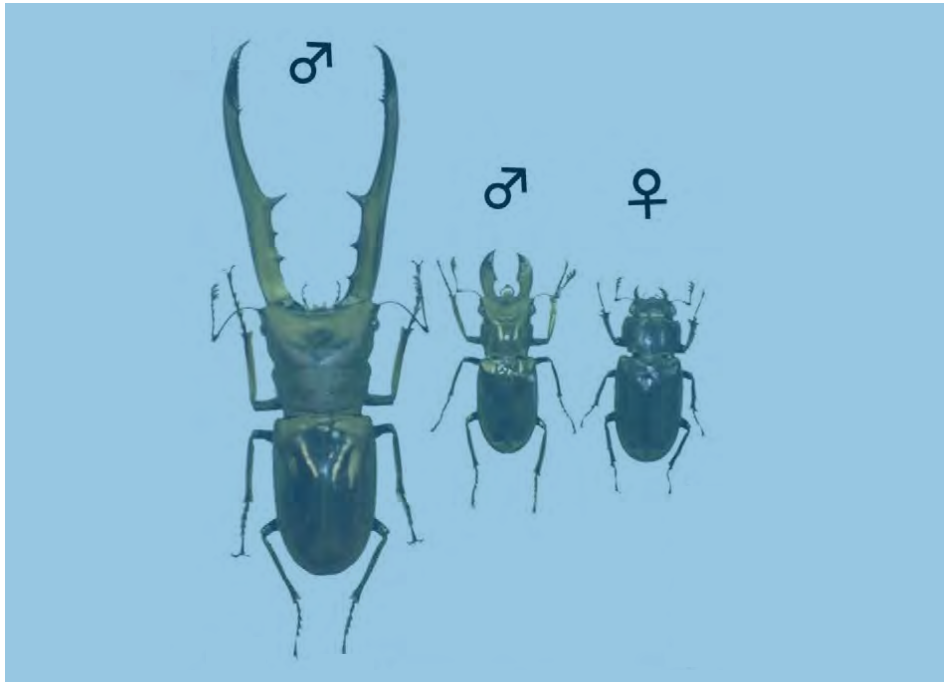
Organism and Tissue Growth



Course 6: External control: coordination and symmetry

Thomas Lecuit

chaire: Dynamiques du vivant

COLLÈGE DE FRANCE 1530

• Organismal Growth: Metabolism and Size

—The organisation, growth, and maintenance at all levels of organisation, molecules, organelles, cells, organs and whole organisms requires constant energy flow and conversion

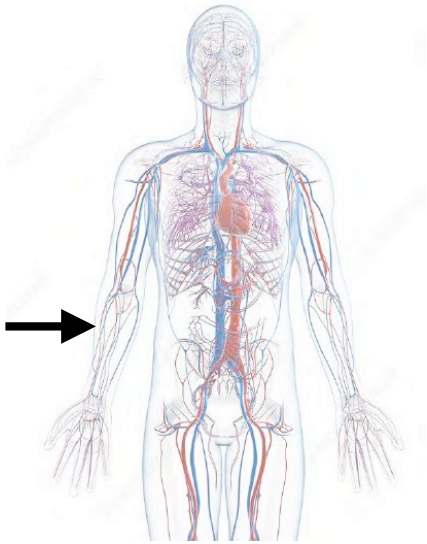
80 Moles ATP/human/day or $3.\ 10^{7}$ ATP/cell/s
($3.\ 10^{13}$ cells and 2000kcal/day)

—Growth is dependent upon energy demands, delivery and conversion across scales

⇨ Metabolic rates (Power)

- Is growth strictly governed by energy demand at the cellular scale?

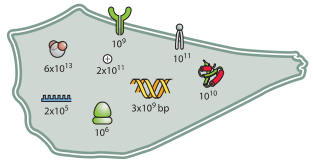
Energy uptake



Energy supply:
nutrient and oxygen flow

Hierarchical energy flow

Intrinsic
Organ size
measurement



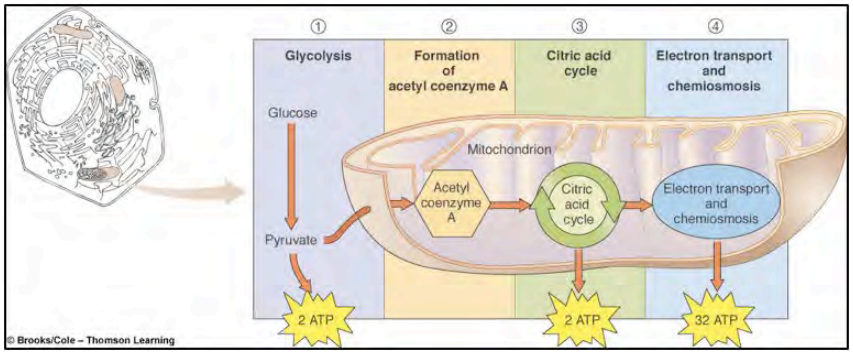
Cellular Energy Demand directs growth rate

Species and Organ specific

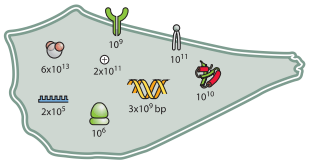
$3.\ 10^{7}$ ATP/cell/s ~ 3.10^{-12} W

• Energy conversion supporting cell growth

—Metabolites (eg. Glucose) can be stored
—Oxygen: cannot be stored



1 Glucose ⟶ 32 ATP



3. 10^7 ATP/cell/s ~ 3.10^{-12} W

Energy conversion: Free Energy of proton gradient converted into Free Energy of Phosphate bonds.

ATP Production rate/ATP Synthase:
300 ATP/s
(100Hz rotation, 3 ATP/rotation)
So it takes 100.000 ATP Synthase/cell

Glycolysis

1 Glucose ⟶ 2 Pyruvate + 2ATP

TCA cycle (tricarboxylic acid cycle)

2 Pyruvate ⟶ 8 NADH + 2 FADH2 + 2 ATP

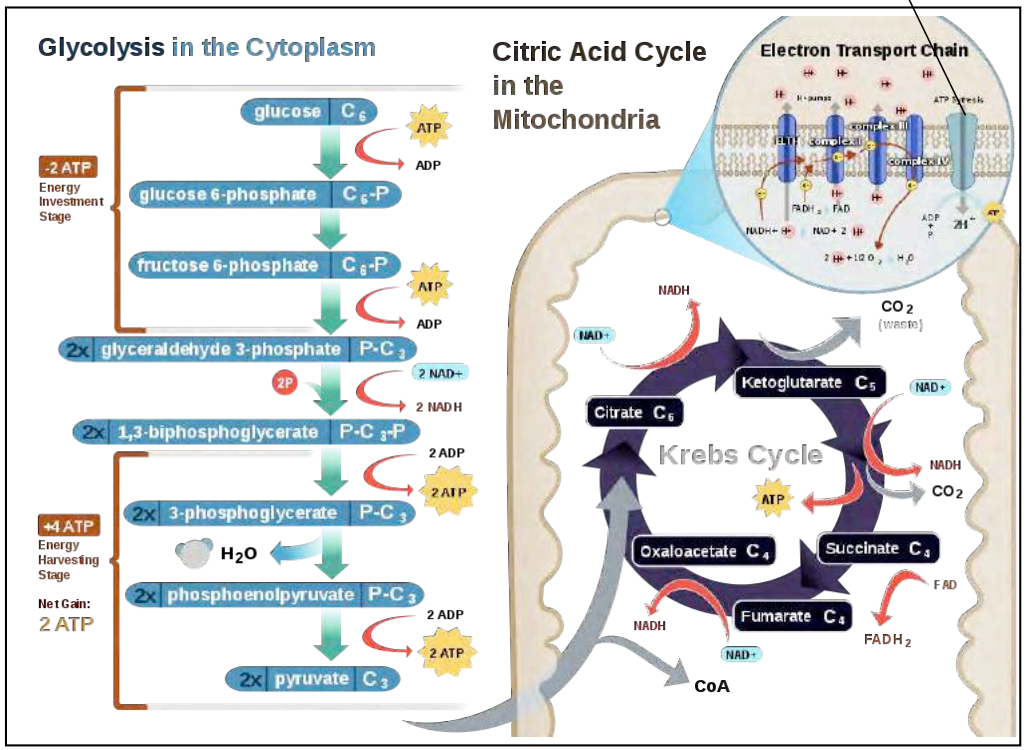
Respiratory chain

8 NADH ⟶ 24 ATP

2 FADH2 ⟶ 4 ATP

Oxydative phosphorylation
by Electron Transport Chain:

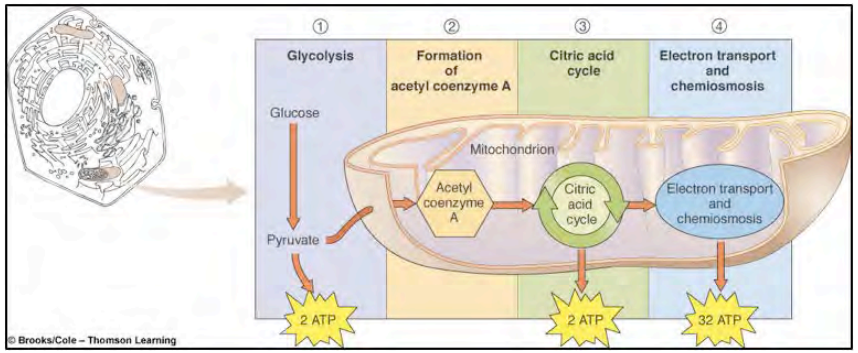
- NADH, $FADH_2$: electron donors
- O_2: electron acceptor



