stavy (alel) mohou být ovlivňovány prostředím, například:

- **chladové působení na semena/rostliny může vést ke změnám struktury chromatinu a metylací DNA, vernalizace**

Metylace DNA a řízení květních procesů



**Elliot M. Meyerowitz
(CalTech)**



Meioticky nepřenášené epigenetické stavy ovlivněné prostředím

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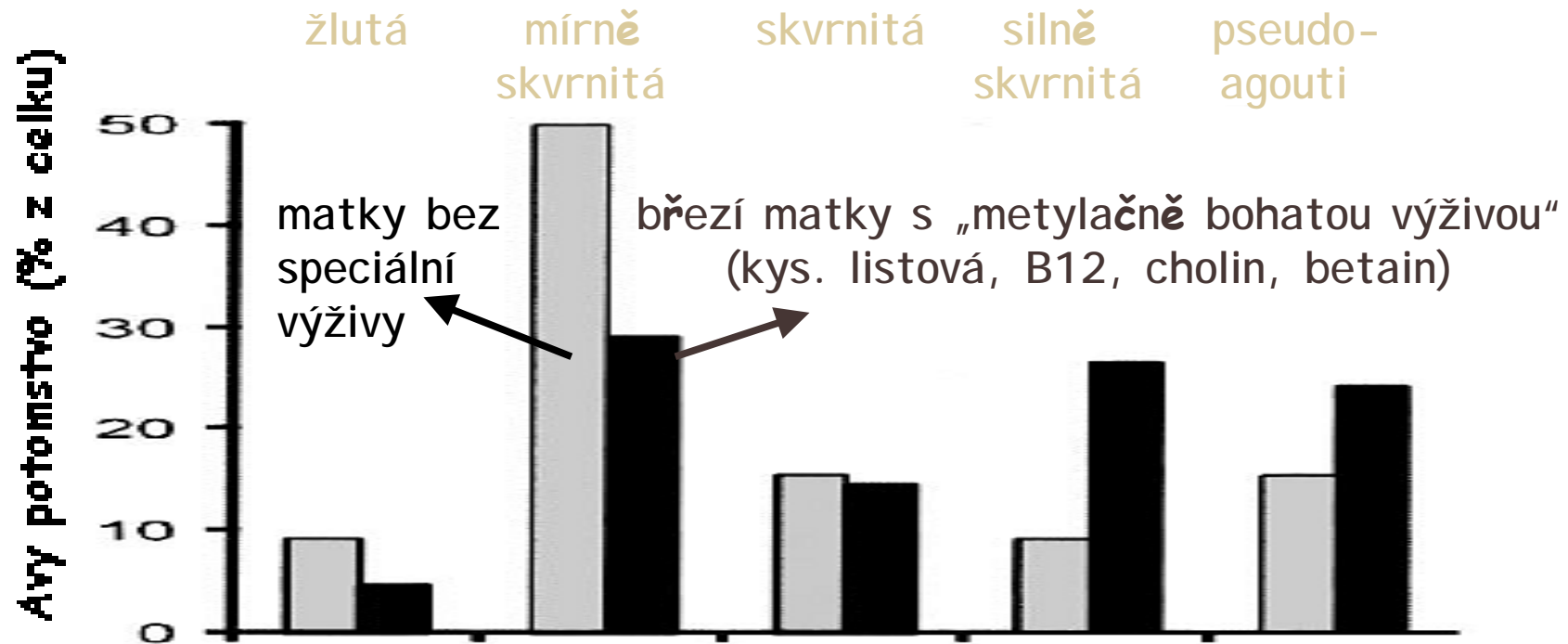
- **chládové působení na semena/rostliny může vést ke změnám struktury chromatinu a metylací DNA, vernalizace**
- **změny metylace DNA v důsledku dietního režimu u hlodavců**

Transposable Elements:
Targets for Early Nutritional Effects
on Epigenetic Gene Regulation

