February 1997 Vol. 13 No. 2
pp. 43–84 ISSN 0168-9525

trends in GENETICS

Vulval development in *C. elegans*

- Bonsai genomics
- Mutation scanning
- MYB proteins in plants
- YAC transgenic mice

Caenorhabditis elegans

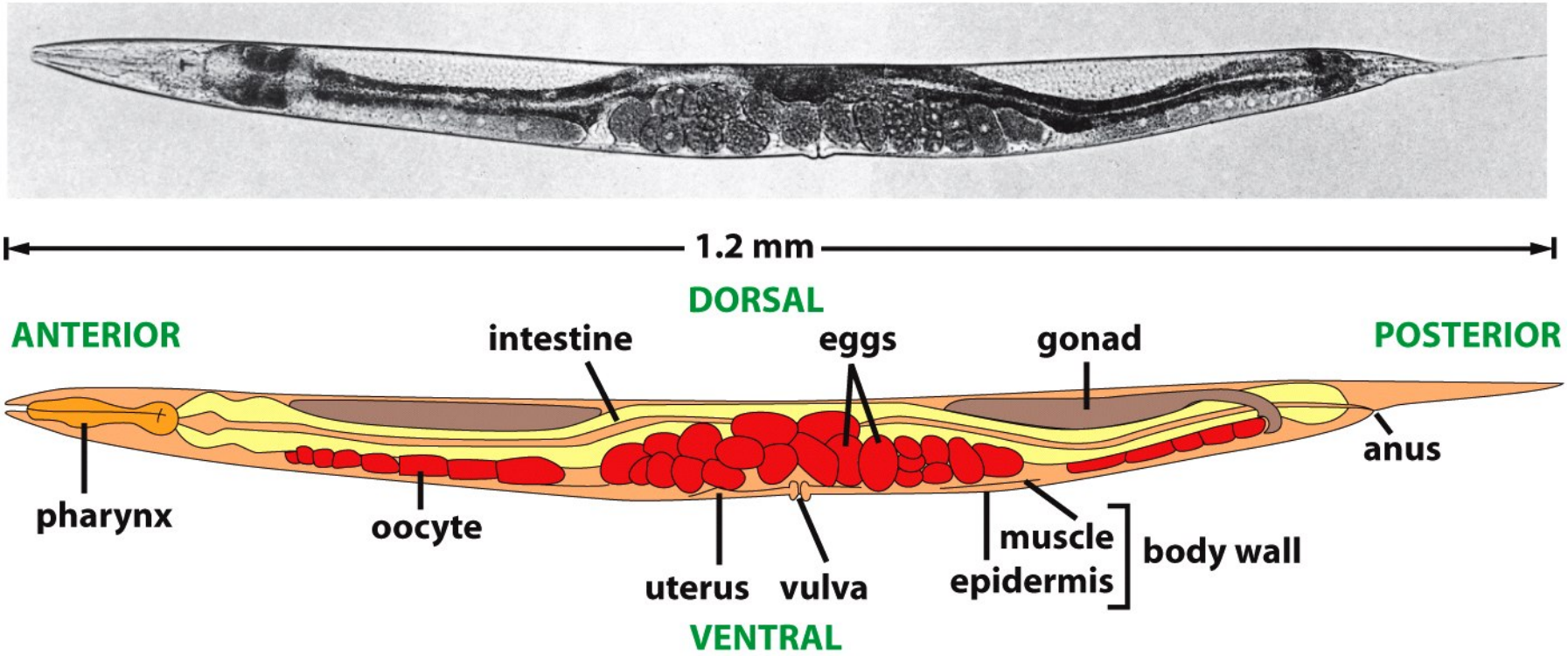


Figure 22-17 Molecular Biology of the Cell 5/e (© Garland Science 2008)

http://www.wormbase.org/

CELL 1321

Caenorhabditis elegans sukkulamato eli nematodi

Hermafrodiitti 959 solua plus 2000 muna/siittiösolua
Koiras 1031 solua plus 1000 siittiösolua

6 paria kromosomeja
17 800 geeniä

Otettiin käyttöön aluksi hermostoa koskevia tutkimuksia varten, koska pystyi elämään ja lisääntymäänkin ilman hermoja. Neuroneja on soluista noin 300, lihassoluja 81 neljässä nipussa

Kehitysbiologian malliksi joutui tuota pikaa

"Kaikki geenit" sekvensoitiin 1998 (80 miljoonaa nukleotidiparia sadasta miljoonasta)

lin	abnormal cell lineage
pop	plenty of pharynx
mom	more mesoderm
let	lethal
sem	sex muscle abnormal
unc	uncoordinated body movements

Mutanttien järjestelmällinen (ja tylsä) nimeäminenkin kertoo, että *C. elegans* otettiin käyttöön vallan tahallaan ja harkitusti, tiettyjen ei-triviaalien kysymysten ratkomiseksi eikä suinkaan huvin vuoksi tai sattumalta

Aloittaja: Sydney Brenner **1963**

What is *Caenorhabditis elegans* and why work on it? An introduction for those unfamiliar with "The Worm".

What is *C. elegans*?

***C. elegans* is a nematode - a member of the phylum Nematoda:**

> **Nematoda. The roundworms and threadworms, a phylum of smooth-skinned, unsegmented worms with a long cylindrical body shape tapered at the ends; includes free-living and parasitic forms both aquatic and terrestrial.**
>
> ***(Academic press Dictionary of Science and Technology)***

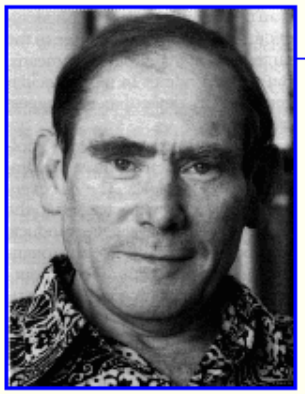
It is small, growing to about 1 mm in length, and lives in the soil - especially rotting vegetation - in many parts of the world, where it survives by feeding on microbes such as bacteria. It is of no economic importance to man.

Why study *C. elegans*?

Around the world many hundreds of scientists are working full time investigating the biology of *C. elegans*. Between October, 1994 and January, 1995 73 scientific articles about this creature appeared in international science journals. Currently an international consortium of laboratories are collaborating on a project to sequence the entire 100,000,000 bases of DNA of the *C. elegans* genome. Why invest so much effort into the study of such an insignificant organism?

C. elegans is about as primitive an organism that exists which nonetheless shares many of the essential biological characteristics that are central problems of human biology. The worm is conceived as a single cell which undergoes a complex process of development, starting with embryonic cleavage, proceeding through morphogenesis and growth to the adult. It has a nervous system with a 'brain' (the circumpharyngeal nerve ring). It exhibits behavior and is even capable of rudimentary learning. It produces sperm and eggs, mates and reproduces. After reproduction it gradually ages, loses vigor and finally dies. Embryogenesis, morphogenesis, development, nerve function, behavior and aging, and how they are determined by genes: the list includes most of the fundamental mysteries of modern biology. (We must, alas, assume that the greatest biological enigma of all, consciousness, is absent from *C. elegans* - although this remains to be demonstrated!) *C. elegans* exhibits these phenomena, yet is only 1 mm long and may be handled as a microorganism - it is usually grown on petri plates seeded with bacteria. All 959 somatic cells of its transparent body are visible with a microscope, and its average life span is a mere 2-3 weeks. Thus *C. elegans* provides the researcher with the ideal compromise between complexity and tractability.

How the *C. elegans* project was initiated by the South African biologist Sydney Brenner can be found via the accompanying link.



Sydney Brenner

In late 1962, Francis Crick and I began a long series of conversations about the next steps to be taken in our research. Both of us felt very strongly that most of the classical problems of molecular biology had been solved and that the future lay in tackling more complex biological problems. I remember that we decided against working on animal viruses, on the structure of ribosomes, on membranes, and other similar trivial problems in molecular biology. I had come to believe that most of molecular biology had become inevitable and that, as I put it in a draft paper, "we must move on to other problems of biology which are new, mysterious and exciting. Broadly speaking, the fields which we should now enter are development and the nervous system." At that time, there were extensive discussions with the Medical Research Council on building an extension to the Laboratory, and Max Perutz, the head of our laboratory, had been exploring the ground with the Council. I have recently found the correspondence on this topic, and in a letter dated 5 June, 1963 (see below), I wrote to Max and explained my views to him. Nematodes have not yet made their appearance, because I had only just started to read about them and had not yet formulated any ideas. Some people thought that our approach was too "biological" and would lead us away from molecular biology, but, in any event, we were asked to make a formal proposal, and a document was accordingly submitted to the Council in October, 1963. During the summer I had formulated my ideas, and as you will see from the document and the Appendix referred to, the now familiar lines of the project had emerged. Note that the paper refers to *C. briggsae*; it was some time before *C. elegans* was selected in preference.

I hope readers will enjoy the last, brief paragraph of the Appendix. They should understand that it has expanded into the contents of this book, and achieving it has taken more than 20 years and the labors of a large number of people.

Sydney Brenner
September 1987

From *The Nematode* Caenorhabditis elegans, WB Wood and the community of C elegans researchers, eds., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, 1988.

Letter to Max Perutz

5 June, 1963

Lääketieteen Nobel 2002

Sydney Brenner

R. Robert Horvitz

John E. Sulston

Linkki

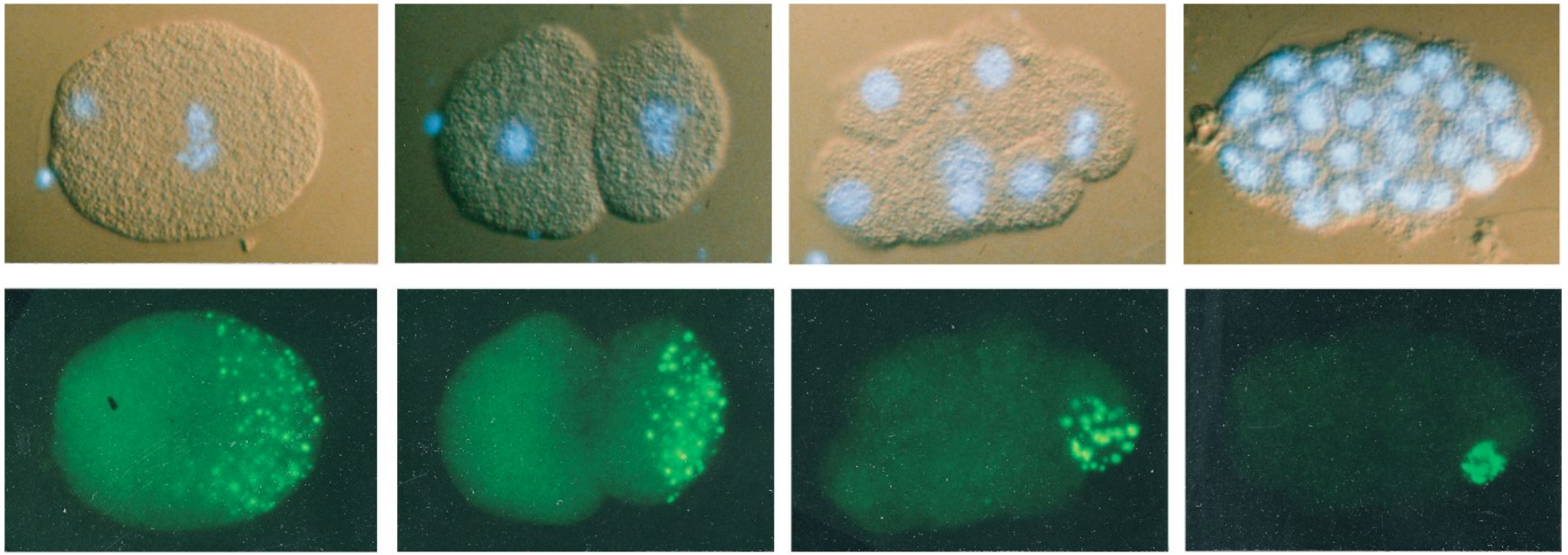


Figure 22-19 Molecular Biology of the Cell 5/e (© Garland Science 2008)

C. elegansin alkion kehitys alkaa solun jakautumisilla ja on alusta (hedelmöityksestä) alkaen epäsymmetristä
Heti pienestä solut alkavat viestiä keskenään. P-jyväset ovat ensimmäinen asymmetrian merkki.