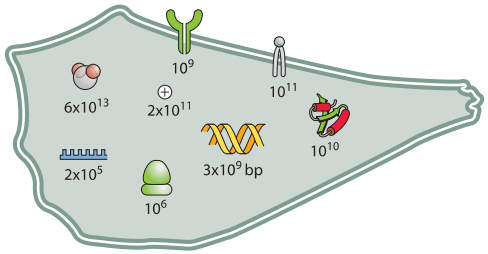
https://steemit.com/steemstem/@davidrhodes124/citric-acid-cycle-and-mitochondrial-electron-transport

• Energy conversion supporting cell growth

—Total energy budget is mostly used for protein synthesis



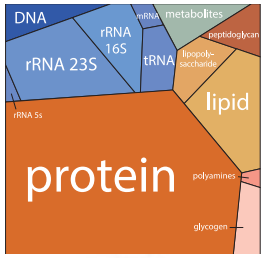
1 Glucose ⟶ 32 ATP

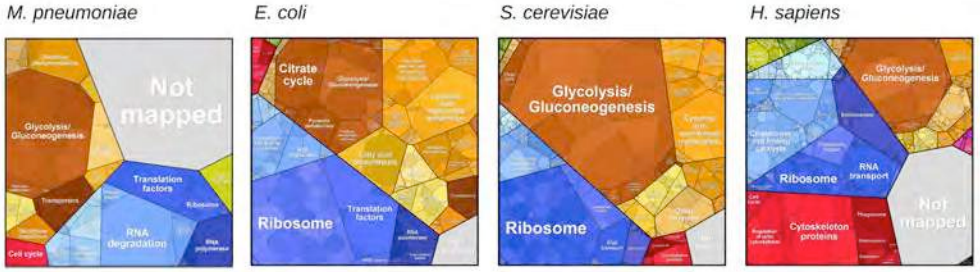


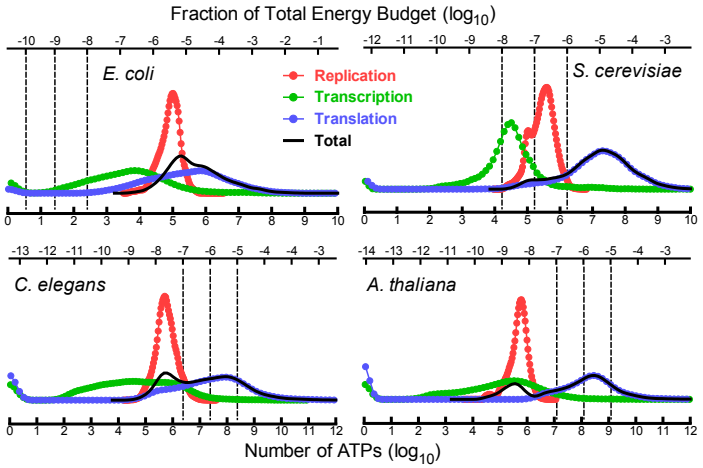
3. 10^7 ATP/cell/s $\sim 3.10^{-12}$W

- Metabolism (especially glycolysis proteins) and Ribosomes are the most part of the proteome

Liebmeister et al, R. Milo. PNAS (2013)
www.pnas.org/cgi/doi/10.1073/pnas.1314810111





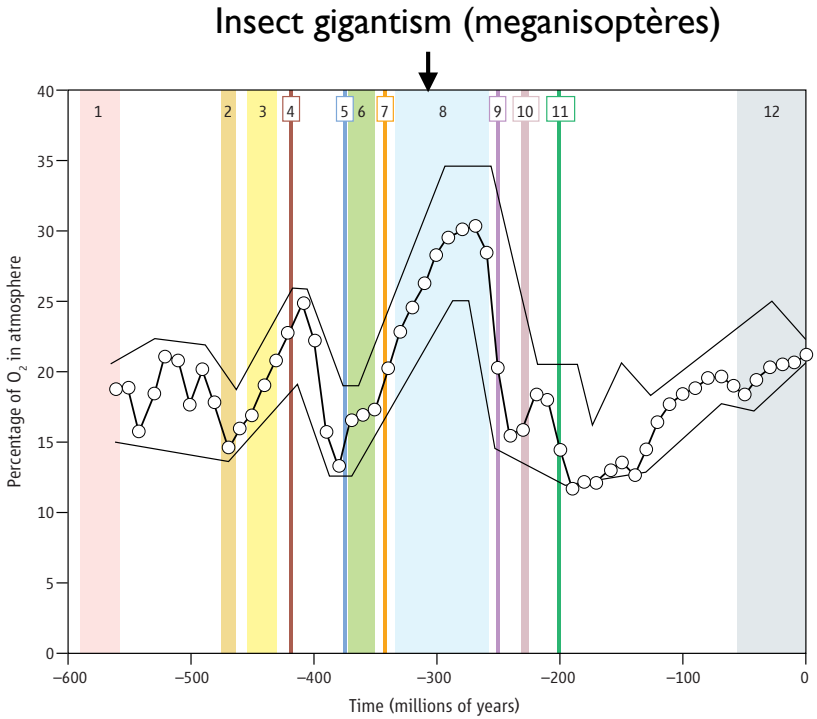


M Lynch and G. Marinov (2015) *PNAS* 112: 15690–15695
www.pnas.org/cgi/doi/10.1073/pnas.1514974112

• Impact of Oxygen on Growth

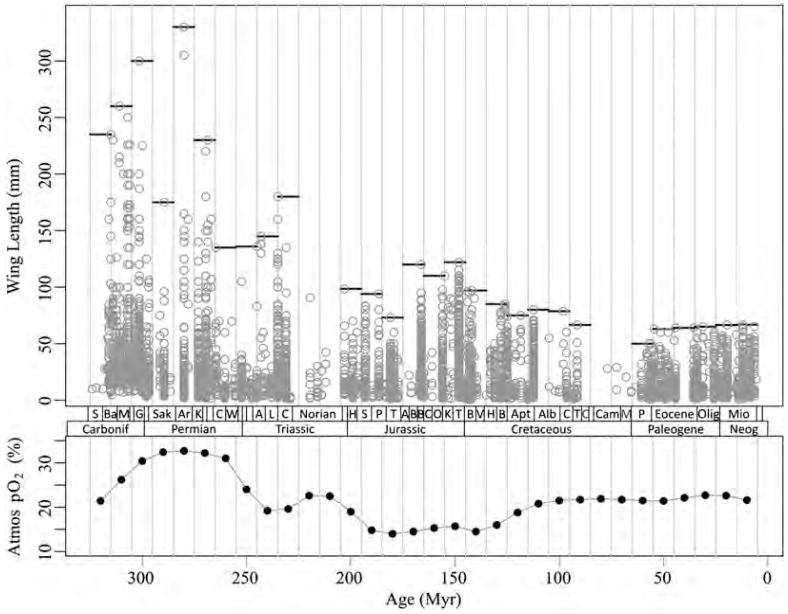
—Evolutionary prospective:

Insect gigantism correlates well with phases of high oxygen concentration in the atmosphere



R. A. Berner, J. M. VandenBrooks and P. D. Ward
Science 316 (5824), 557-558. DOI: 10.1126/science.1140273

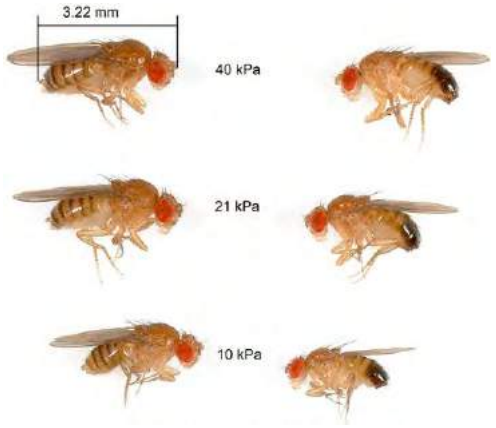
Stephanotypus schneideri (30 cm



M. Clapham and J. Karr. *PNAS.* 109:10927–10930
DOI: 10.1073/pnas.1204026109

• Impact of Oxygen on Growth

—Reduced oxygen concentration (hypoxia) induces reduced growth in insects



C.Jaco Klok and J.F. Harrison. (2009) PLoS ONE 4(1): e3876. doi:10.1371/journal.pone.0003876

Drosophila melanogaster

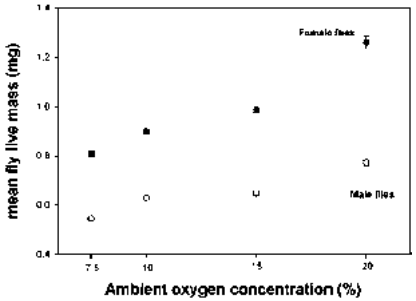
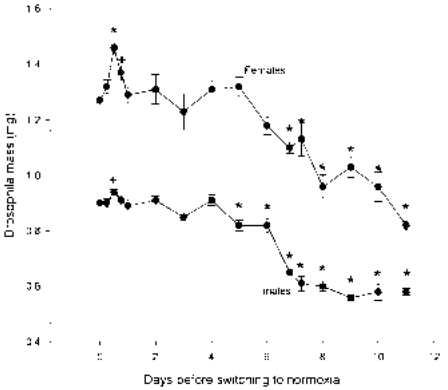
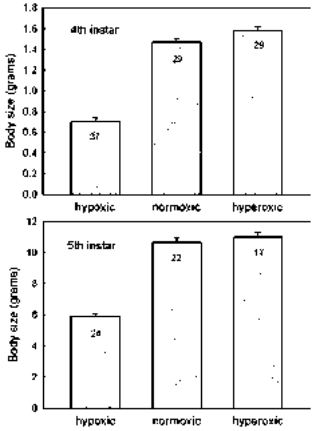


Fig. 1. Mean mass (±SE) of male and female *Drosophila melanogaster* grown in atmospheric oxygen concentrations ranging from 7.5% to 20%. Data shown were from experiment 1, for each point $n = 30$. For females mass = 0.663+0.033% oxygen ($r^2 = 0.67$, $F = 254$, $P < 0.0001$, 126 d.f.). For males, mass = 0.492+0.0215% oxygen ($r^2 = 0.69$, $F = 337$, $P < 0.0001$, 149 d.f.).