Robert A. Waterland and Randy L. Jirtle

MICB
Molecular and Cellular Biology





Meioticky nepřenášené epigenetické stavy ovlivněné prostředím

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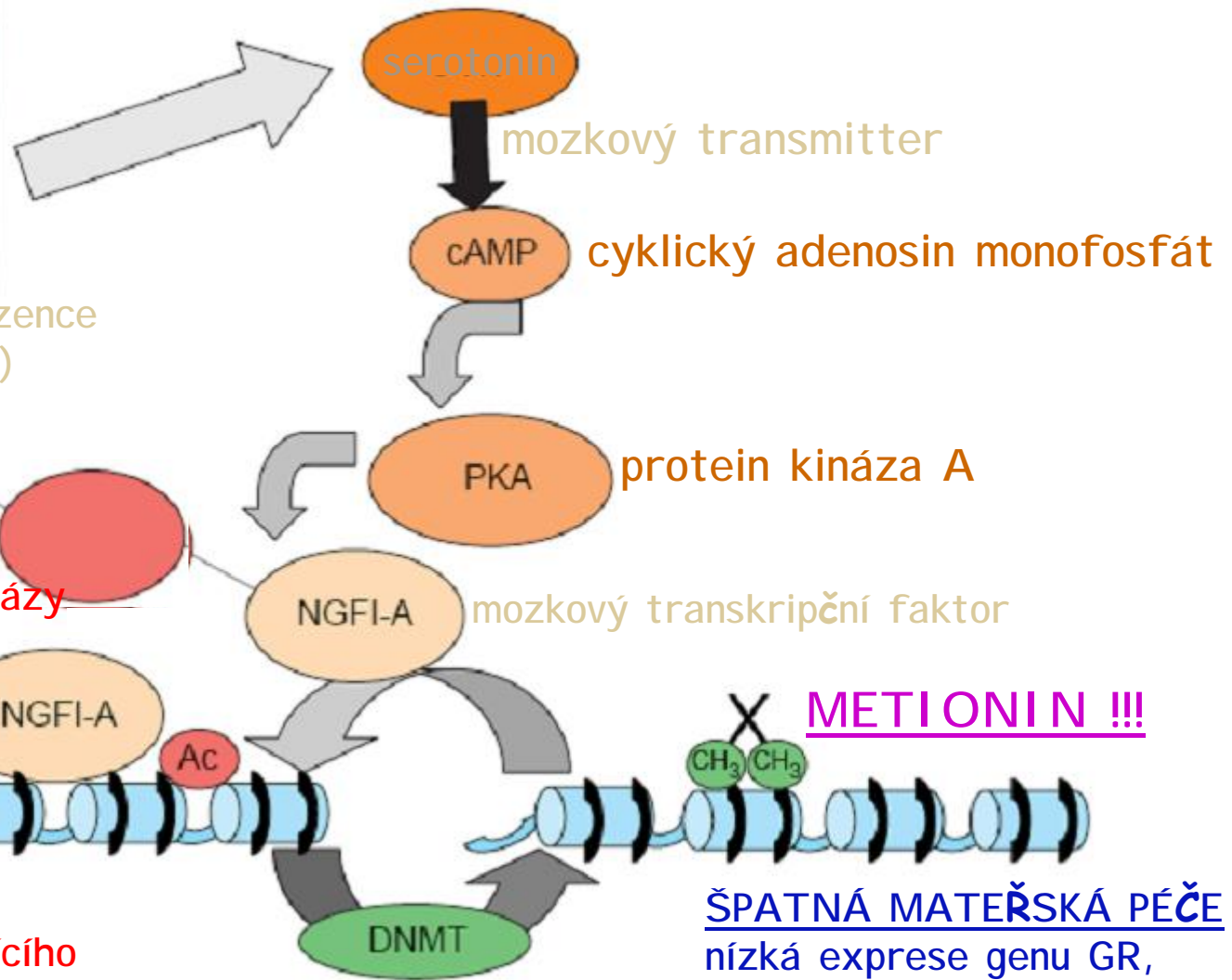
- **chládové působení na semena/rostliny může vést ke změnám struktury chromatinu a metylací DNA, vernalizace**
- **změny metylace DNA v důsledku dietního režimu u hlodavců**
- **mateřská péče vede k postnatálnímu remodelování epigenetických stavů glukokortikoidního receptorového genu**

Maternální programování epigenetických stavů

Maternální péče jako model „experience-dependent“ chromatinové plasticity



mateřská péče o novorozence (lízání a mazlení)



TRICHOSTATIN !!!