CELL 1323

Galli & van den Heuvel (2008) Determination of the cleavage plane in early *C. elegans* embryos. Ann. Rev. Genet. 42:389-411

CELL 1324

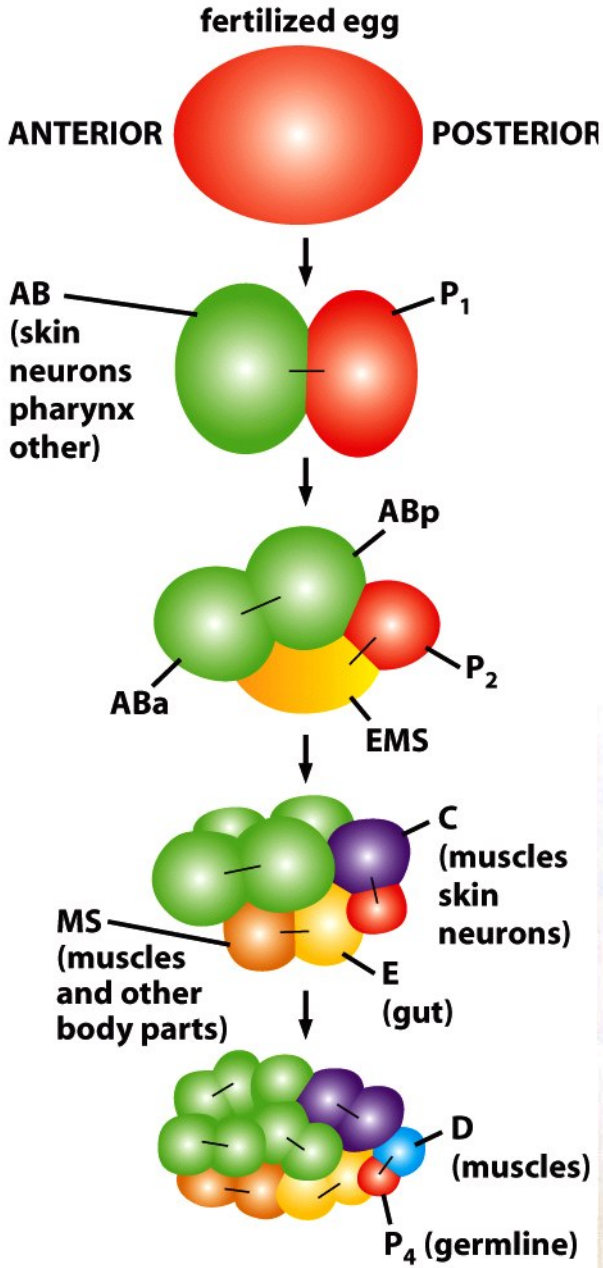
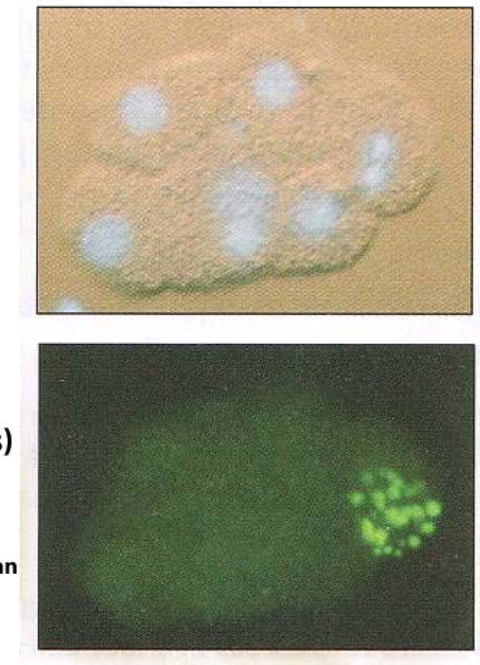
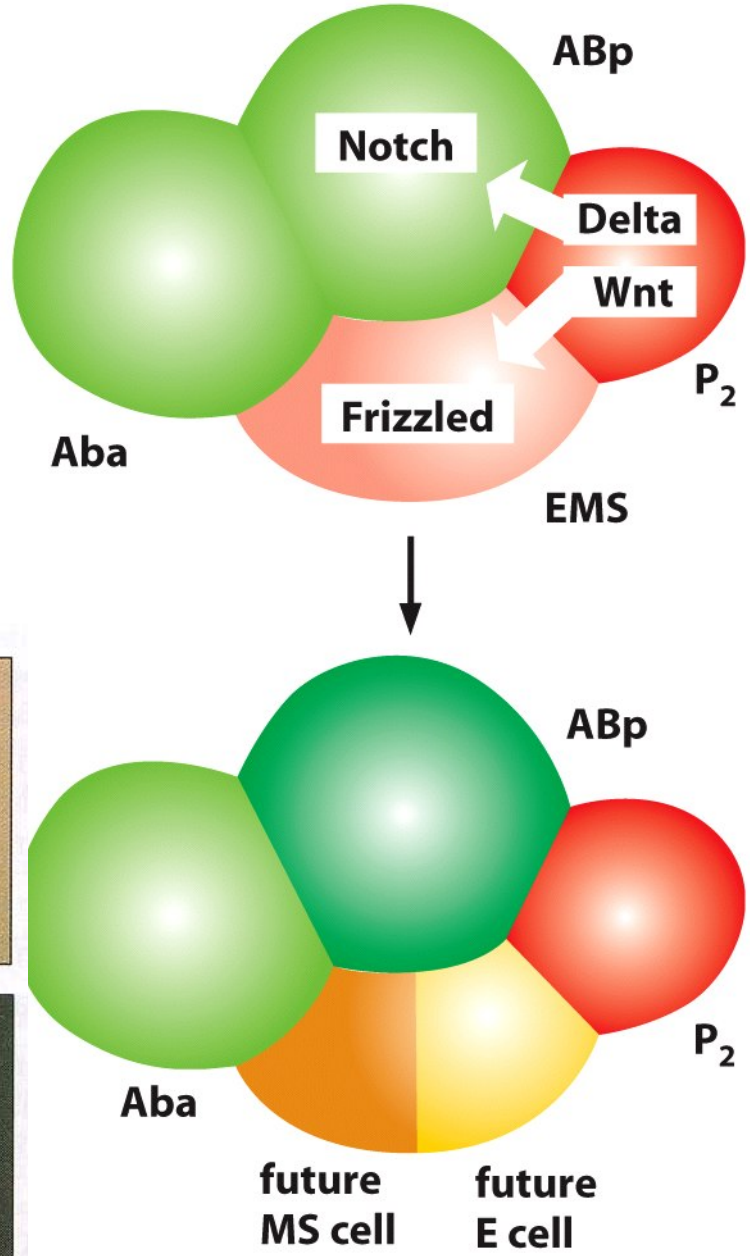
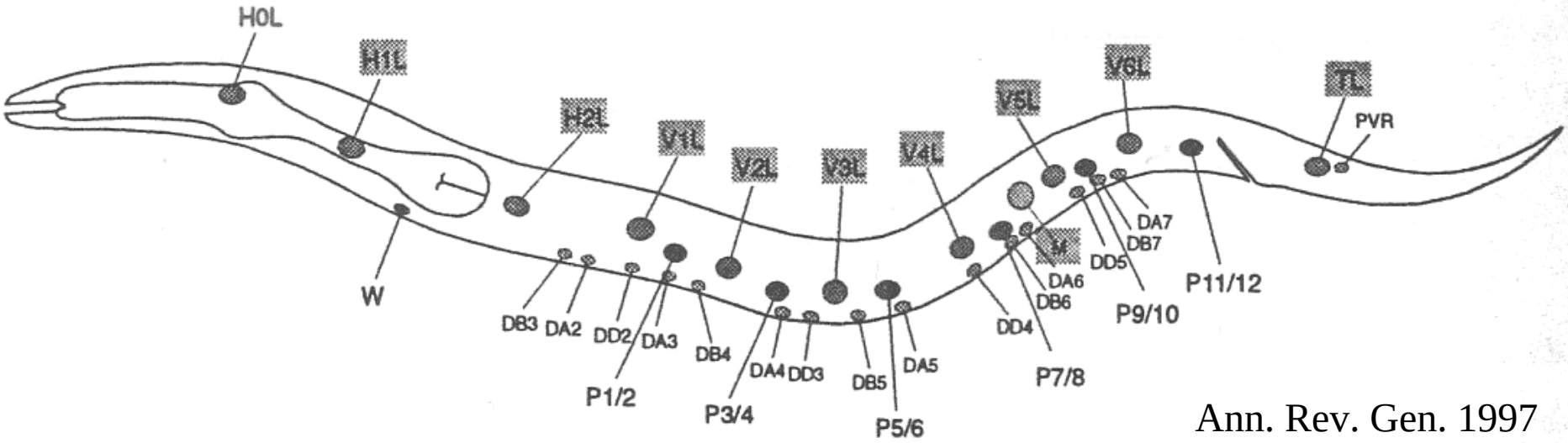


Figure 22-20 Molecular Biology of the Cell 5/e (© Garlan



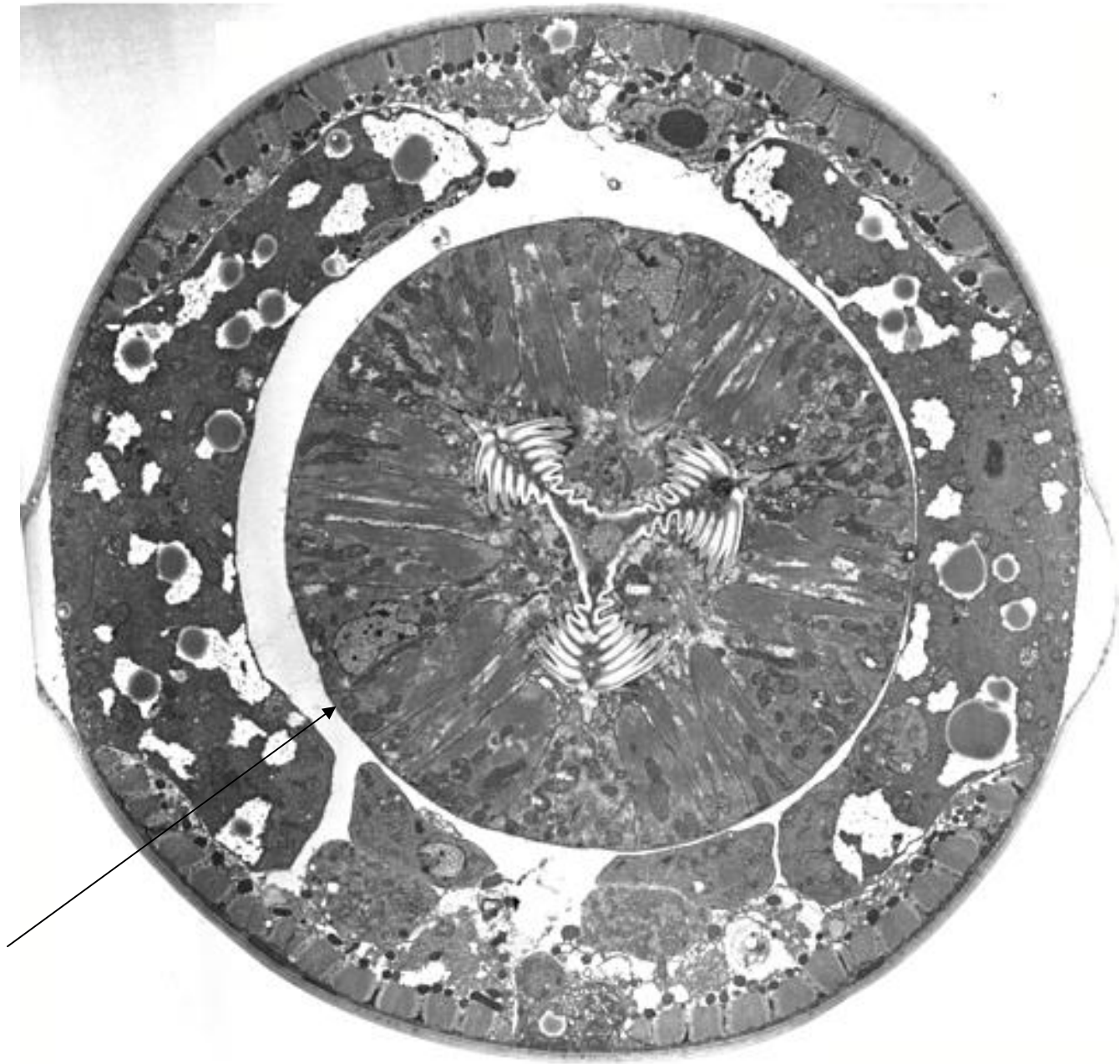


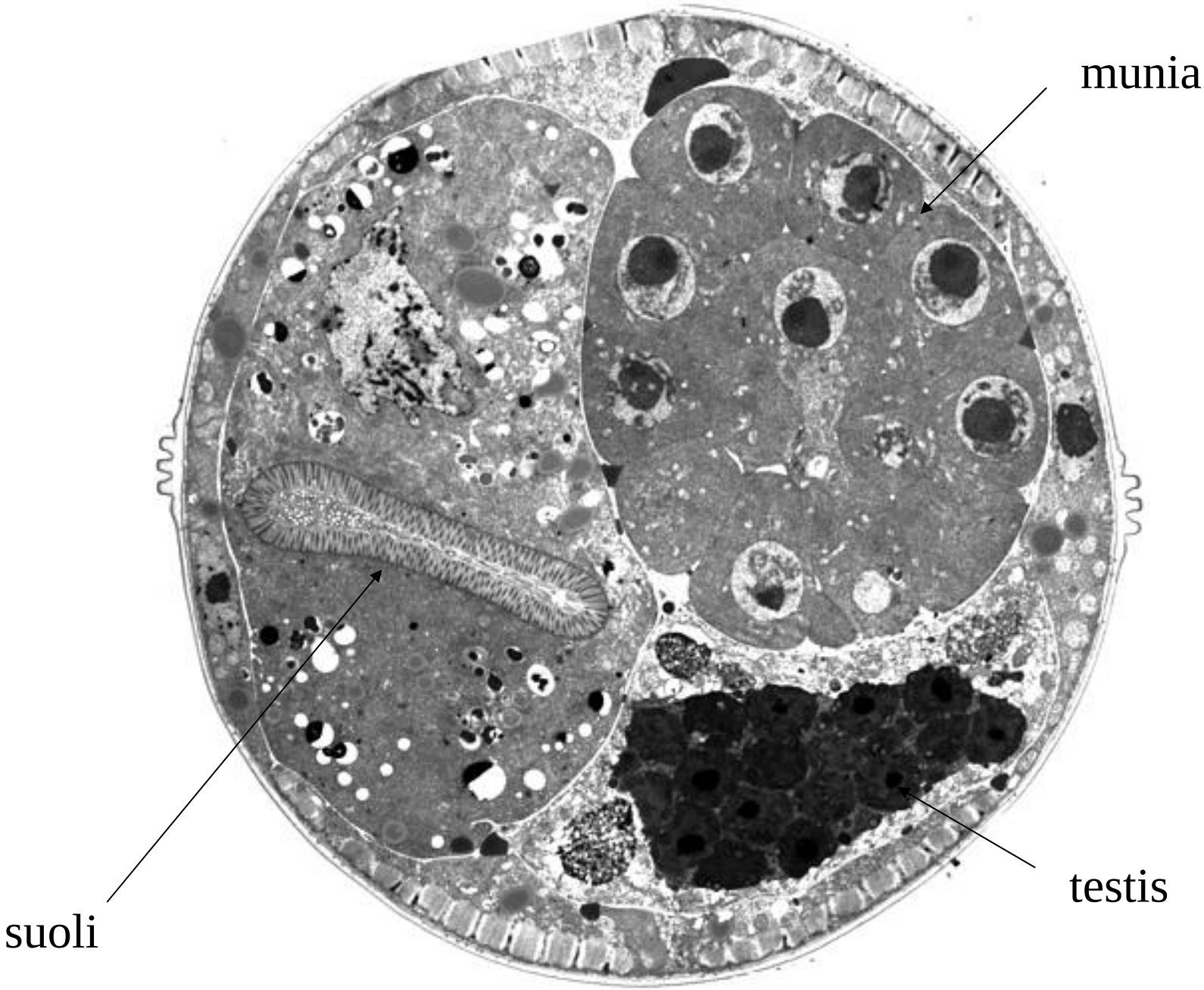
gure 22-21 Molecular Biology of the Cell 5/e (© Garland Science 2008)