L.S. Peck AND S. H.P. Maddrell *J.Exp. Zool.* 303A:968–975 (2005)

Manduca sexta



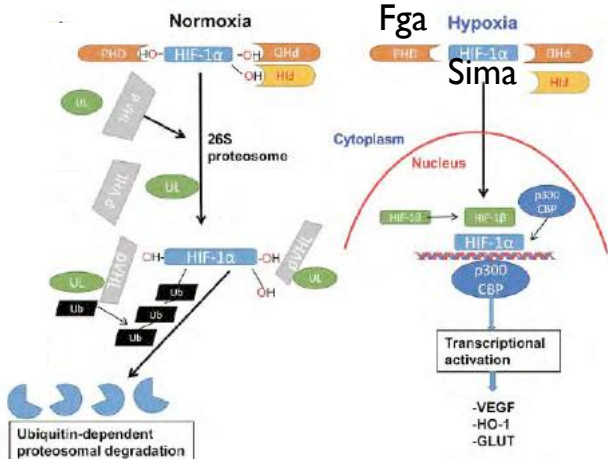
V. Callier and F. Nijhout *Proc Natl Acad Sci U S A.* 2011 Aug 30;108(35):14664-9. doi: 10.1073/pnas.1106556108

• Impact of Oxygen on Growth

—Hypoxia induces inhibits cell and tissue growth

—Oxygen sensing pathway

The HIF pathway responses to hypoxia.
PHDs are oxygen sensor and regulate (degrade) HIF when O_2 is present



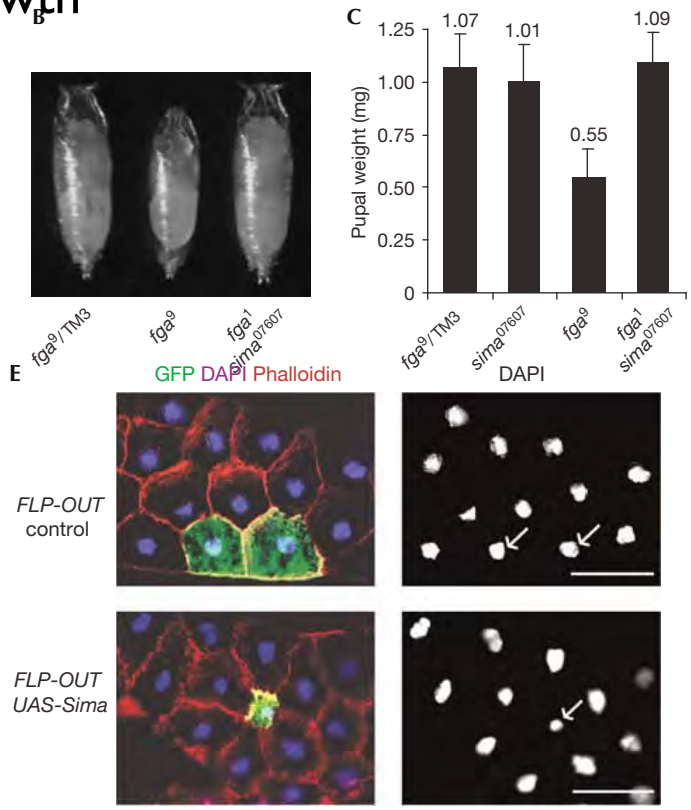
sima mutant: no response to hypoxia

sima overexpression: induction of hypoxia gene

fga mutant: sima is constitutively active:

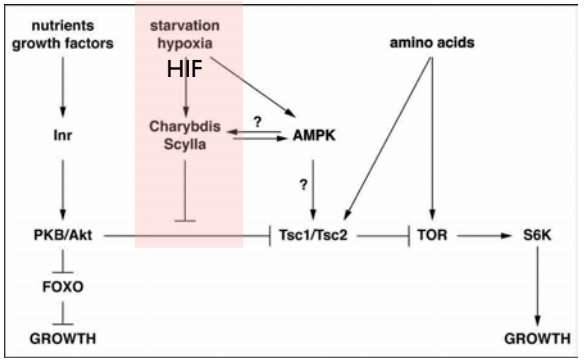
—cell growth is reduced

—organism size is smaller (50%).



L. Centanin, P.J. Ratcliffe & P. Wappner

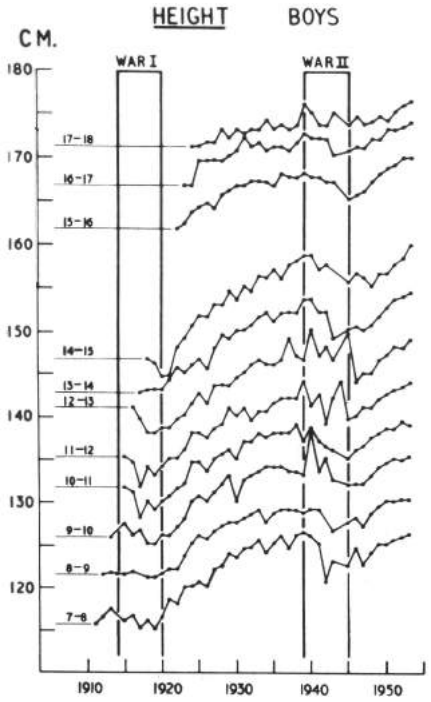
EMBO reports (2005) 6, 1070–1075. doi:10.1038/sj.embor.7400528



Jan H. Reiling and Ernst Hafen *Genes Dev.* 2004 18: 2879-2892 doi:10.1101/gad.322704

• Impact of Food and Nutrients on Growth

—Nutrients can be stored (liver in vertebrates, fat body in insects) and converted depending on demand.

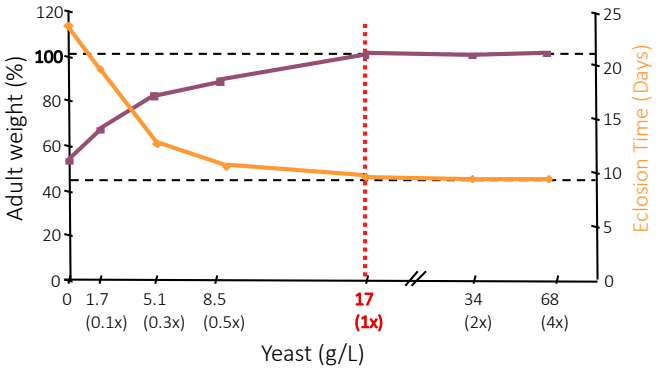


Size of infants and adolescents is reduced during starvation phases

Tanner, J.M. (1962) Growth at adolescence. 2nd Edition, Blackwell Scientific Publications, Oxford.

1.7g/l Yeast

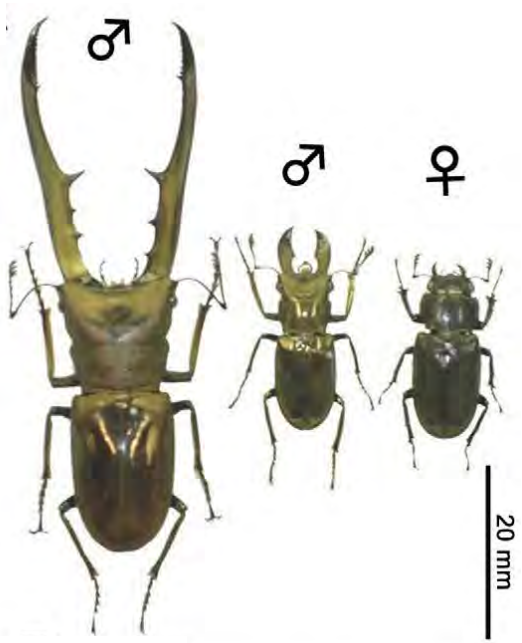
17g/l Yeast



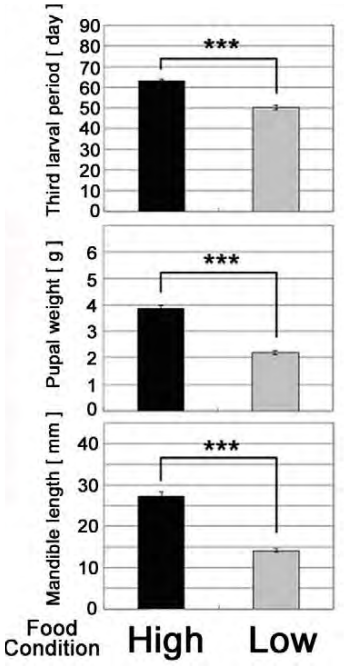
data:: Pierre Leopold (Institut Curie)