DOBŘÁ MATEŘSKÁ PÉČE
vysoká exprese genu kódujícího
glukokortikoidní receptor -
STABILNÍ PSYCHIKA DOSPĚLÉHO
POTOMSTVA (Ac = acetylace histonů)

METIONIN !!!

ŠPATNÁ MATEŘSKÁ PÉČE
nízká exprese genu GR,
STŘEŠOVÁ PSYCHIKA
DOSPĚLÉHO POTOMSTVA
(CH₃ = metylace DNA)

The preceding examples show that epigenotypes can respond to an organism's physical, nutritional and even behavioural environment. Although these examples do not involve meiotic transmission of the environmentally induced epialleles, this is not always the case.

Environmentálně indukované dědičné epigenetické změny, příklady:

- aplikace disruptorů endokrinních funkcí na gravidní krysy způsobuje poruchy samčí fertility v řadě generací, F1-F4

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Science 3 June 2005:

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DOI: 10.1126/science.1108190

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REPORTS

Epigenetic Transgenerational Actions of Endocrine Disruptors and Male Fertility

Matthew D. Anway, Andrea S. Cupp,^{*} Mehmet Uzumcu,[†] Michael K. Skinner[‡]

Transgenerational effects of environmental toxins require either a chromosomal or epigenetic alteration in the germ line. Transient exposure of a gestating female rat during the period of gonadal sex determination to the endocrine disruptors vinclozolin (an antiandrogenic compound) or methoxychlor (an estrogenic compound) induced an adult phenotype in the F₁ generation of decreased spermatogenic capacity (cell number and viability) and increased incidence of male infertility. These effects were transferred through the male germ line to nearly all males of all subsequent generations examined (that is, F₁ to F₄). The effects on reproduction correlate with altered DNA methylation patterns in the germ line. The ability of an environmental factor (for example, endocrine disruptor) to reprogram the germ line and to promote a transgenerational disease state has significant implications for evolutionary biology and disease etiology.

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[†] Present address: Department of Animal Science, Rutgers University, 84 Lipman Drive, New Brunswick, NJ 08901-8525, USA.

[‡] To whom correspondence should be addressed. E-mail: skinner@mail.wsu.edu

The preceding examples show that epigenotypes can respond to an organism's physical, nutritional and even behavioural environment. Although these examples do not involve meiotic transmission of the environmentally induced epialleles, this is not always the case.

Environmentálně indukované dědičné epigenetické změny, příklady:

- klonování myši cestou transplantace jader somatických buněk vede k dědičným změnám genové exprese, růstovým defektům a metylace DNA



Title: Epigenetic inheritance in the mouse

Author(s): [Roemer I](#), [Reik W](#), [Dean W](#), [Klose J](#)

Source: CURRENT BIOLOGY 7 (4): 277-280 APR 1 1997

Abstract: Acquired **epigenetic** modifications, such as DNA methylation or stable chromatin structures, are not normally thought to be inherited through the germline to future generations in mammals [1,2]. Studies in the mouse have shown that specific manipulations of early embryos, such as nuclear transplantation, can result in altered patterns of gene expression and induce phenotypic alterations at later stages of development [3-5]. These effects are consistent with acquired **epigenetic** modifications that are somatically heritable, such as DNA methylation. Repression and DNA methylation of genes encoding major urinary proteins, repression of the gene encoding olfactory marker protein, and reduced body weight can be experimentally induced by nuclear transplantation in early embryos M. Strikingly, we now report that these acquired phenotypes are transmitted to most of the offspring of manipulated parent mice. This is the first demonstration of **epigenetic** inheritance of specific alterations of gene expression through the germline. These observations establish a mammalian model for transgenerational effects that are important for human health, and also raise the question of the evolutionary importance of **epigenetic** inheritance.