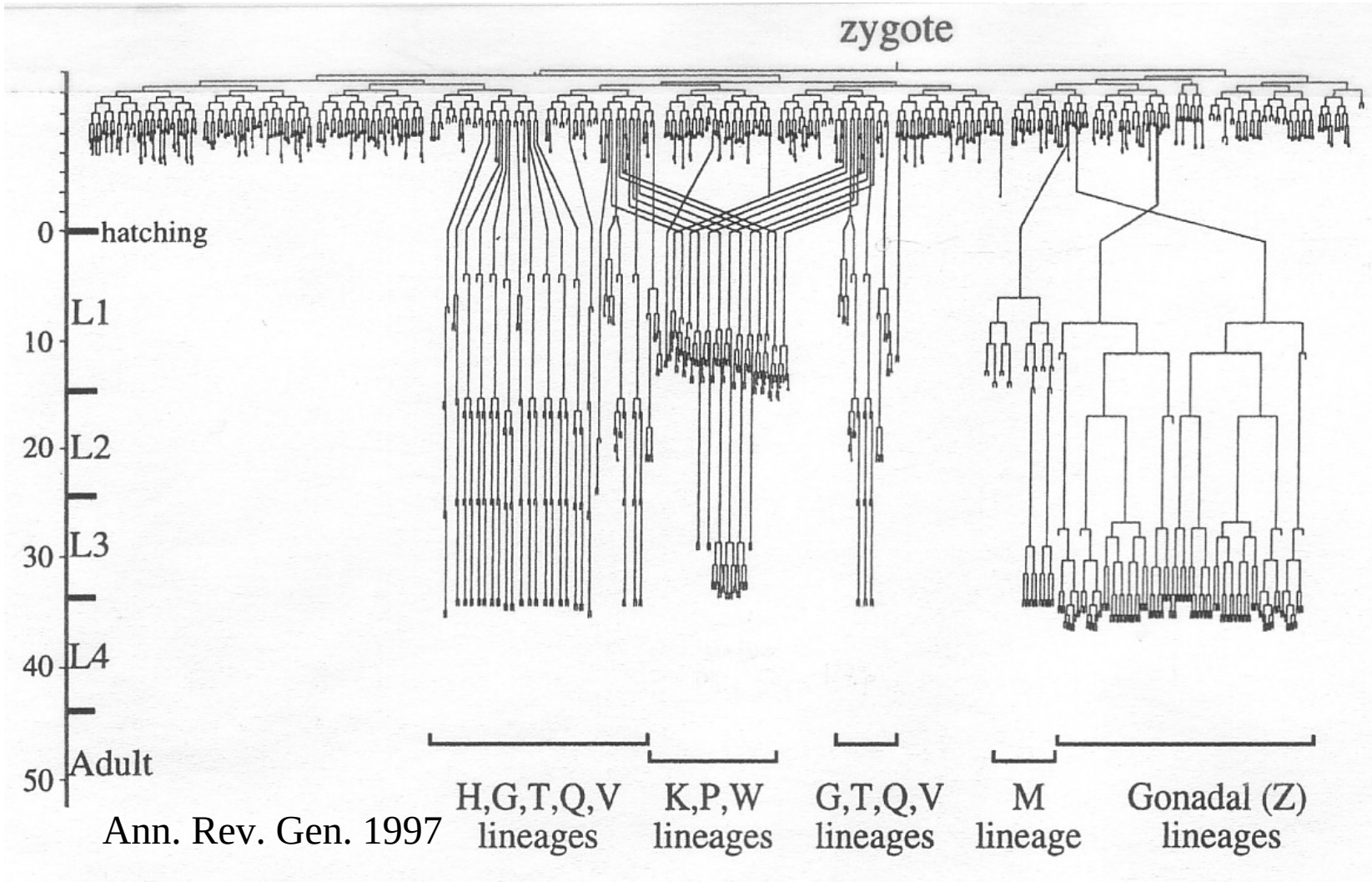


Ann. Rev. Gen. 1997

Figure 2 Arrangement of certain neuronal, hypodermal, and muscle nuclei of a newly hatched L1 animal [modified from (46)]. The shaded labels indicate nuclei of blast cells affected by the well-characterized heterochronic mutations.


nielu

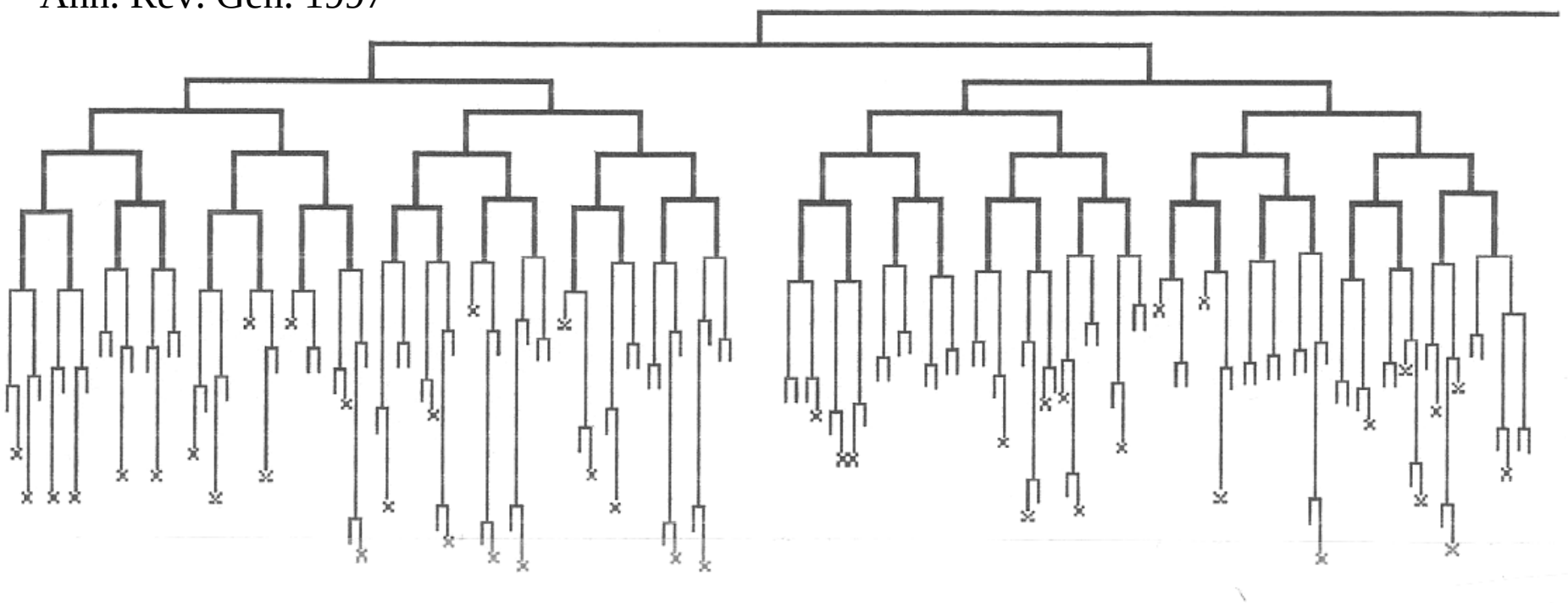

munia
suoli
testis



C. elegansin solujen historiaa seurataan soluyksilön tarkkuudella

CELL 1322

Ann. Rev. Gen. 1997



Edellisen kuvan vasemman nurkan tarkennus

Ohjelmoitu solukuolema (x apoptoosi) on useiden solujen kohtalo

CELL pieni uusi kappale 18 kertoo lisää apoptoosista!