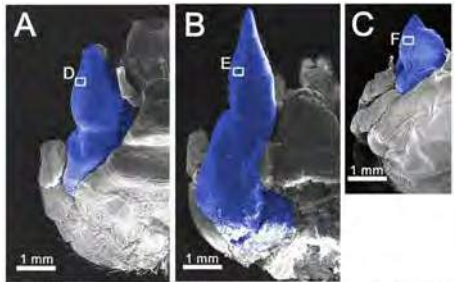
• Impact of Food and Nutrients on Growth

—Nutrient uptake can, in some instances, regulate the size of adult organs



Cyclommatus metallifer



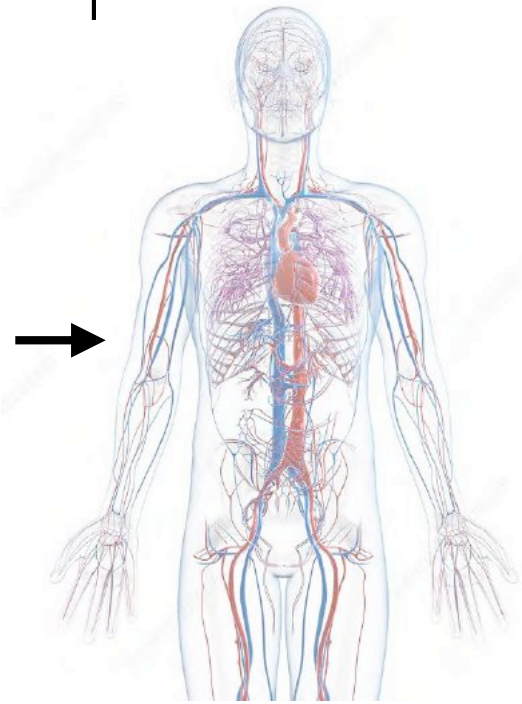


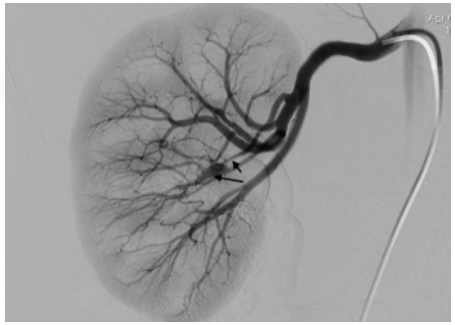
Gotoh H, Cornette R, Koshikawa S, Okada Y, Lavine LC, et al. (2011) *PLoS ONE* 6(6): e21139. doi:10.1371/journal.pone.0021139

- However, Energy delivery constraints organism growth and size

Energy delivery $B = B_0 M^{3/4}$

Energy uptake →

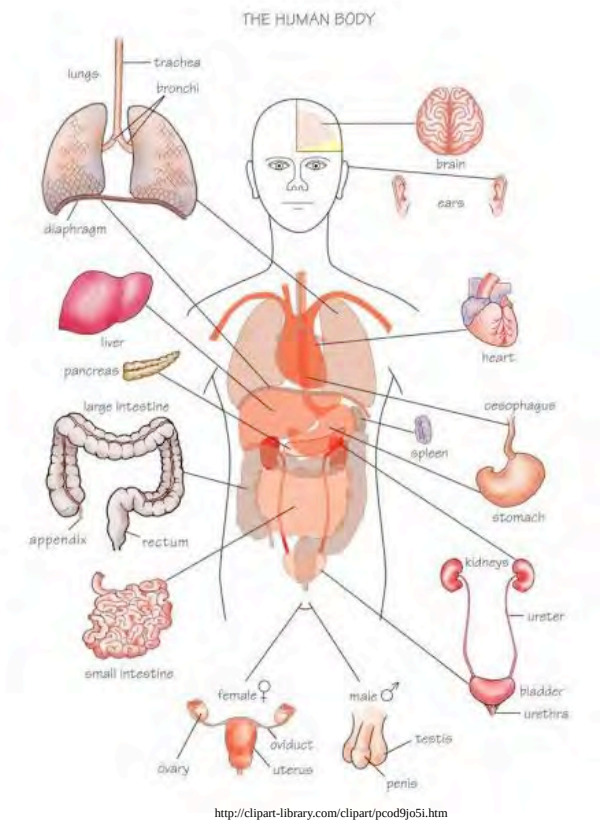




https://www.researchgate.net/

Each organ receives energy flux to sustain its growth

→



http://clipart-library.com/clipart/pcod9jo5i.htm

Organ specific mechanism to arrest growth based on local size-sensing

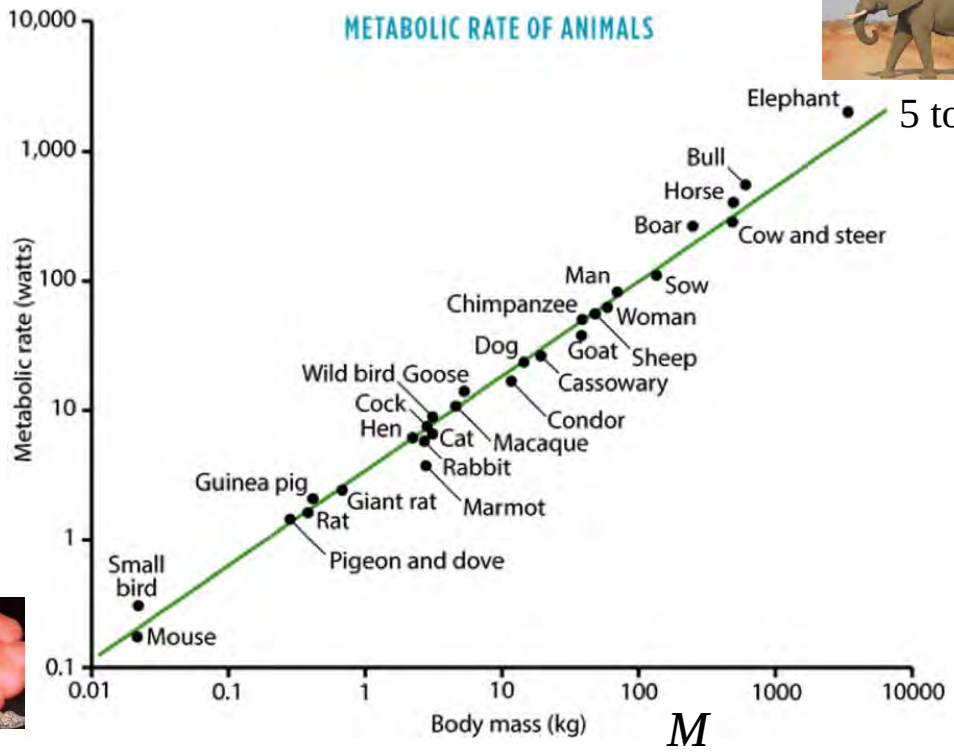
Hierarchical energy flow through self-similar network constrained by invariant termini (cell size and metabolism)

Size-measurement (signalling, mechanics)

- Energy delivery constraints organism growth and size

$$B = B_0 M_b^{3/4} \qquad t \propto M_b^{1/4} e^{E/kT}$$

2g



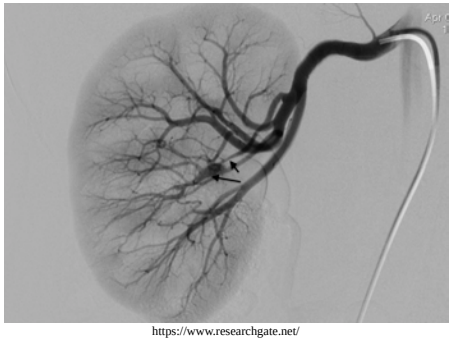
5 tonnes

http://www.physicstoday.org . 2004 American Institute of Physics, S-0031-9228-0409-010-6

• Organ growth arrest and energy delivery constraints

— Hypothesis: An asymptotic mass emerges from imbalance between energy supply and energy demand associated with Kleiber law for each organ?

- Organ level scaling law: the whole organism power law scaling of metabolic power to mass can be explained by organ-level scaling of metabolic power to organ mass.
- Organ specific properties: cell size and metabolic power (genetically controlled)



https://www.researchgate.net/

$$\mathrm{REE}_p = \Sigma\left(a \times M^b \times T_i\right).$$

$$K_i = a \times M^b,$$

for liver: $(K \times T) = 19.56 \times M^{0.6046}$; $r = 0.9694$,

for brain: $(K \times T) = 4.82 \times M^{0.6446}$; $r = 0.9538$,

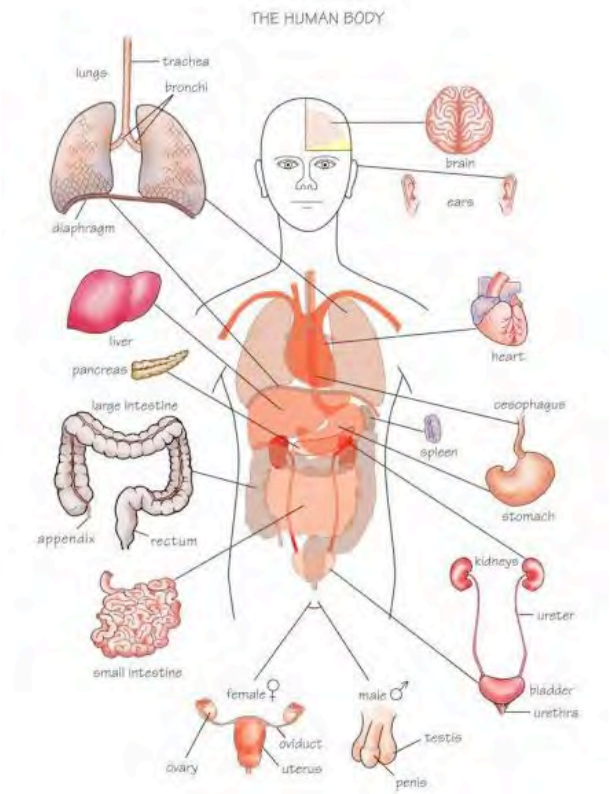
for heart: $(K \times T) = 5.16 \times M^{0.8137}$; $r = 0.9830$, (9)

for kidneys: $(K \times T) = 4.35 \times M^{0.7441}$; $r = 0.9825$,

for residual: $(K \times T) = 28.16 \times M^{0.8402}$; $r = 0.9996$.