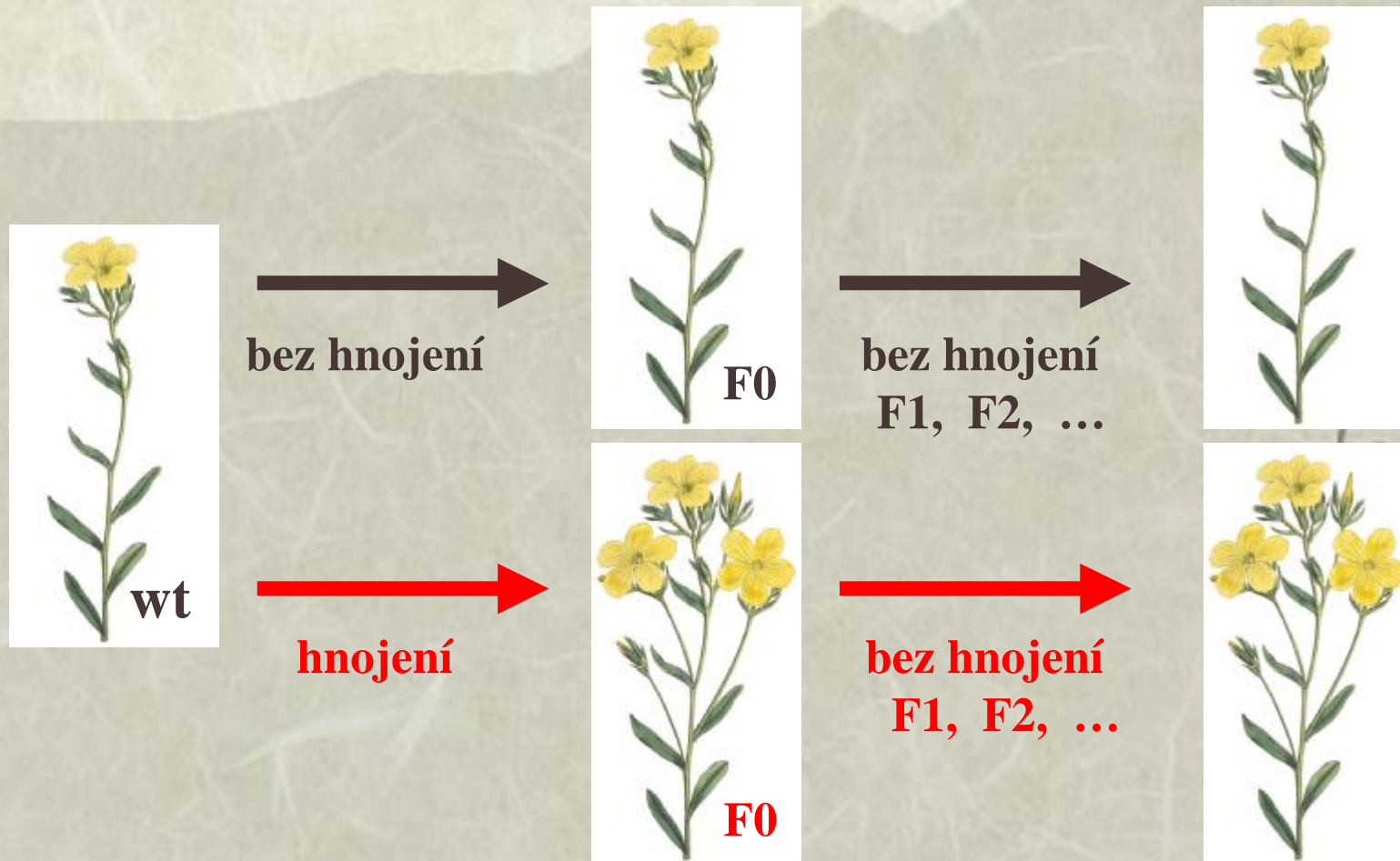
The preceding examples show that epigenotypes can respond to an organism's physical, nutritional and even behavioural environment. Although these examples do not involve meiotic transmission of the environmentally induced epialleles, this is not always the case.