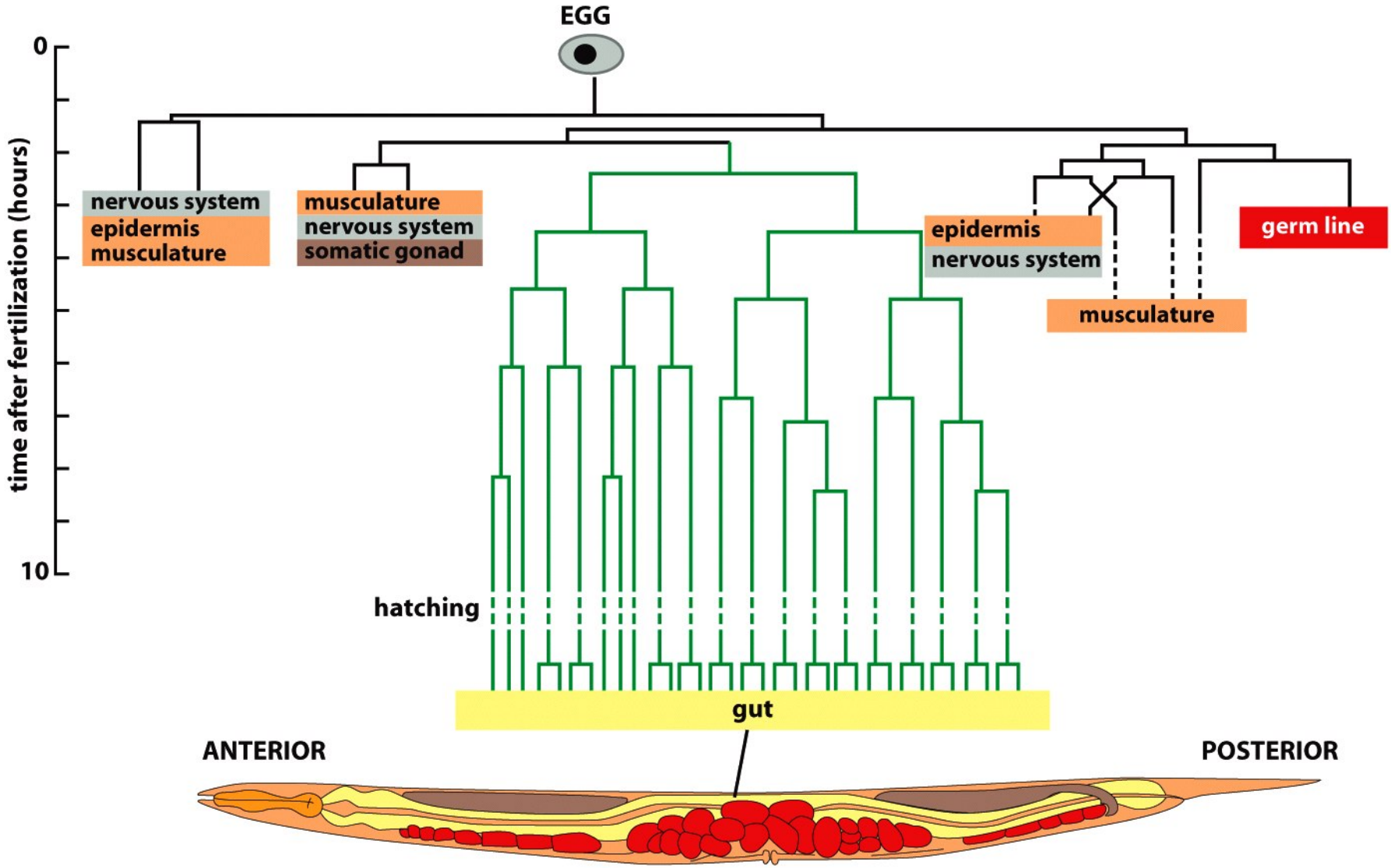


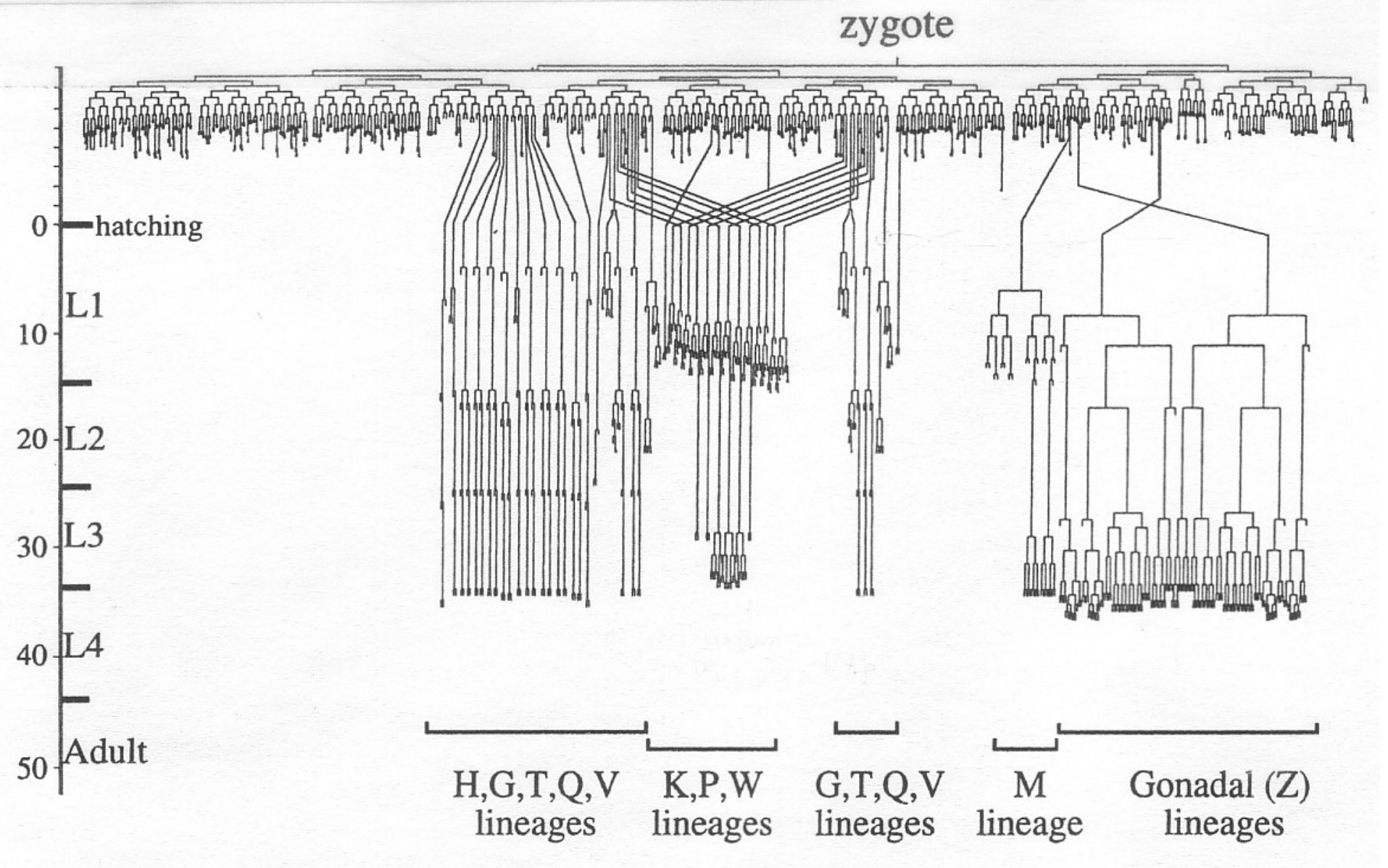
Figure 22-18 Molecular Biology of the Cell 5/e (© Garland Science 2008)

CELL 1322

Geenitoiminnan ajoitus

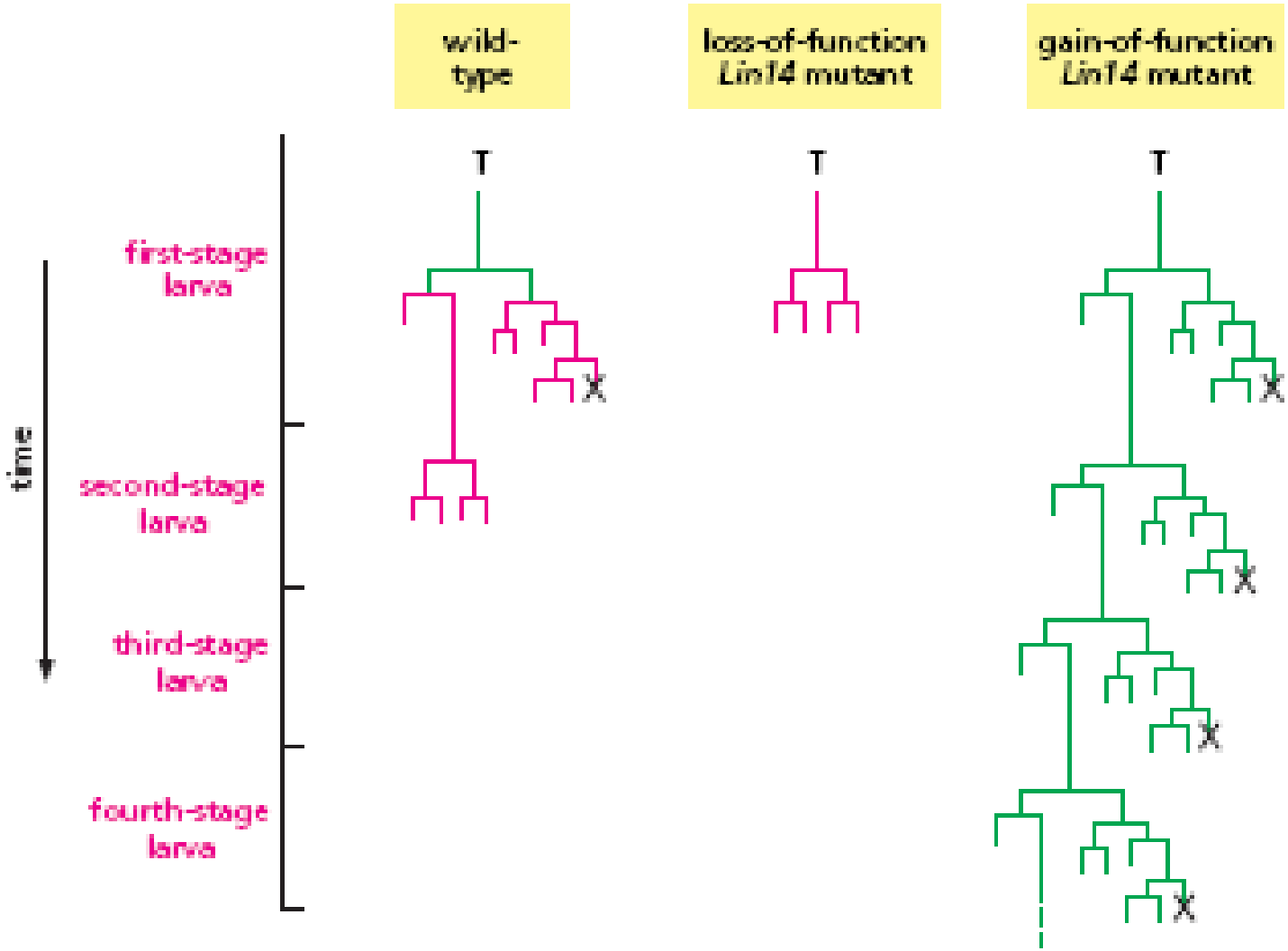
Heterokroniset mutaatiot: ajoitus pielessä

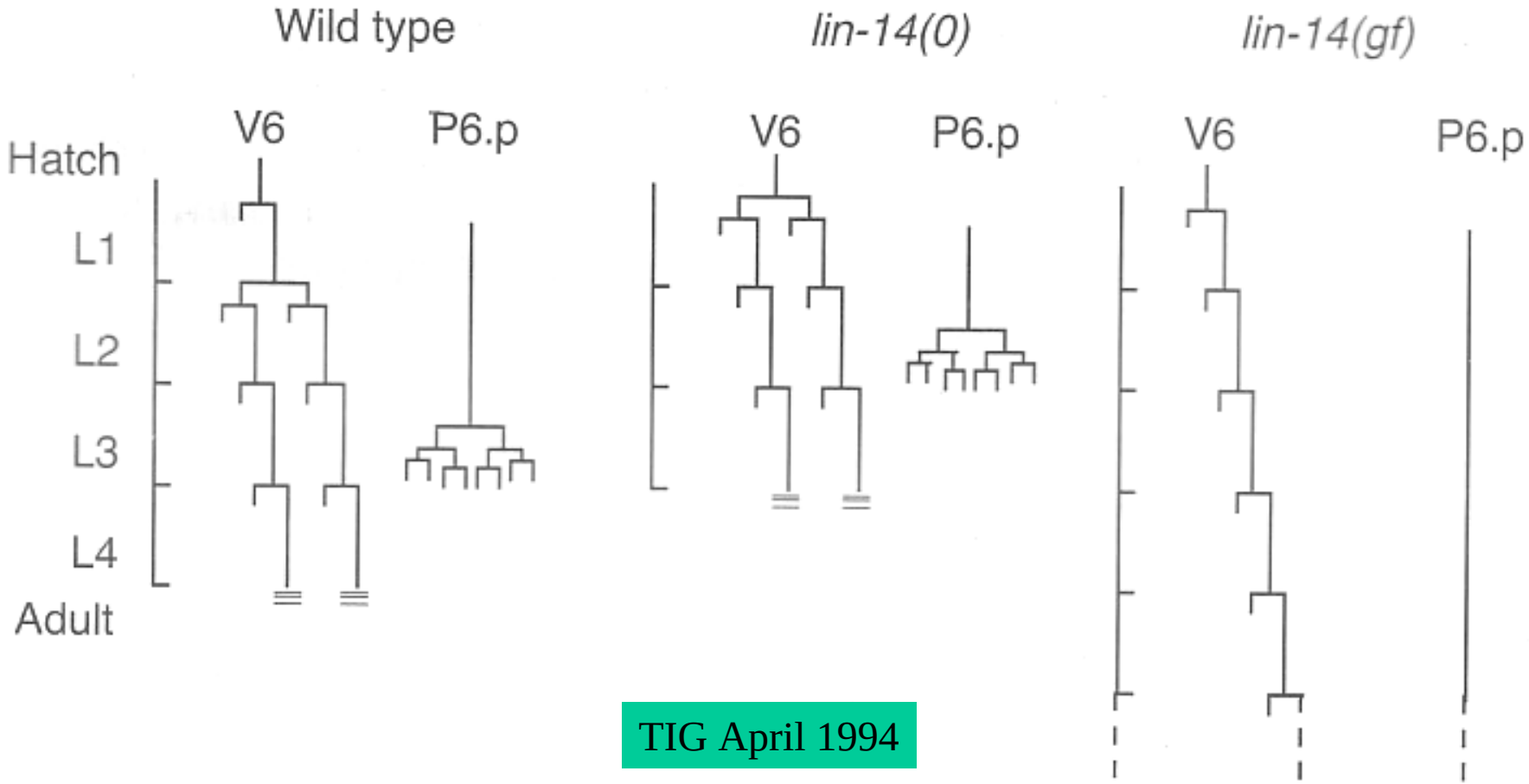
CELL 1326



C. elegansin solujen historiaa seurataan soluyksilön tarkkuudella

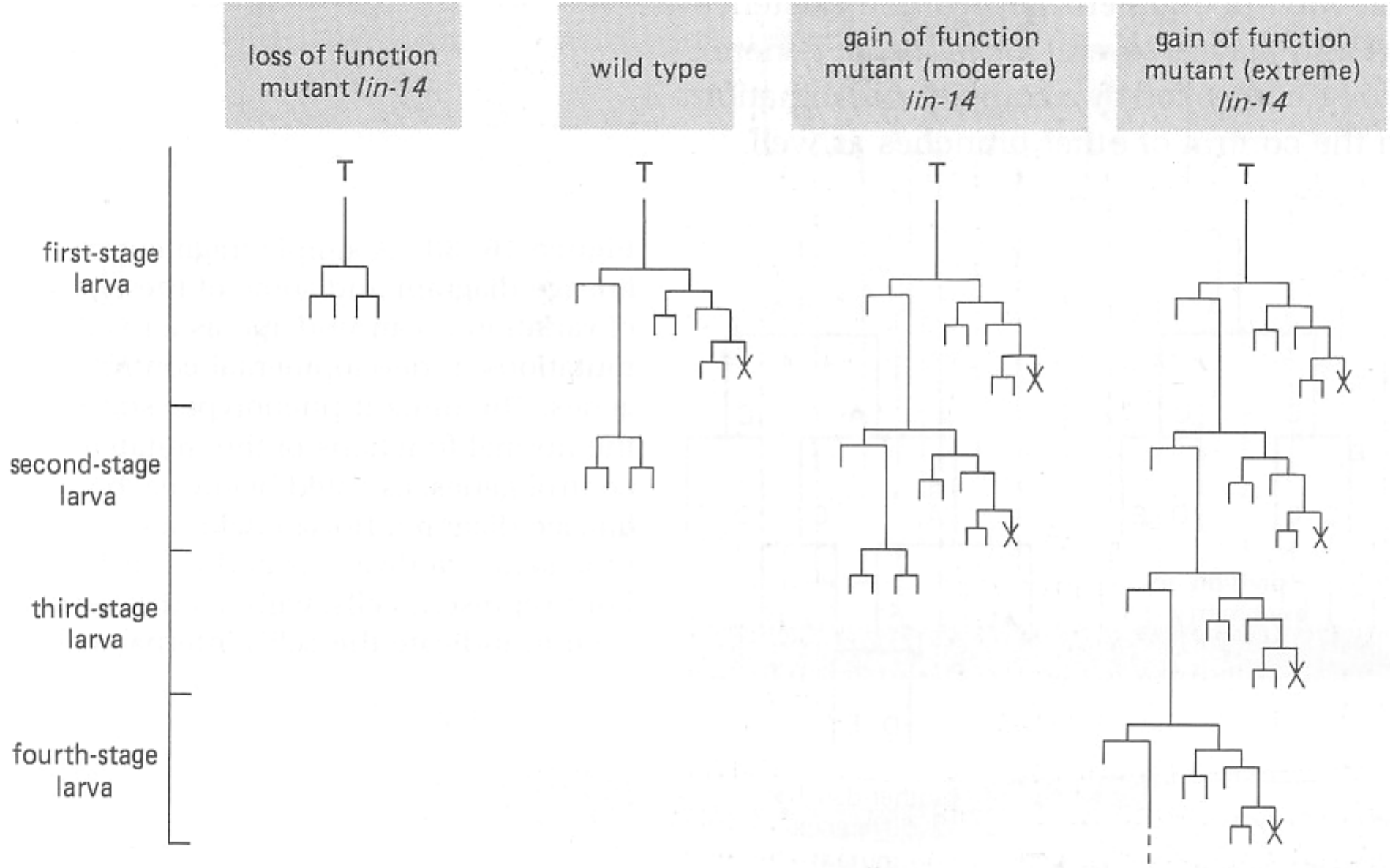
Ann. Rev. Gen. 1997


wild-type
loss-of-function Lin14 mutant
gain-of-function Lin14 mutant
time
first-stage larva
second-stage larva
third-stage larva
fourth-stage larva
T
T
T
X
X
X
X
X