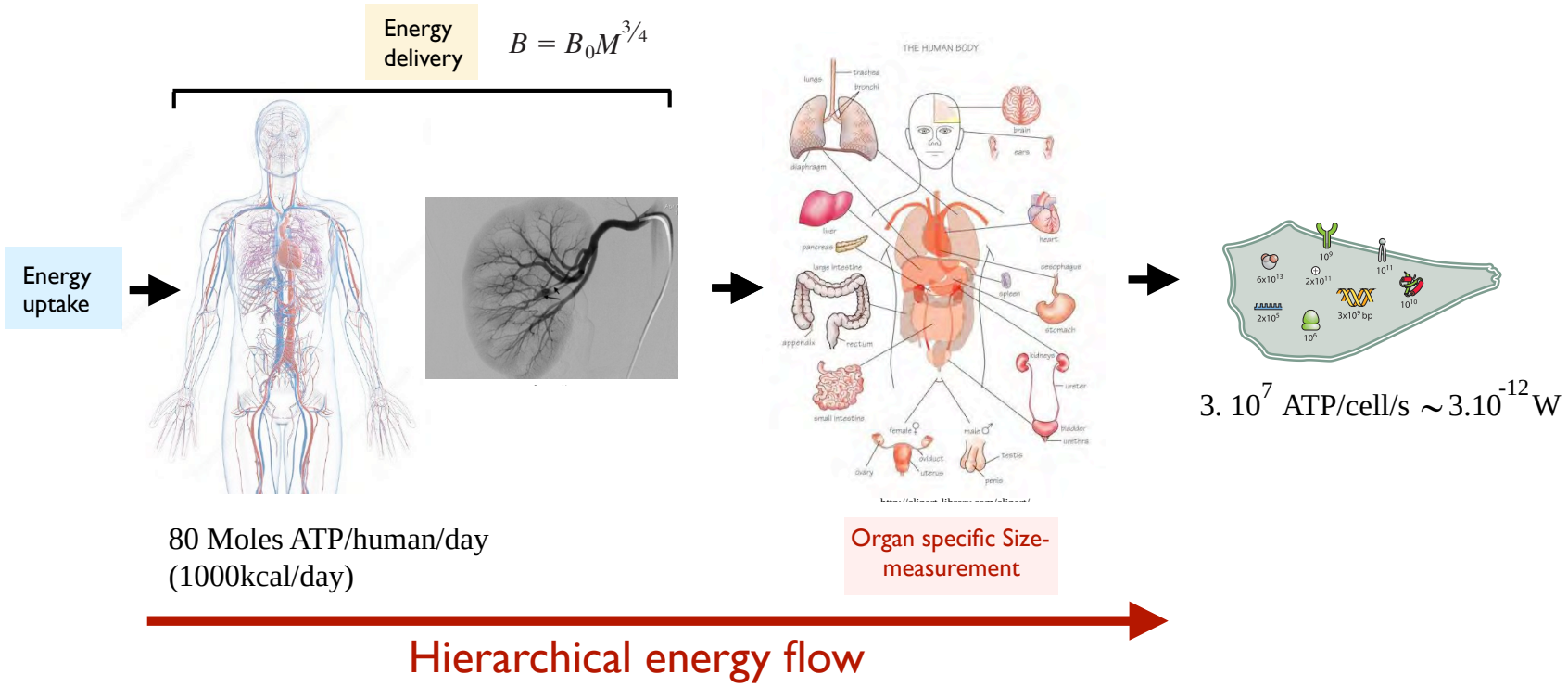
Z. Wang, et al and S.B. Heymsfield

International Scholarly Research Network ISRN Zoology (2012)
doi:10.5402/2012/673050



http://clipart-library.com/clipart/pcod9jo5i.htm

• Energy delivery and organ size



Questions:

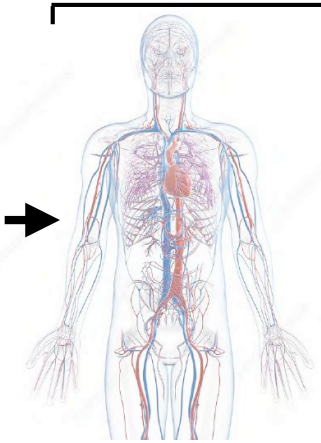
1) Is the growth of different organs programmed deterministically (ie. genetically)?
   Is growth and metabolic rate deterministically controlled at each scale?
   Is there a species specific, cell fate dependent cellular metabolic power that determines that of each organ and organism?

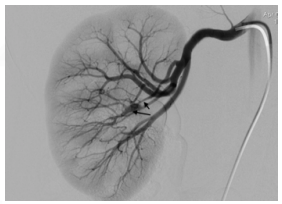
• Energy delivery and organ size

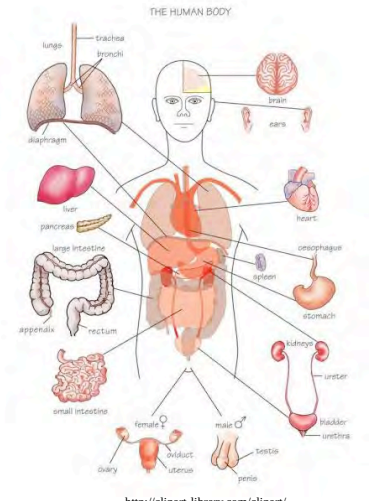
Energy delivery

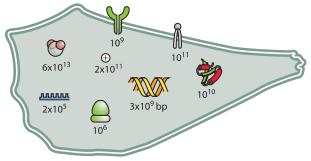
$B = B_0 M^{3/4}$

Energy uptake







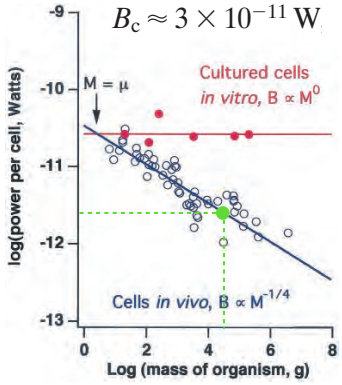


3. 10^7 ATP/cell/s $\sim 3.10^{-12}$ W

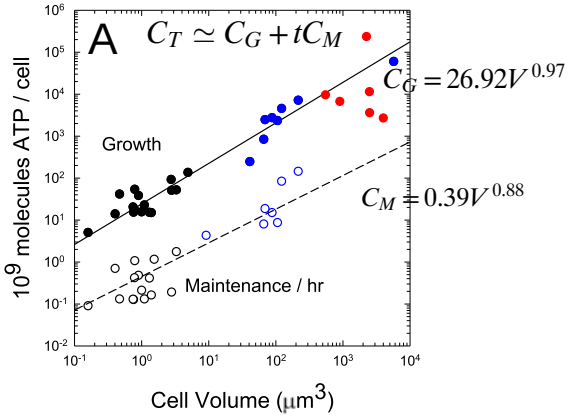
80 Moles ATP/human/day
(1000kcal/day)

Organ specific Size-measurement

Hierarchical energy flow



West, G. B., Woodruff, W. H. and Brown, J. H. (2002). PNAS 99, 2473-2478.

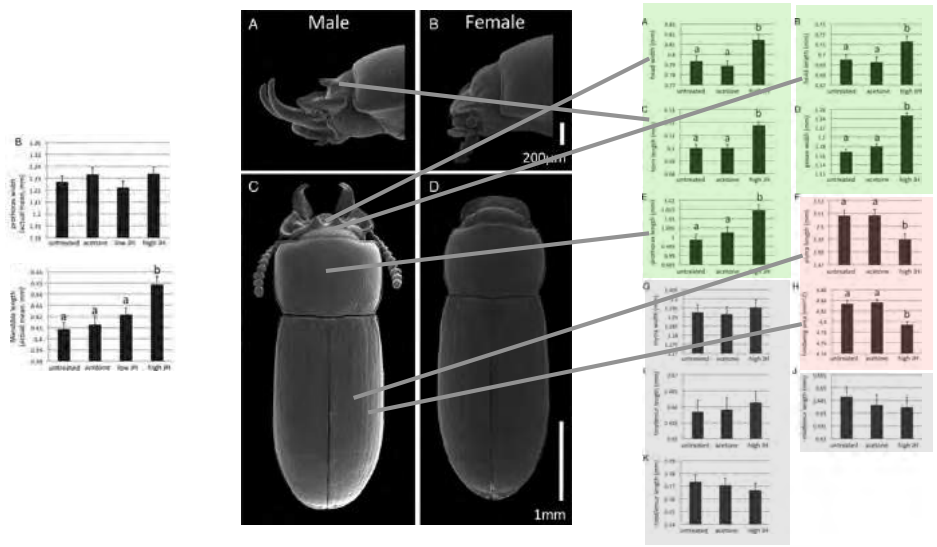


Basal cellular metabolic rate and energy required for growth are chiefly dependent on cell size. Cost of growth is generally dominant.