Environmentálně indukované dědičné epigenetické změny, příklady:

- četné jsou případy dědičných změn u krytosemenných rostlin vzhledem k nepřítomnosti pravé zárodečné dráhy (genotrofy indukované podnebím u lnu, hypometylací-DNA indukovaná sex-reverze u knotovky)

Meiotický přenos epigenetického stavu (fenotypu) aneb environmentální indukce dědičných změn

- genotrofy u Inu (vliv podnebí a hnojení na větvení)

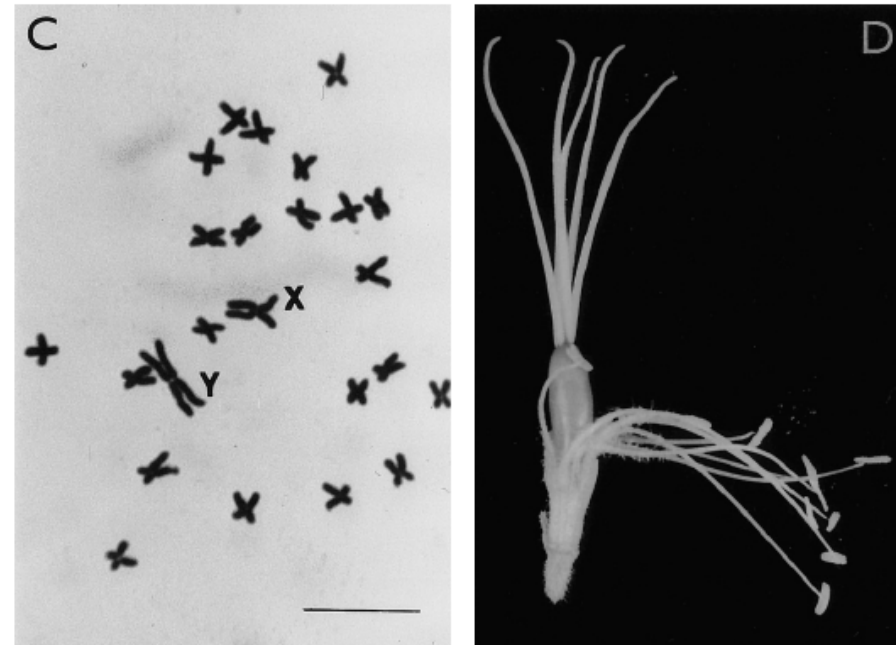


ORIGINAL PAPER

Bohuslav Janoušek · Jiří Široký · Boris Vyskot

**Epigenetic control of sexual phenotype in a dioecious plant,
*Melandrium album***

Abstract *Melandrium album* (syn. *Silene latifolia*) is a model dioecious species in which the Y chromosome, present only in heterogametic males, plays both a male-determining and a strict female-suppressing role. We showed that treatment with 5-azacytidine (5-azaC) induces a sex change to androhermaphroditism (andromonoecy) in about 21% of male plants, while no apparent phenotypic effect was observed in females. All of these bisexual androhermaphrodites (with the standard male 2n, 2A + XY karyotype) were mosaics possessing both male and hermaphrodite flowers and, moreover, the hermaphrodite flowers displayed various degrees of gynoecium development and seed setting. Southern hybridization analysis with a repetitive DNA probe showed that the 5-azacytidine-treated plants were significantly hypomethylated in CG doublets, but only to a minor degree in CNG triplets. The bisexual trait was transmitted to two successive generations, but only when androhermaphrodite plants were used as pollen donors. The sex reversal was inherited with incomplete penetrance and varying expressivity. Based on the uniparental inheritance pattern of androhermaphroditism we conclude that it originated either by 5-azaC induced inhibition of Y-linked female-sup-



C Representative male karyotype of the A1 androhermaphrodite (sex chromosomes indicated, scale bar 10 μ m). **D** Perfect hermaphrodite flower from the self progeny of A1

Was Lamarck a little bit right ?



Jean-Baptiste Lamarck (1744-1829)