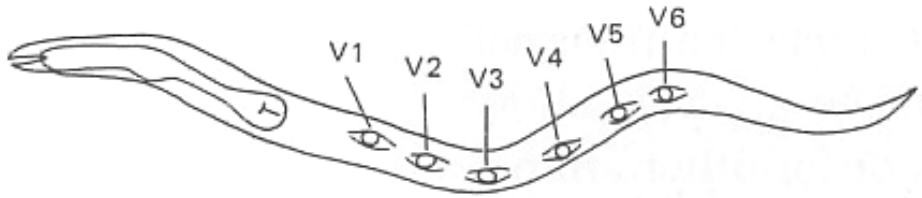
TIG April 1994

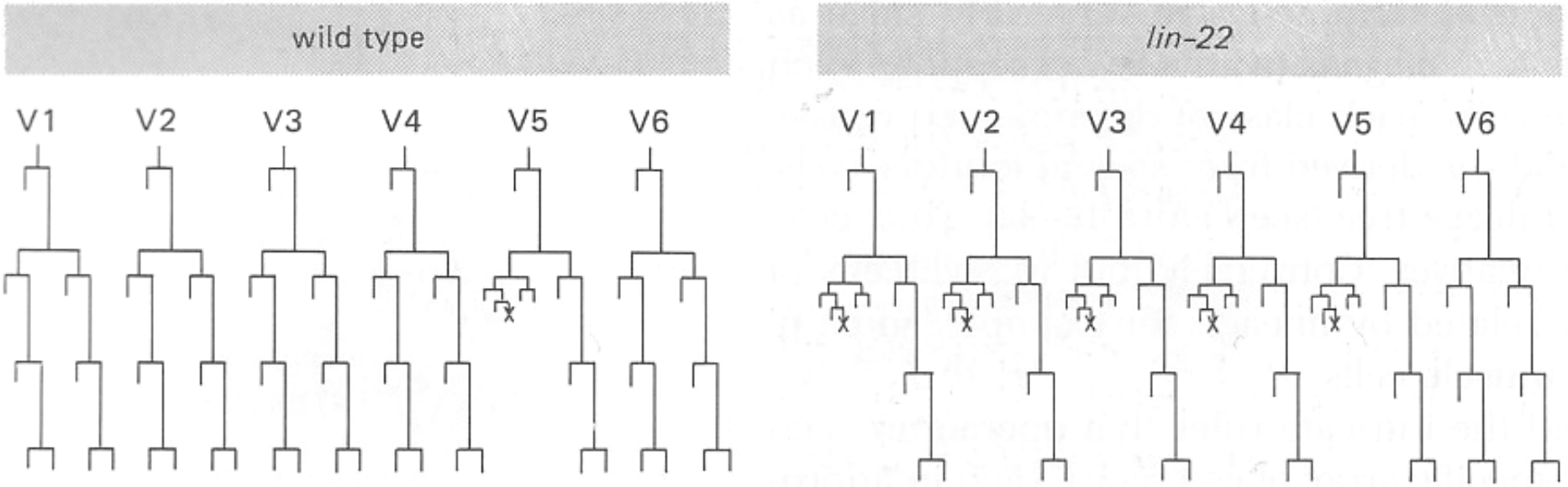
CELL 1326



CELL 1326

CELL 1989

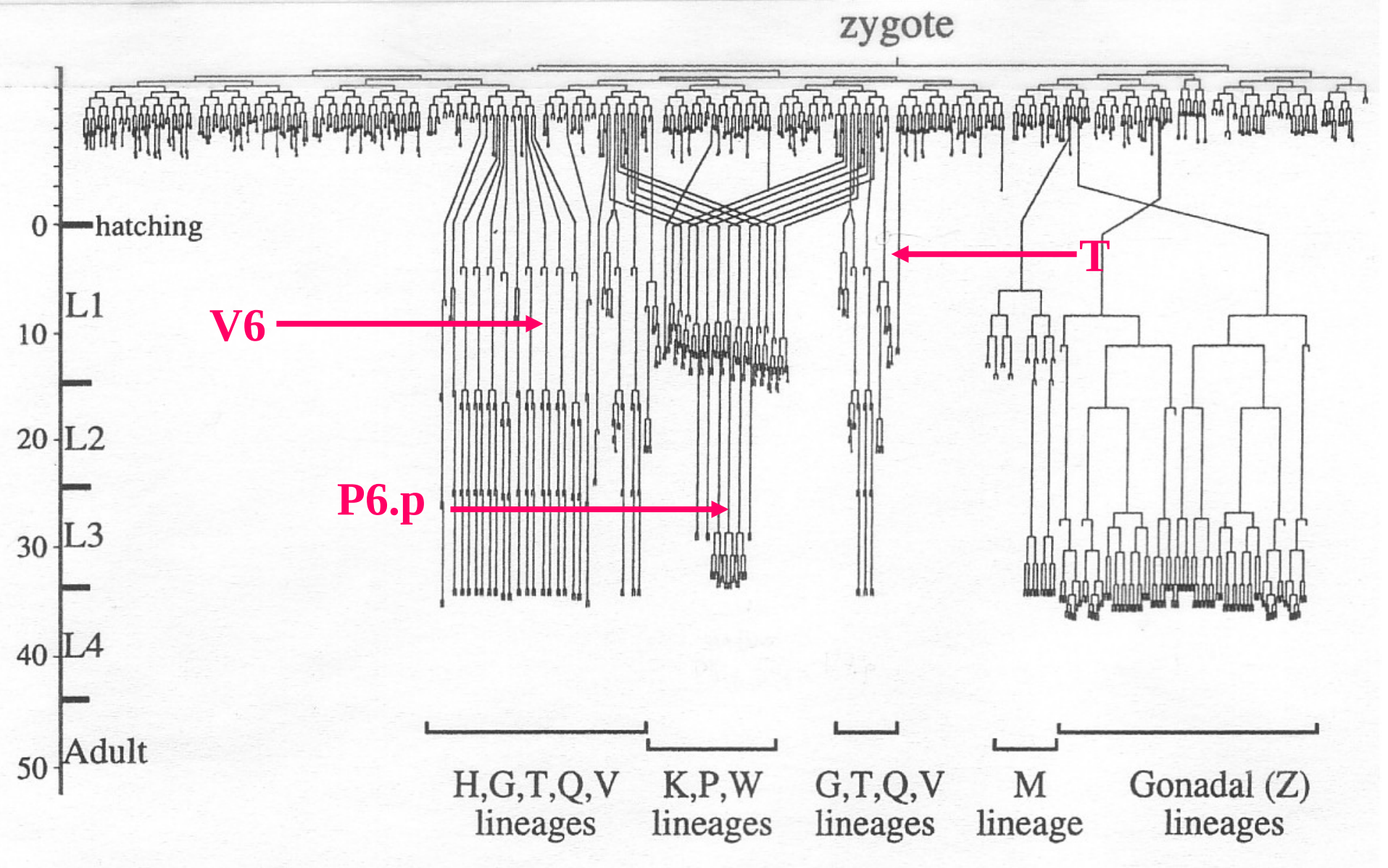




Voi muutakin olla pielessä kuin ajoitus. Tässä V1-V4 luulevat olevansa V5.

CELL 1326

CELL 1989



CELL 1326

Ann. Rev. Gen. 1997

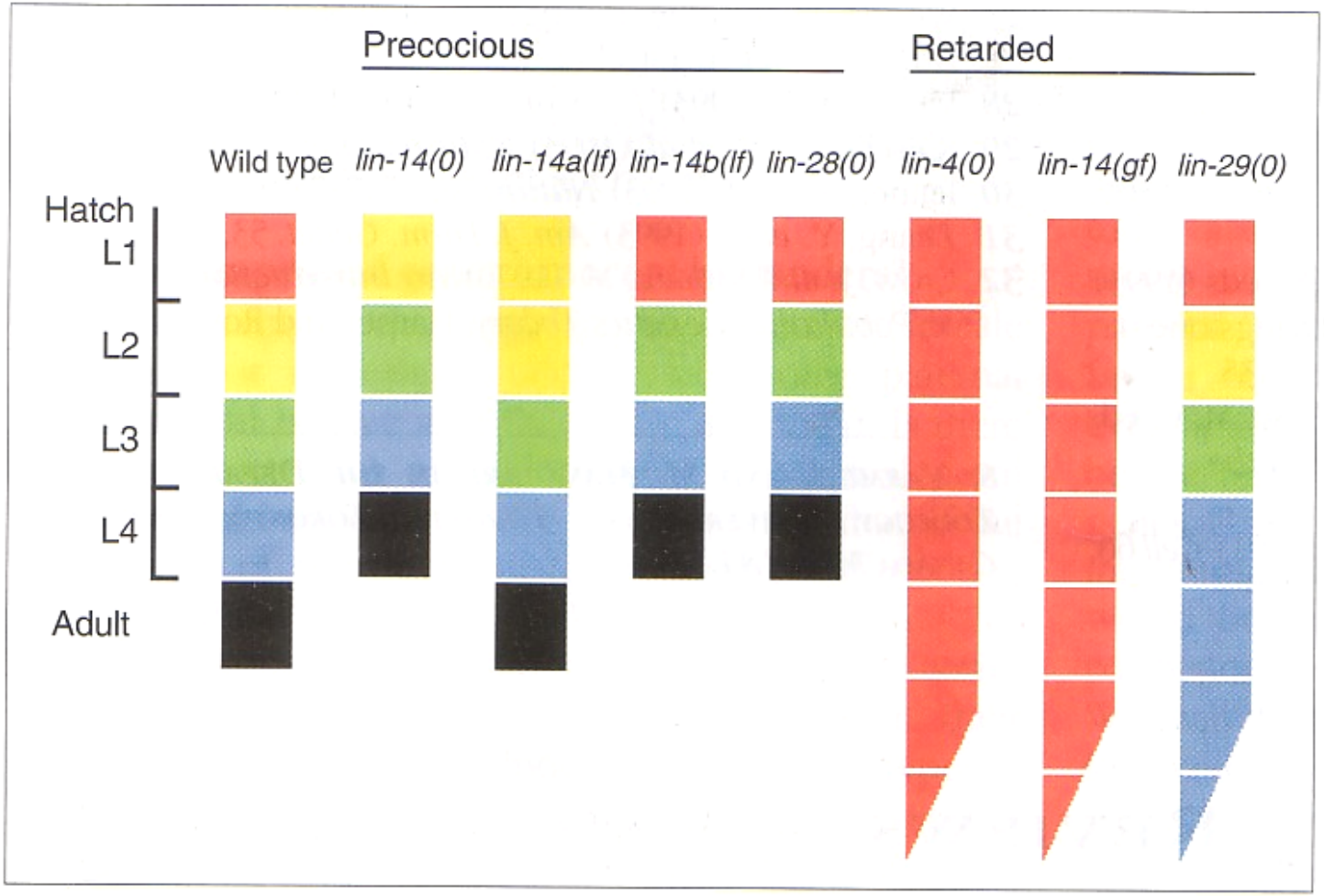


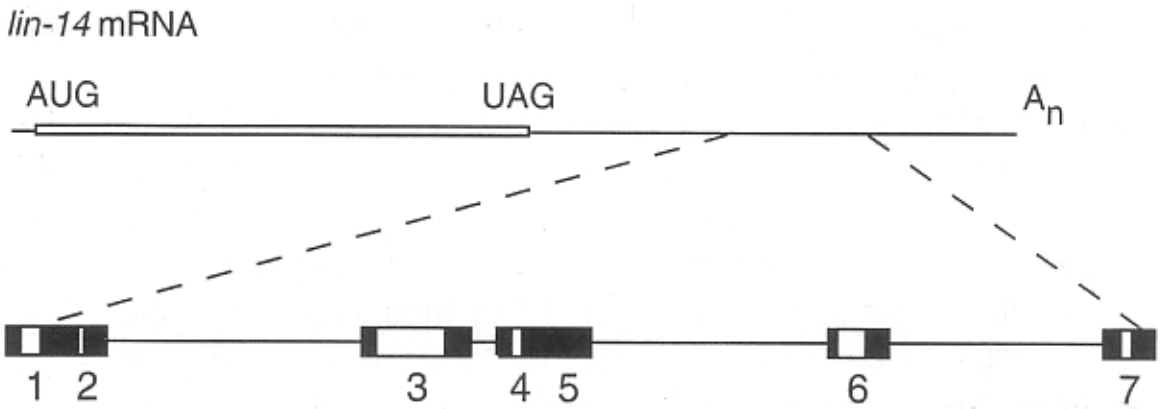
FIGURE 1. Temporal patterns of development in *C. elegans* heterochronic mutants compared with wild-type animals. Colors identify developmental events that are characteristic of each larval stage in the wild type, indicated to the left. Stage-specific transformations of cell fates occur in a variety of lineages and tissues. Molts punctuate the stages. Certain precocious mutants have fewer molts, because of precocious terminal differentiation of the hypodermis. Retarded mutants have extra molts, because the hypodermis fails to undergo terminal differentiation. *0*, null mutation; *lf*, loss-of-function mutation; *gf*, gain-of-function mutation[2,5,10].