M Lynch and G. Marinov (2015) *PNAS* 112: 15690–15695
www.pnas.org/cgi/doi/10.1073/pnas.1514974112

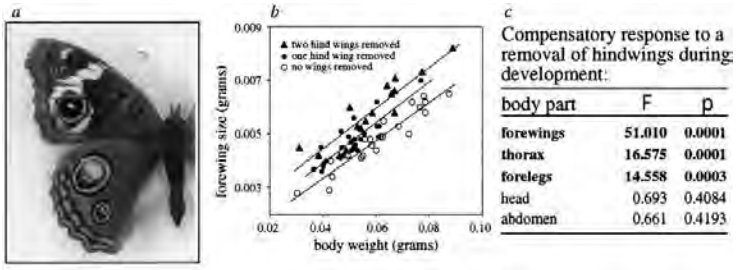
• Competition in ressource allocation between organs

—Differential ressource allocation and growth of different organs



Y. Okada et al. and K. Okada. (2012) *Evolution and Development* 14:4, 363–371 (2012) DOI: 10.1111/j.1525-142X.2012.00554.x

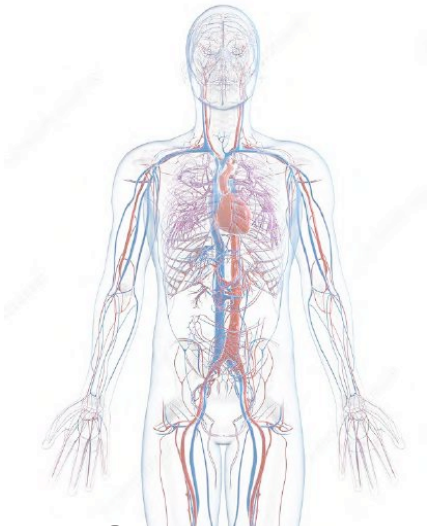
—Ressource allocation and competition between different morphological traits within an organism given limited resources



body part	F	p
forewings	**51.010**	**0.0001**
thorax	**16.575**	**0.0001**
forelegs	**14.558**	**0.0003**
head	0.693	0.4084
abdomen	0.661	0.4193

Nijhout, H. F., and Emlen, D. J. 1998. Competing body parts in the development and evolution of insect morphology. *Proc. Natl. Acad. Sci. USA* 95: 3685–3689.
Nijhout, H. F., and Wheeler, D. E. 1996. Growth models of complex allometries in holometabolous insects. *Am. Nat.* 148: 40–56.

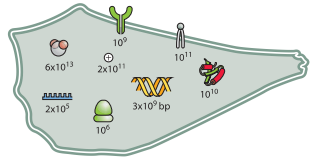
• Summary: Hierarchical energy flow and growth



Organismal
multi scale
Energy Supply
constraints growth rate

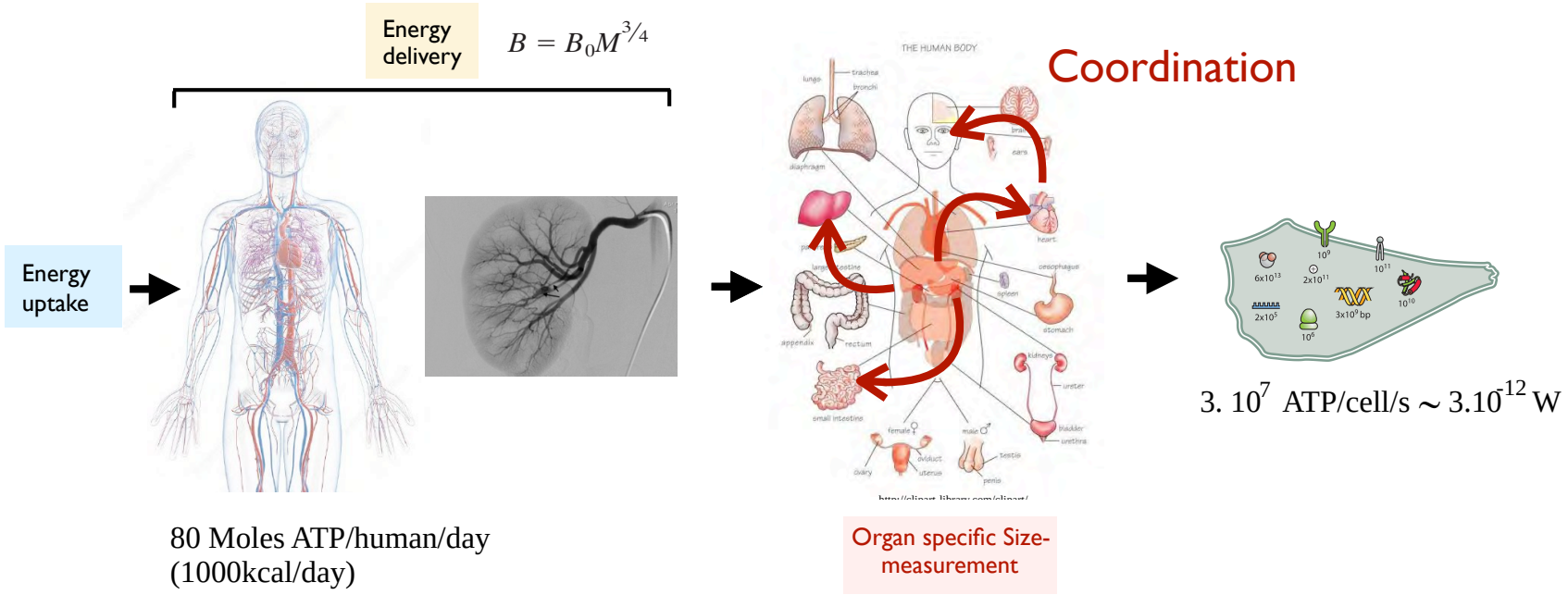
Hierarchical energy flow

Intrinsic
Organ size
measurement



Cellular Energy Demand
directs growth rate
Species and Organ specific

• Energy delivery and organ size



Questions:

1) Is the growth of different organs programmed deterministically (ie. genetically)? **Autonomous growth.**
2) Is organ growth rather coordinated between organs, via feedback mechanisms? **Regulative growth.**
3) How is growth between the left and right sides adjusted to minimise fluctuations and asymmetry?

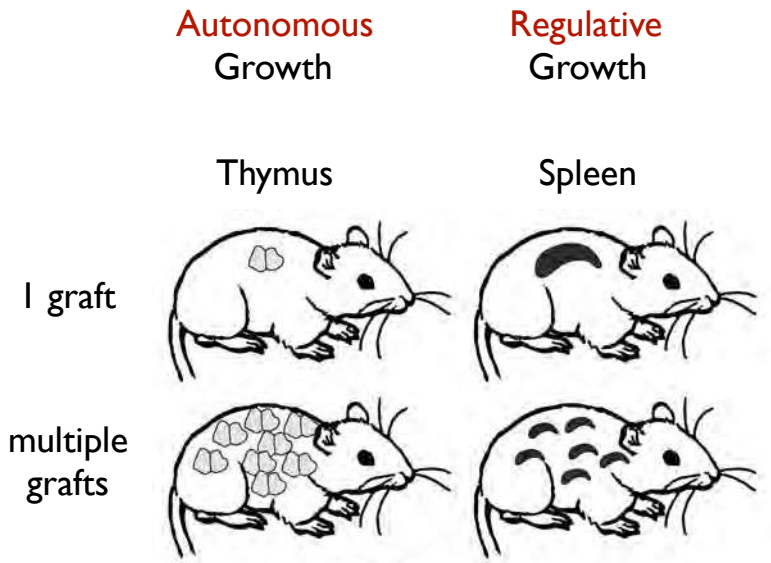
Programmed vs Self-organised regulation of Growth

- hierarchical
- modular
- deterministic rules (ie. genetically encoded)

- no hierarchy
- feedbacks
- statistical rules

• Intrinsic and Extrinsic regulation of growth: organ and lineages

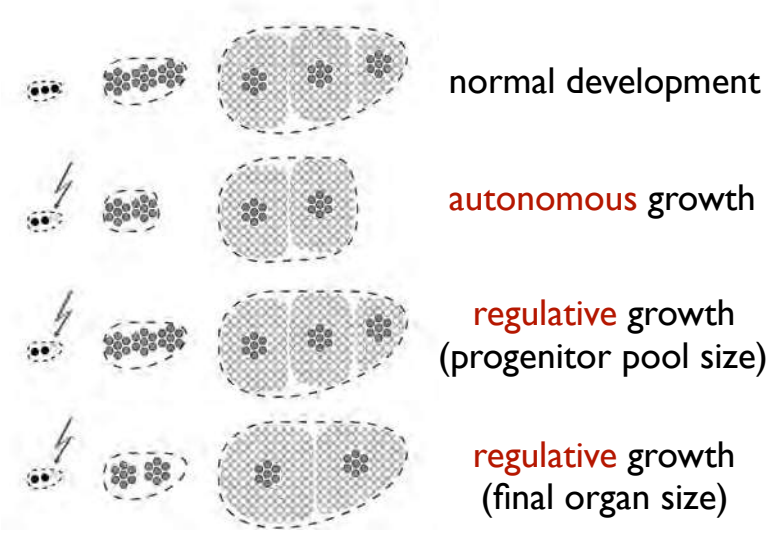
- Graft experiments



Metcalf D. *Transplantation*. (1964); 2:387–392.

Metcalf D. *Austr J Exp Biol Med Sci.* (1963); 41:437– 447

- Cell ablation experiments

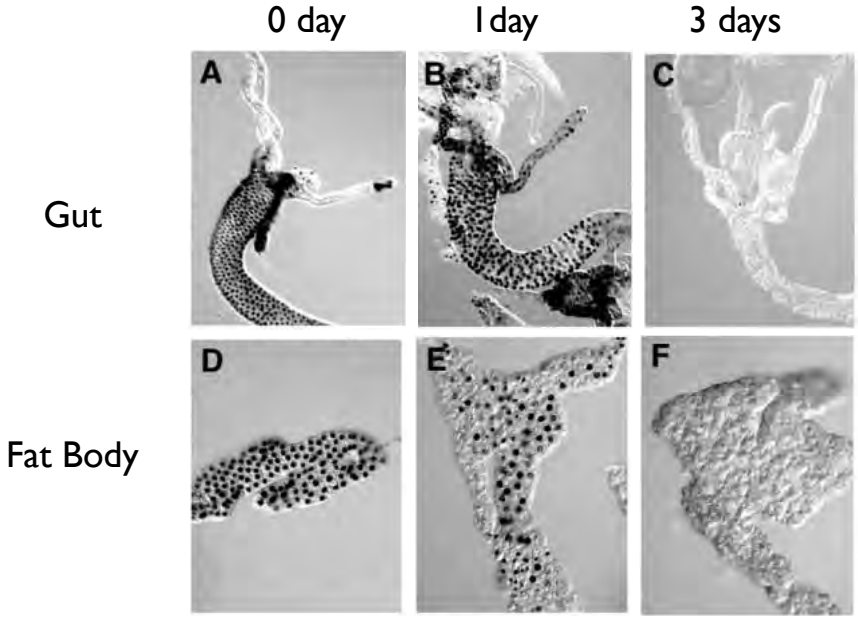


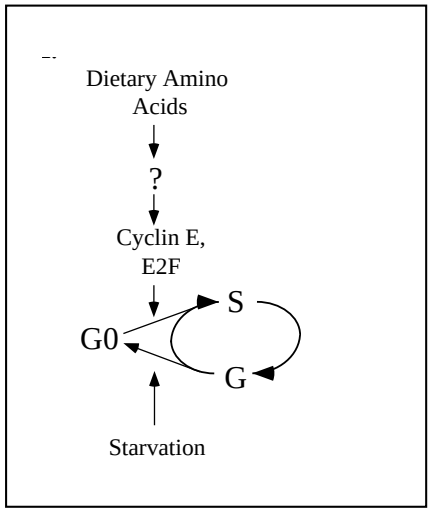
Roselló-Díez A, Joyner AL. *Endocr Rev*. (2015);36(6):646-80. Review.

AI Penzo-Mendez and BZ Stanger. (2015) *CSH Perspect Biol* doi: 10.1101/cshperspect.a019240 Review

• Extrinsic control of growth: existence of a humoral relay signal

—Endoreplicating cells arrest growth and become quiescent following starvation
(no amino acids, only sucrose)

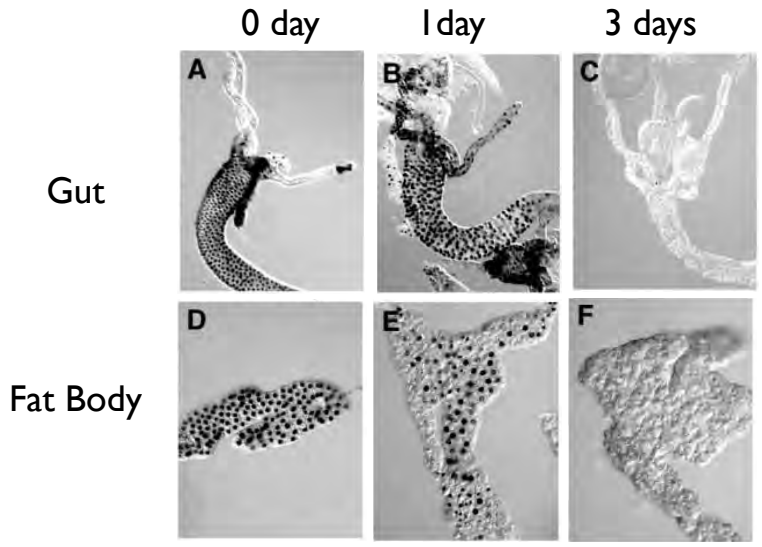


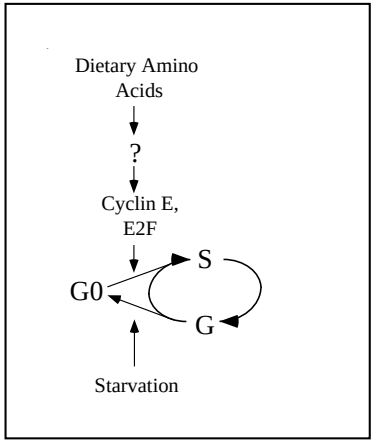


J. Britton and B. Edgar. *Development* 125, 2149-2158 (1998)

• Extrinsic control of growth: existence of a humoral relay signal

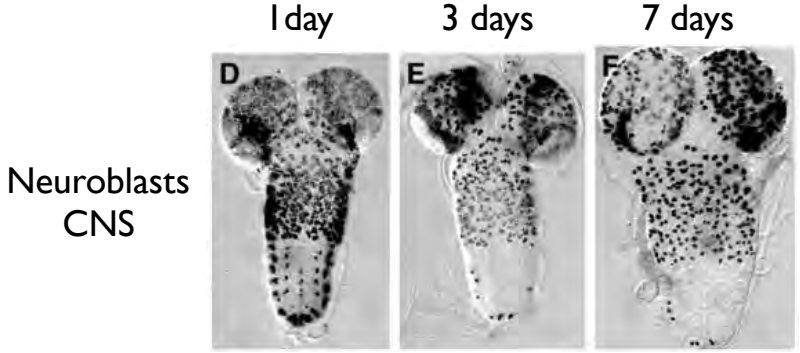
—Endoreplicating cells arrest growth following starvation

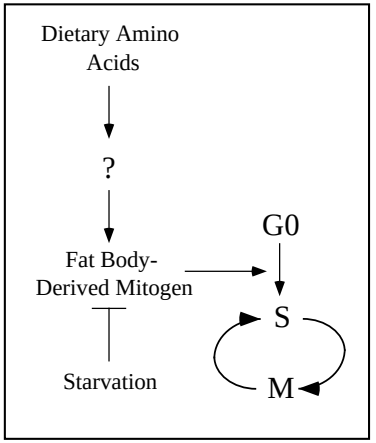


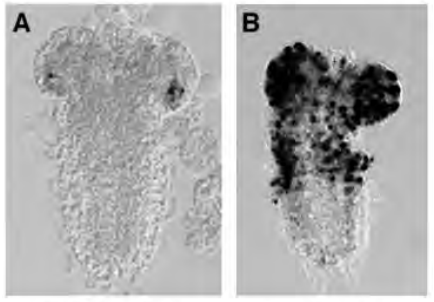


—Other tissues (eg. neuroblasts, imaginal discs) do not arrest cell division and cell growth following starvation.

—Growth requires a factor produced by the Fat body







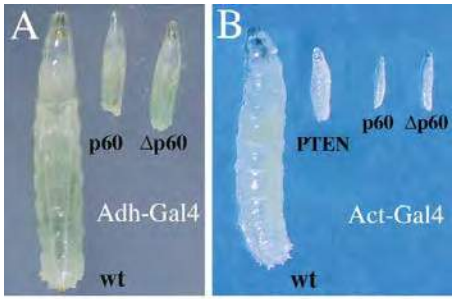
food deprived + serum containing Fat Body

J. Britton and B. Edgar. *Development* 125, 2149-2158 (1998)

• Existence of a humoral relay signal required for growth

—Insulin/PI3-Kinase Pathway Coordinates Cellular Metabolism with Nutritional Conditions

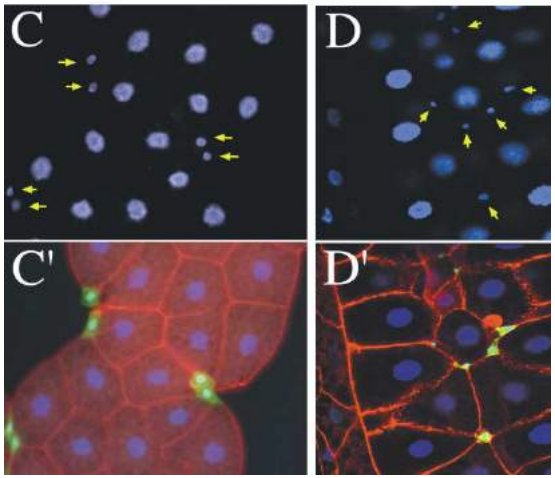
- Inhibition of Pi3K pathway in the fat body is sufficient to strongly reduce growth the whole organism
- Thus the Fat Body is likely involved in growth control at the organismal scale