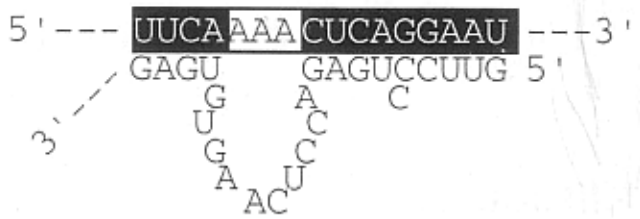
TIG Apr 94

(a)

Stage	*lin-4*	*lin-14*	Lineage pattern
L1	Off	High	L1-specific
L2	On	Low	L2-specific
L3	On	Off	L3-specific

(b)





TIG Apr 94

RNAi

CELL 451

CELL 1326

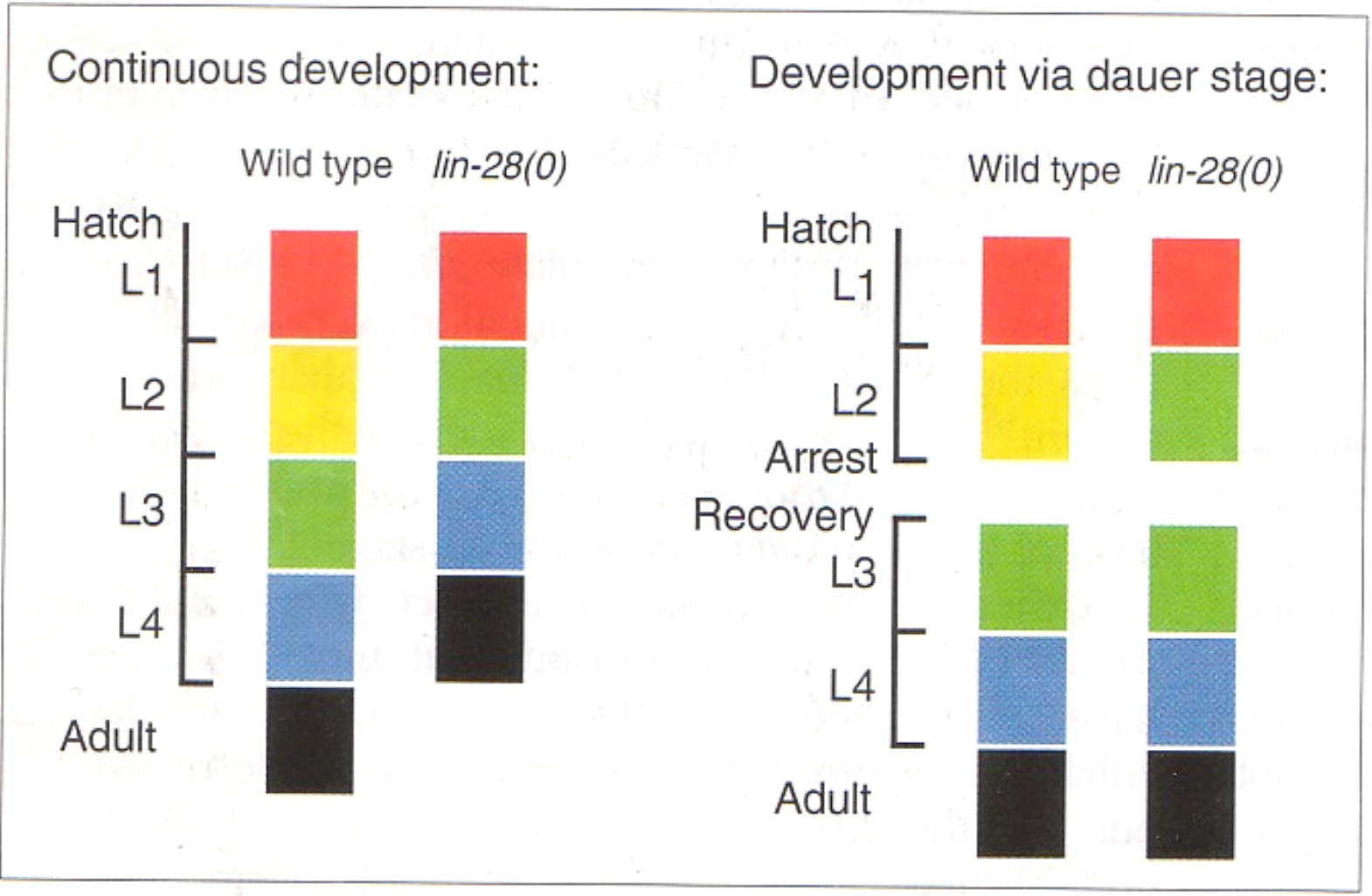
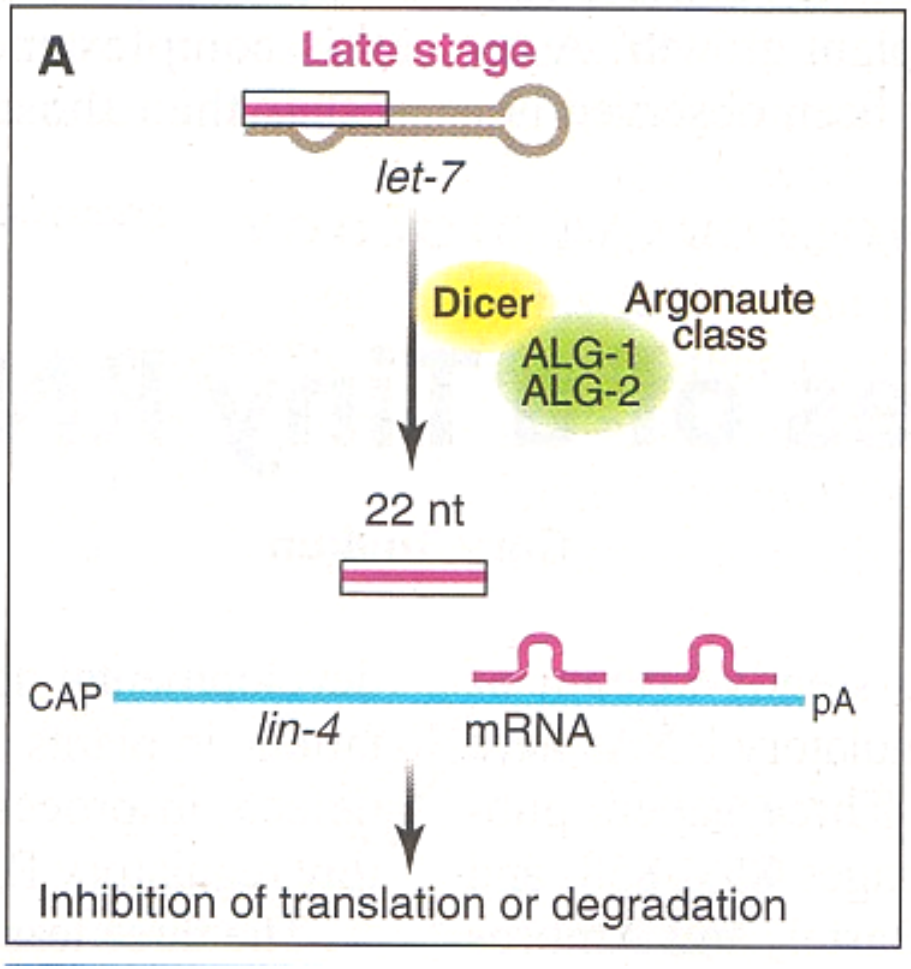


FIGURE 5. Reprogramming of precocious development after dauer larva arrest[15]. In continuous development, a *lin-28(0)* mutant fails to execute L2-specific patterns in the hypodermal lineage, and precociously executes patterns specific to the L3, L4 and adult stages. When *lin-28(0)* mutants develop by way of the dauer larva stage, the L3 and later stages develop in the same way as wild-type animals.



let-7 geenin tuote on miRNA

22 nt osa irroitetaan

Niitä on monta ja ne takertuvat toisen geenin, *lin-4*, mRNA:n loppupäässä olevaan UTR-jaksoon

Tällä systeemillä *let-7* säätelee, milloin *lin-4* (ja muutama muu) toimii translaatiotasolla

Pienet RNA:t osallistuvat usein kehitystapahtuminen ajoitukseen

CELL 493-, 571

Science 26 Oct 2001

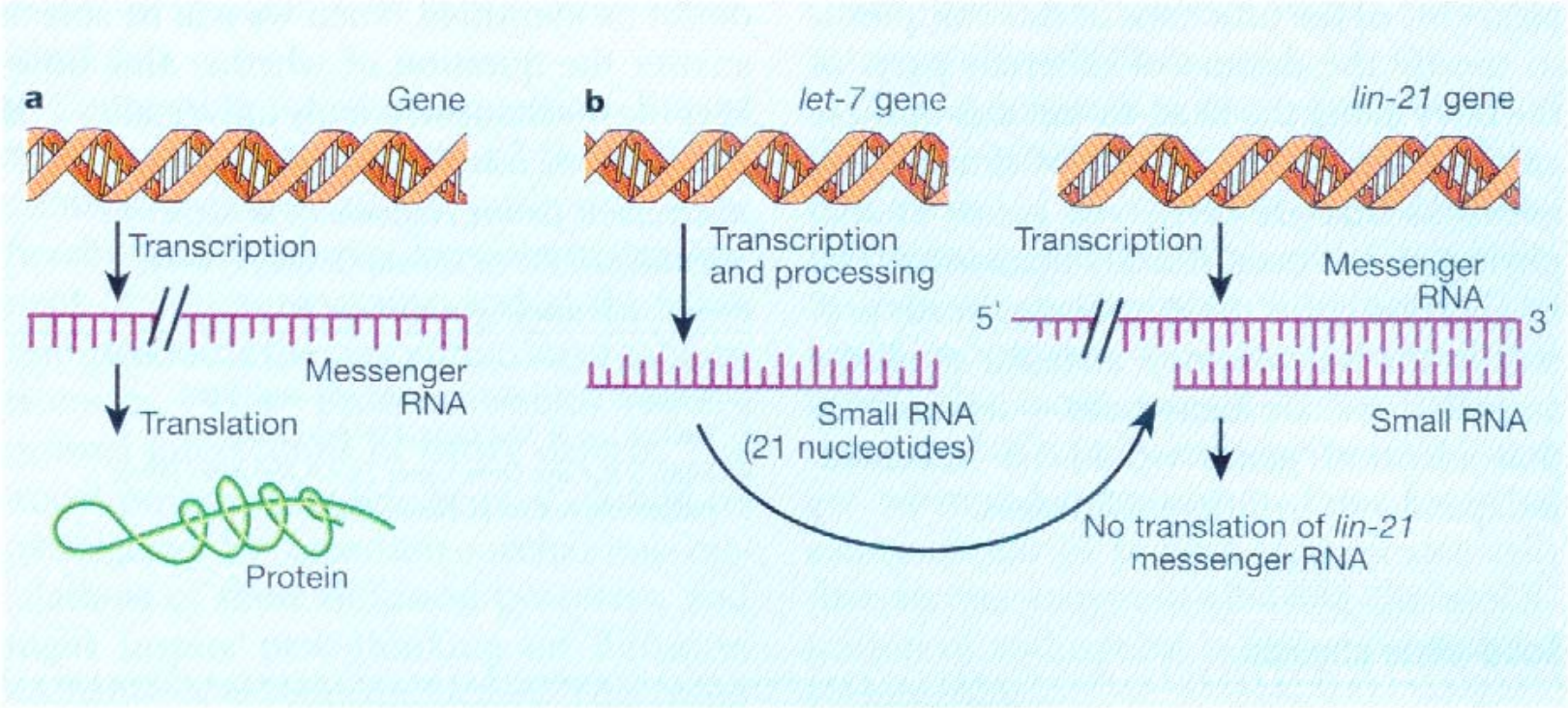
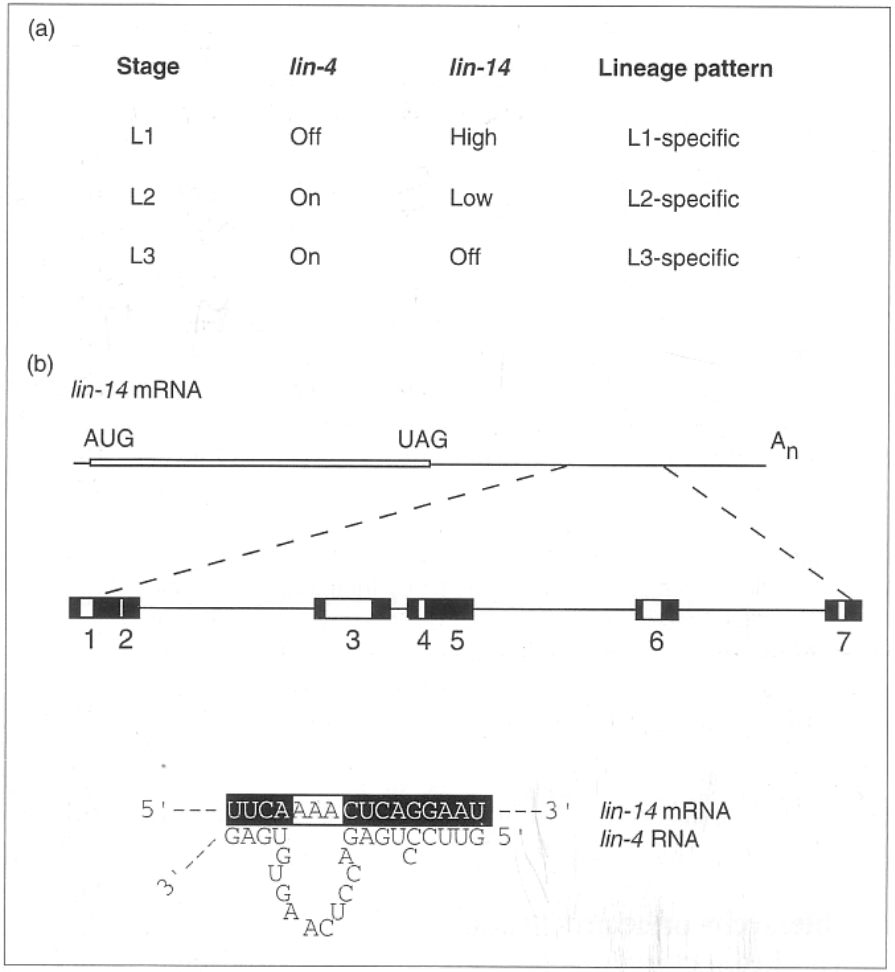


Figure 1 **Keeping time with small RNAs.** a, **Conventionally, genes are transcribed into messenger RNAs, which are then translated into proteins. It is the proteins that do the 'work' specified by the gene sequences.** b, **A few genes, such as the nematode *let-7* gene (left), are instead transcribed in response to upstream signals (not shown) and processed to produce small RNAs — the *let-7* small RNA is a mere 21 nucleotides in length. Here it is the small RNA that does the work: it pairs up with the untranslated nucleotide sequence at the 3′ untranslated end of a target messenger RNA (the *in-41* RNA in the case of *let-7*), and probably prevents it from being translated into protein. This relieves the inhibition on other genes, setting off a genetic cascade (not shown) that steers the organism through a major developmental transition. This mechanism of gene inhibition by small RNAs is probably not the same as 'RNA silencing', which also involves small RNAs but results in the degradation of the target RNAs. Pasquinelli *et al.*[5] have found the *let-7* small RNA in all major groups of bilaterally symmetrical animals, a result that hints that this mechanism of developmental timekeeping is also conserved.**

Nature 2 Nov 2000 p. 37-38



Fire

Mello

TIG Apr 94

RNA -interferenssi

CELL 495-, 571

Nobel 2006

Perinpohjainen selostus

Mellon slidet!

Induktio

Solut vaikuttavat naapureihinsa

Viestin lähettäminen, kulku, vastaanotto ja oikea reaktio

Solunjakautuminen

February 1997 Vol. 13 No. 2
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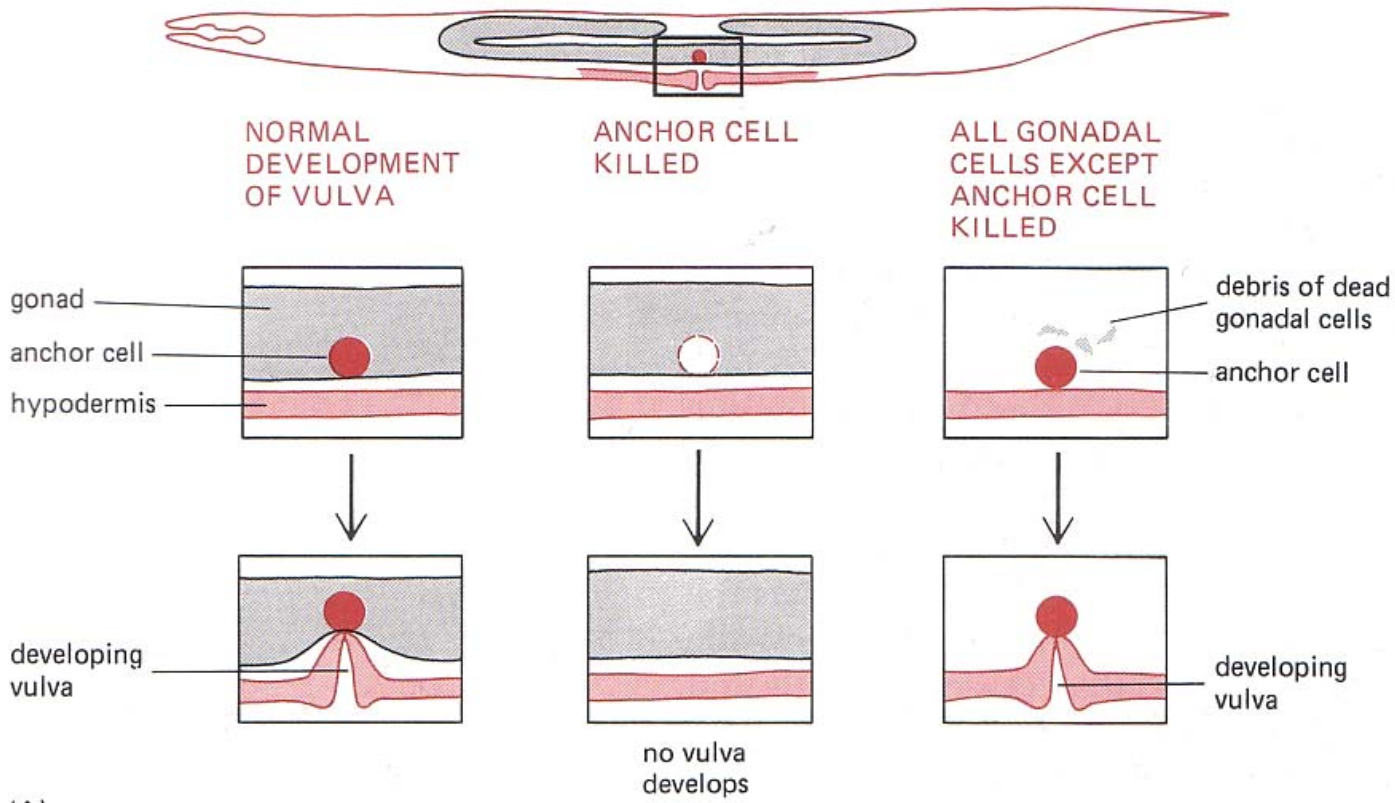
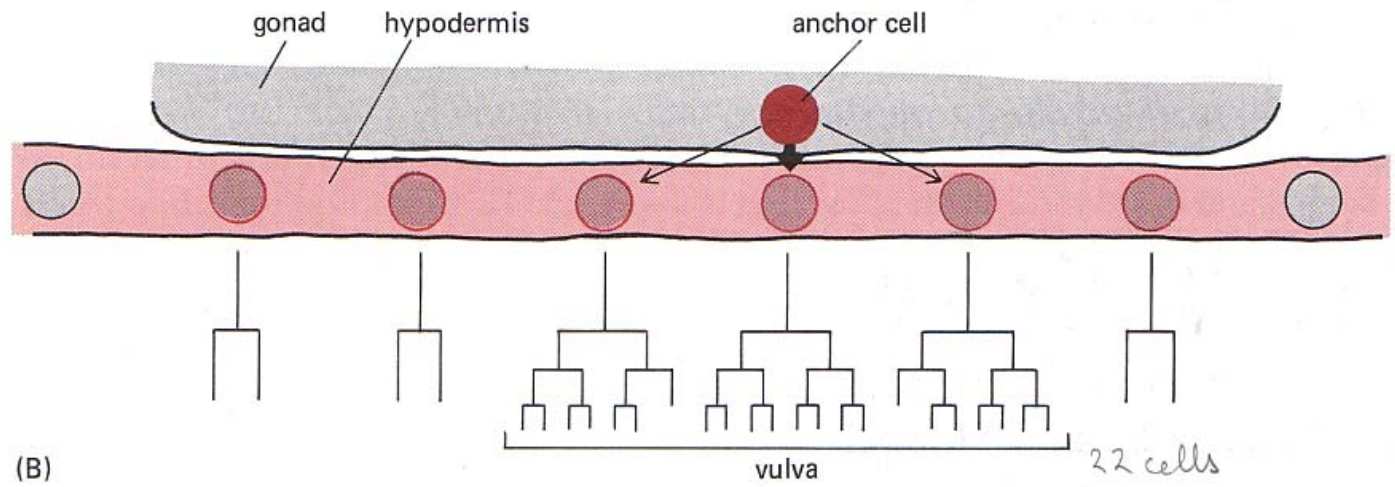
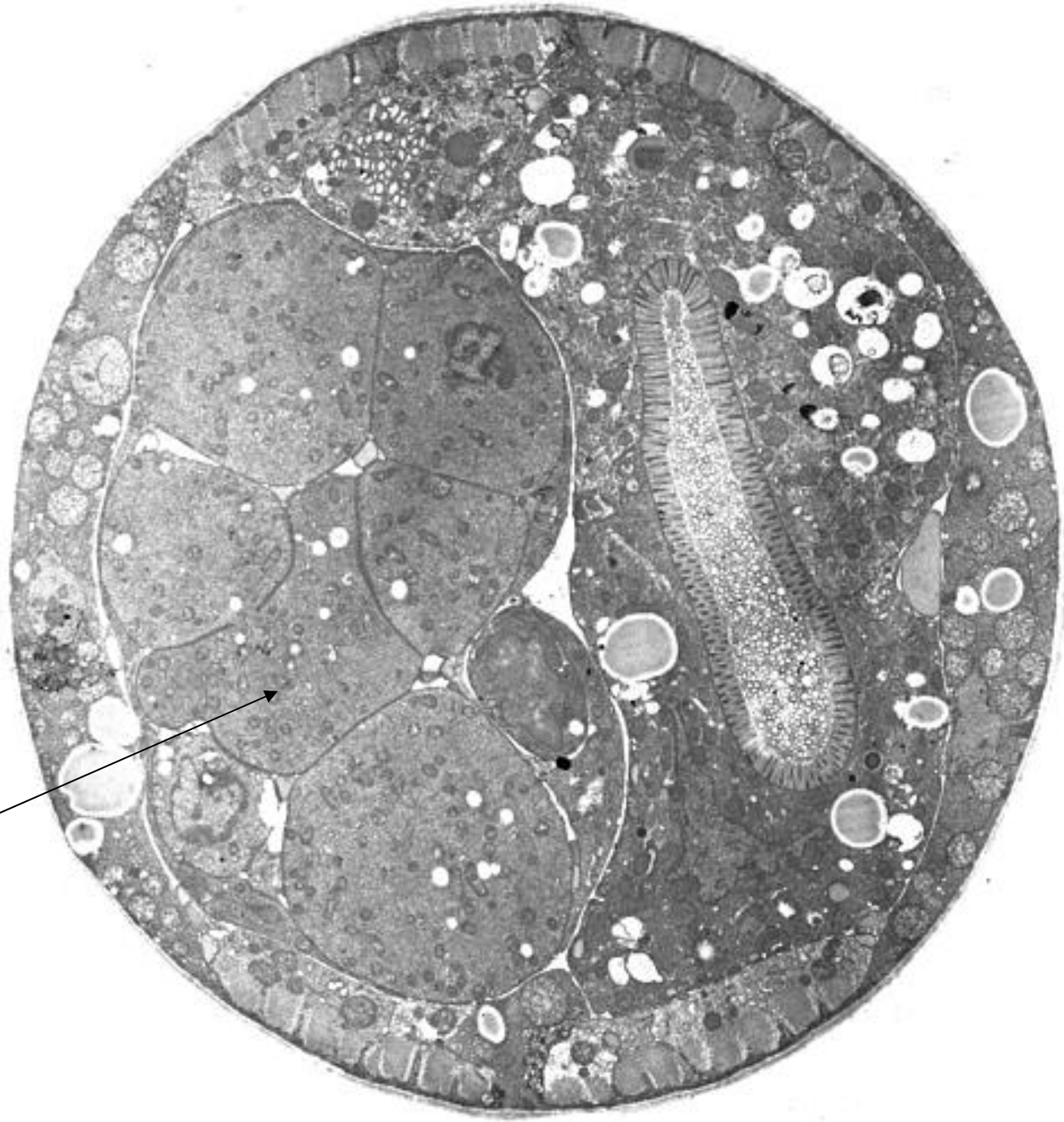
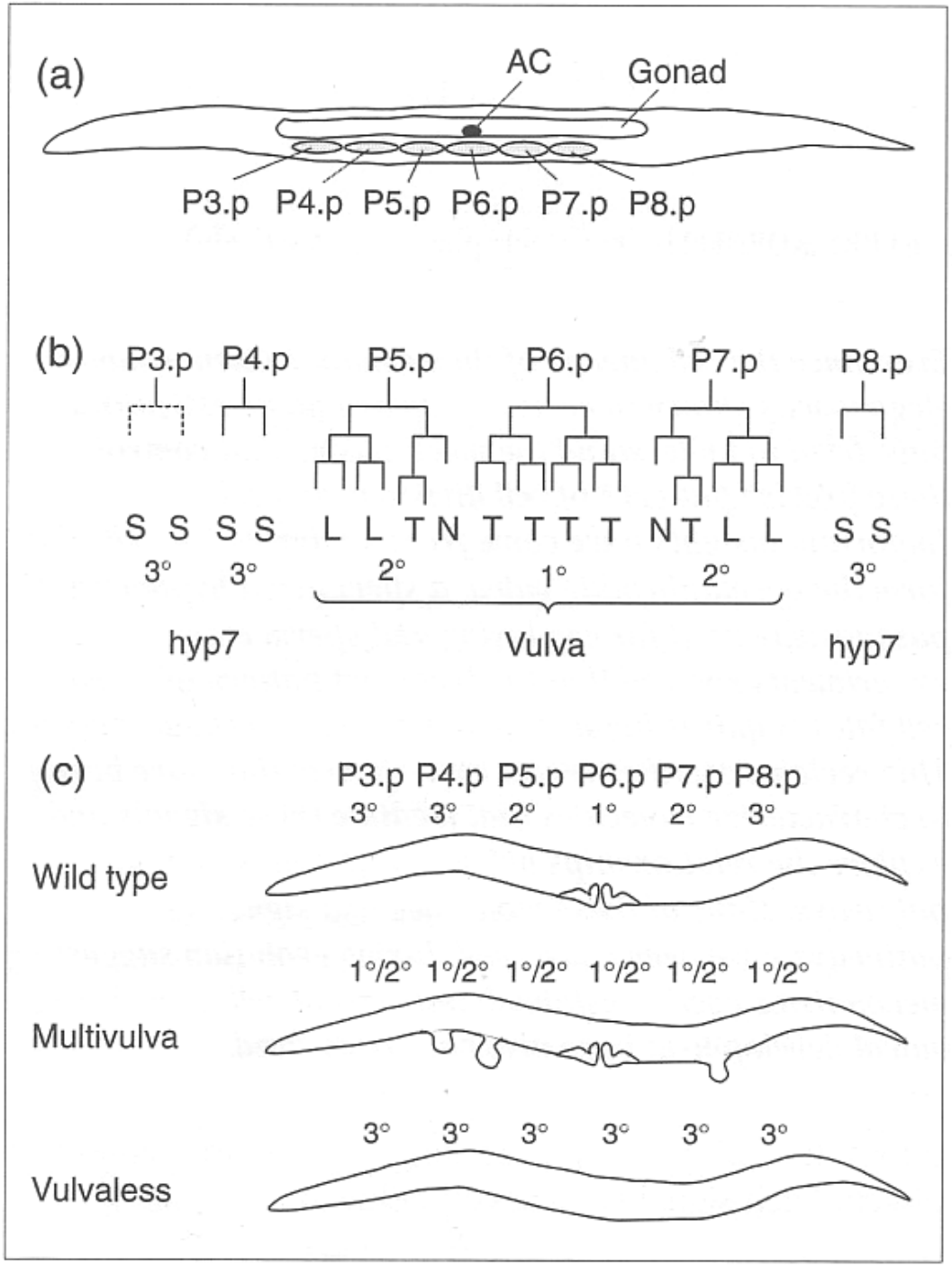

NORMAL DEVELOPMENT OF VULVA
ANCHOR CELL KILLED
ALL GONADAL CELLS EXCEPT ANCHOR CELL KILLED
gonad
anchor cell
hypodermis
developing vulva
debris of dead gonadal cells
anchor cell
developing vulva
no vulva develops
(A)

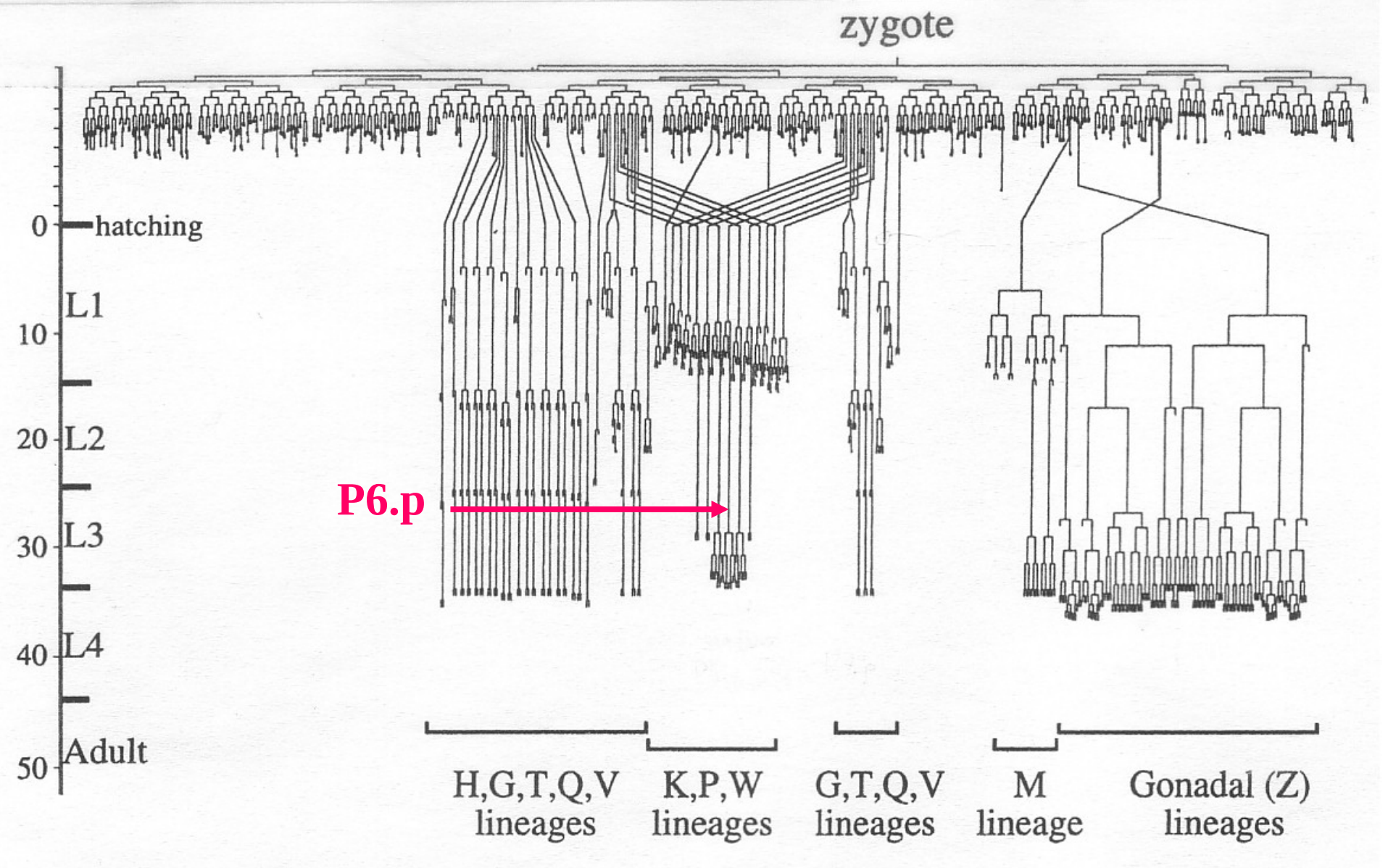

gonad
hypodermis
anchor cell
vulva
22 cells
(B)



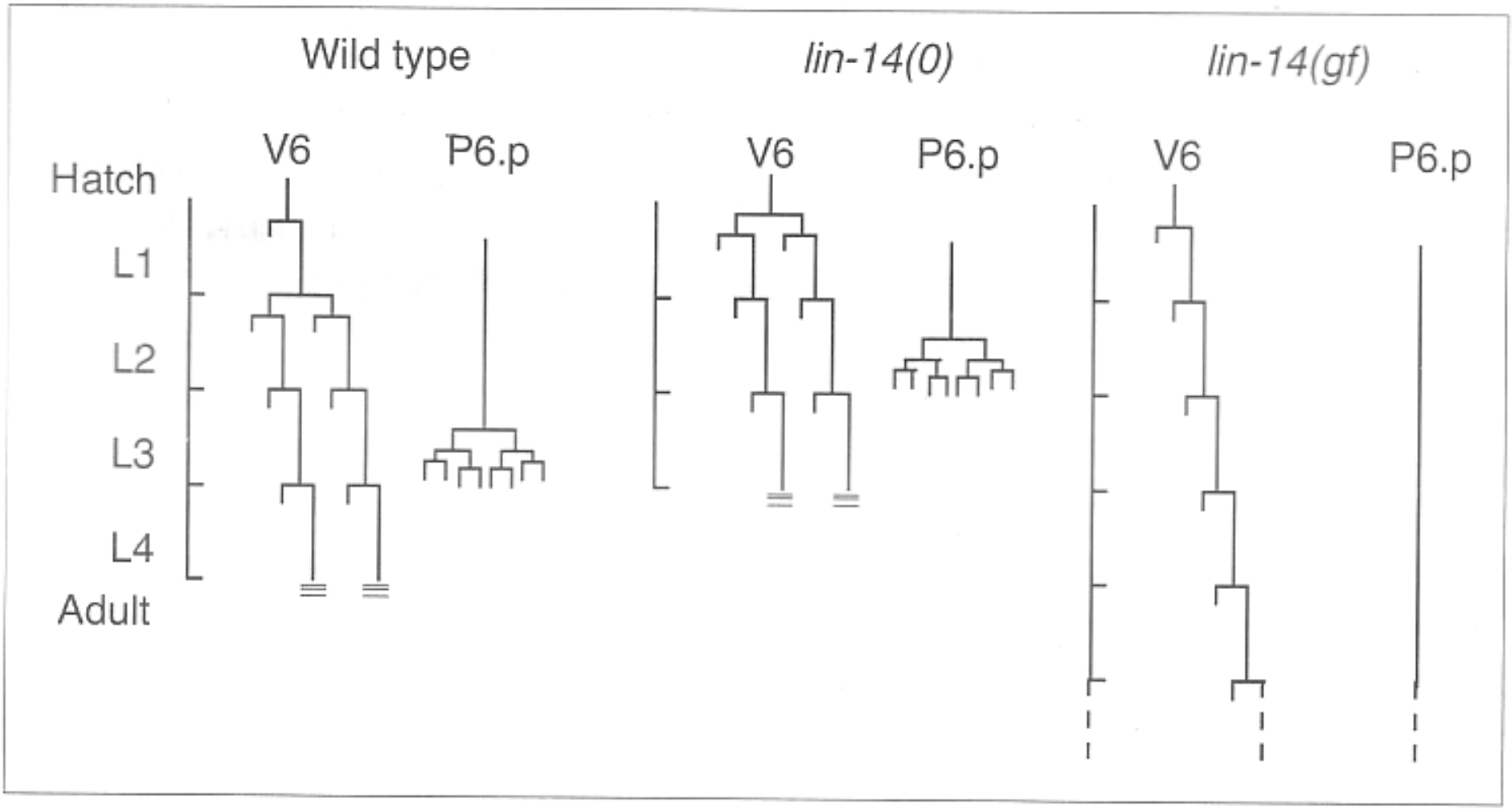
munia



AC on ankkurisolu, joka alkaa ohjata P-sarjan soluja muodostamaan muninta-aukkoa



Ann. Rev. Gen. 1997


Wild type
lin-14(0)
lin-14(gf)
V6
P6.p
V6
P6.p
V6
P6.p
Hatch
L1
L2
L3
L4
Adult

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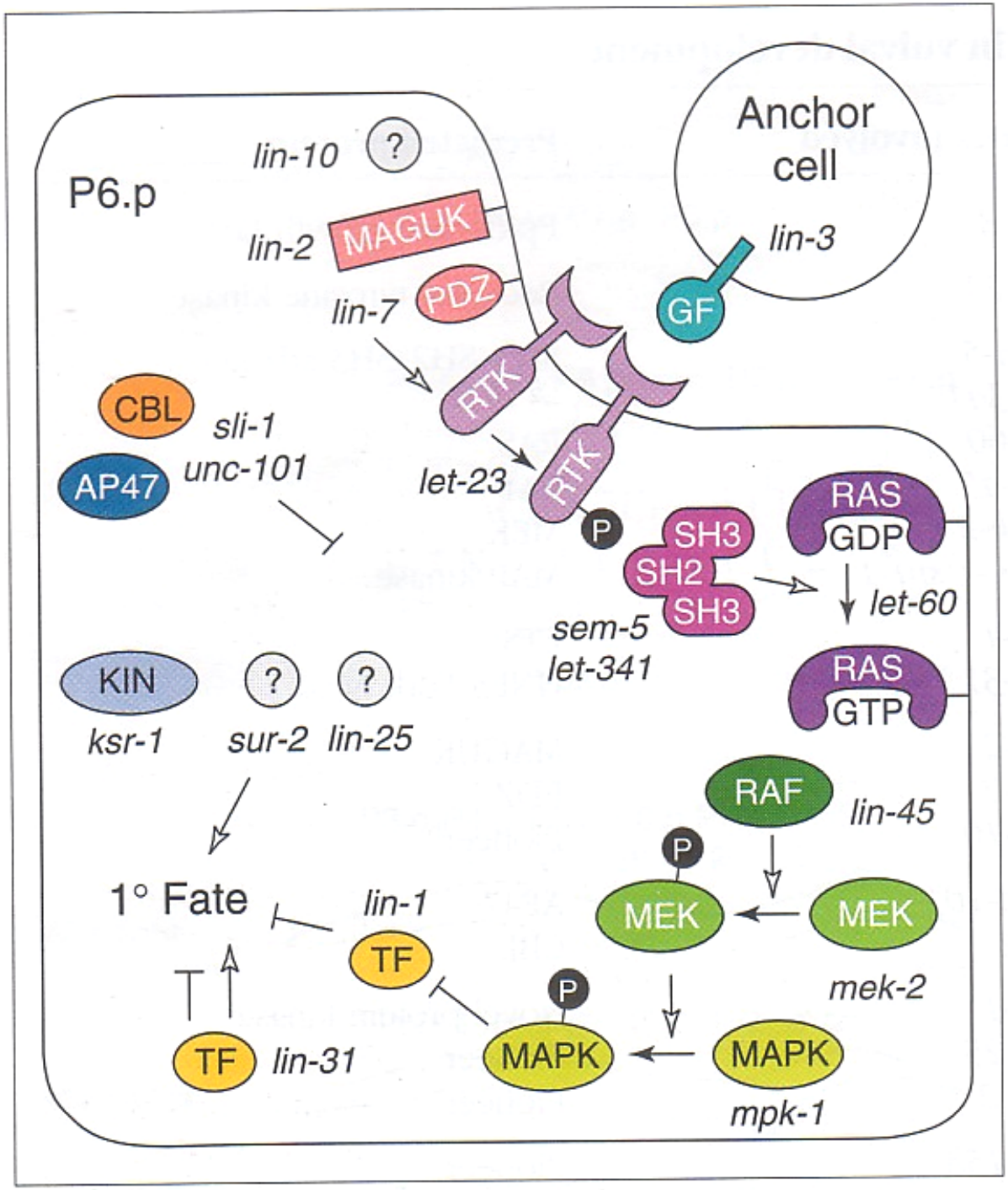

Ankkurisolu viestittää yleisellä (epidermal) growth factorilla (*GF*)

P6.p alkaa suunnitella jakautumissarjaa sekä parin naapurin herättämistä

Näissä onkin sitten useita geenejä, joilla on tekemistä ihmisenkin **syöpien eli solusyklin** säätelyn kanssa

TIG Feb 97