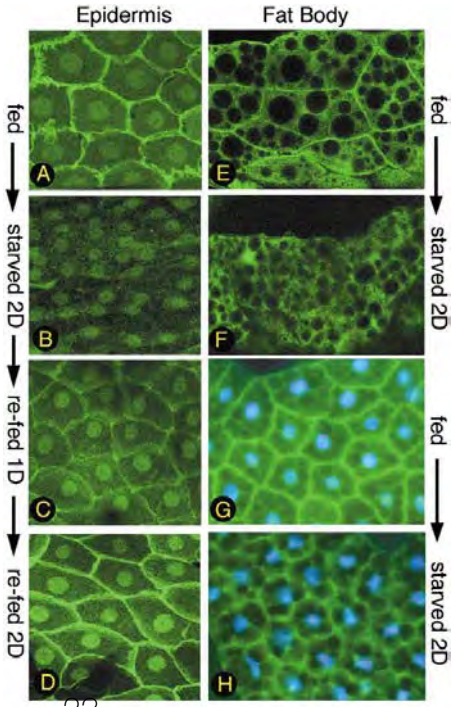
Fat Body ubiquitous

p60 expression clones (inhibit Pi3K)

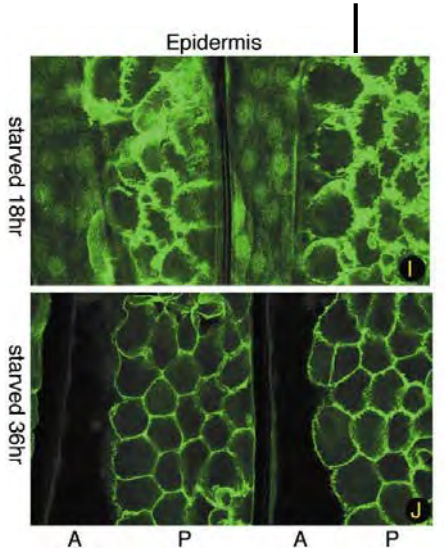
fat body salivary gland



- The Pi3K pathway signalling is reduced in starved animals in epidermis and fat body.
- Forced expression of p110 rescues Pi3K signalling in starved animals
- Thus, Pi3K signalling is nutrition dependent



dp110 expression

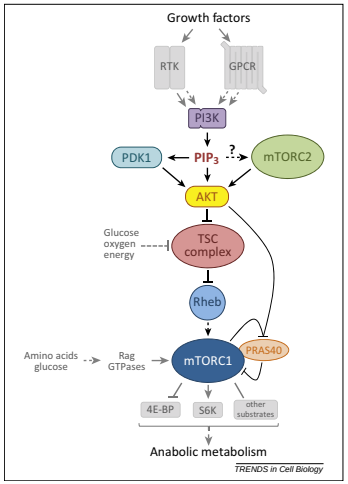


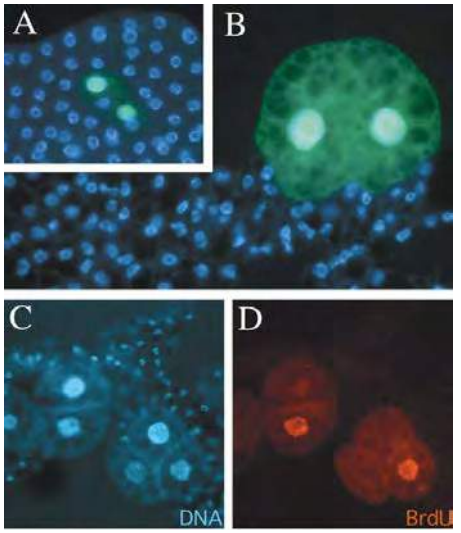
J. Britton et al and B. Edgar (2002) *Developmental Cell*, Vol. 2, 239–249

• Existence of a humoral relay signal required for growth

—Insulin/PI3-Kinase Pathway Coordinates Cellular Metabolism with Nutritional Conditions

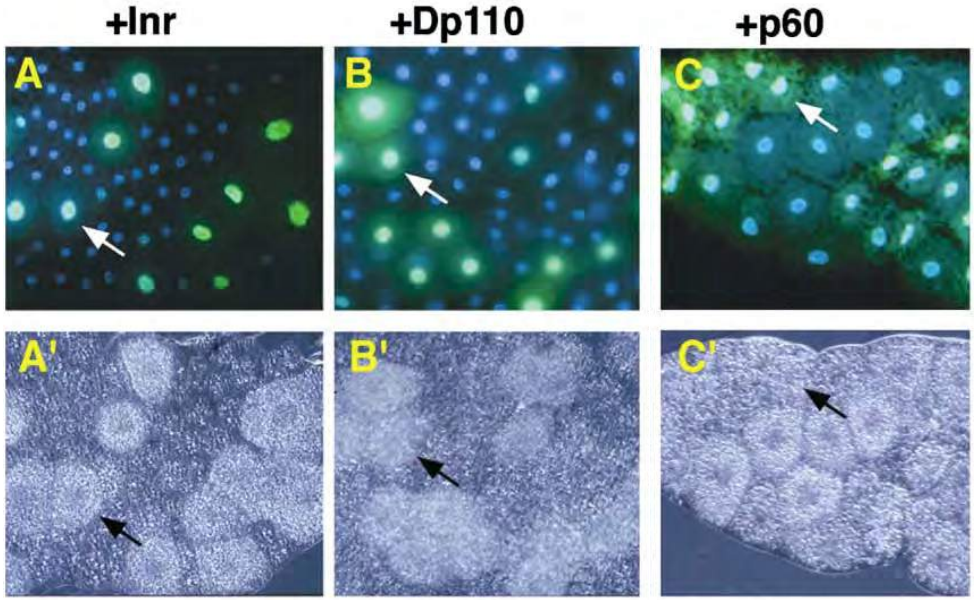
- Clonal activation of Pi3K signalling in starved animals induces cell growth and division.





- Insulin and Pi3K signalling modulates cellular growth and energy storage

- Thus, nutritional conditions modulate cellular growth mediated by Pi3K presumably via a fat body hormonal relay signal.



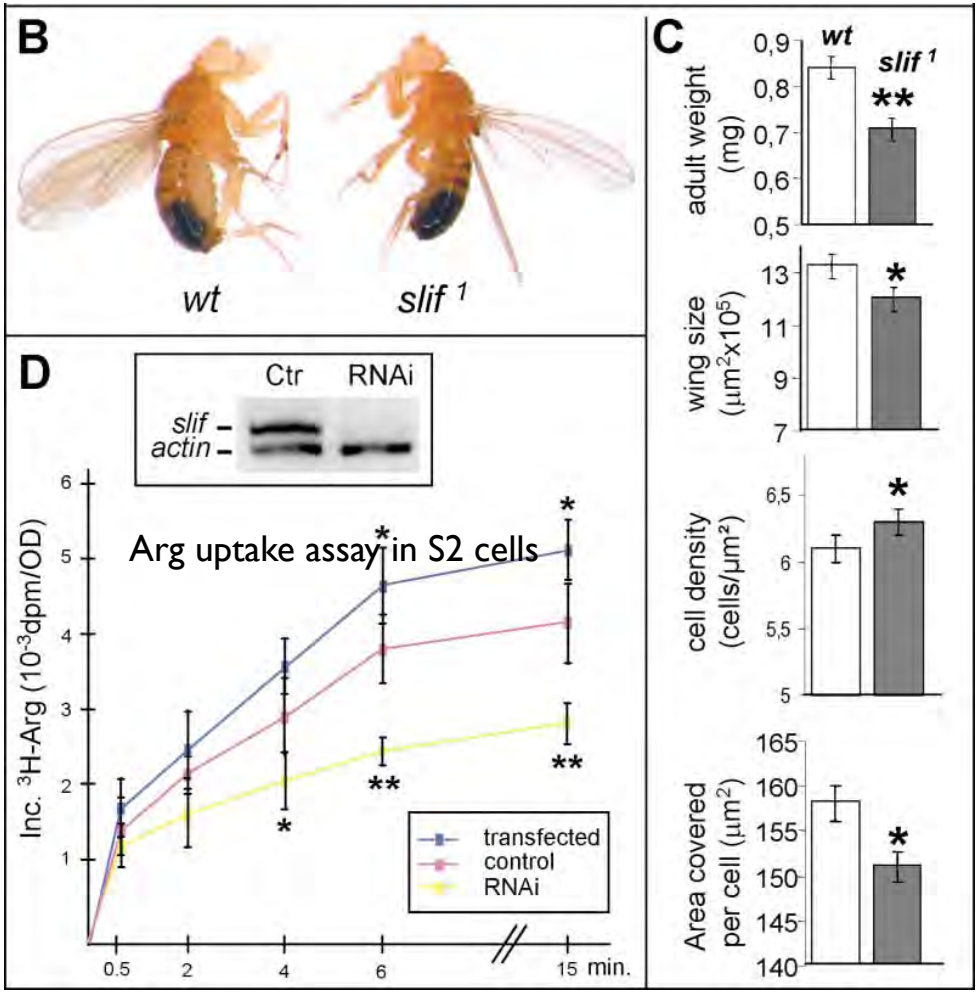
J. Britton et al and B. Edgar (2002) *Developmental Cell*, Vol. 2, 239–249

• Existence of a humoral relay signal from Fat Body

—Amino-acid transport inside cells is required for growth of cells and organisms in flies

- Amino acid withdrawal blocks translation before aa pools are depleted in cells so there is a cellular amino acid sensing mechanism
- Aa levels tune the binding of repressor 4EBP1 to translation initiation factor EIF4E as well as activity of the S6K kinase via TOR signalling
- Slimfast (Slif) is an amino acid permease of the cationic amino acid transporter (CAT) family
- In mutants, flies are smaller, and cells are smaller/ higher density.

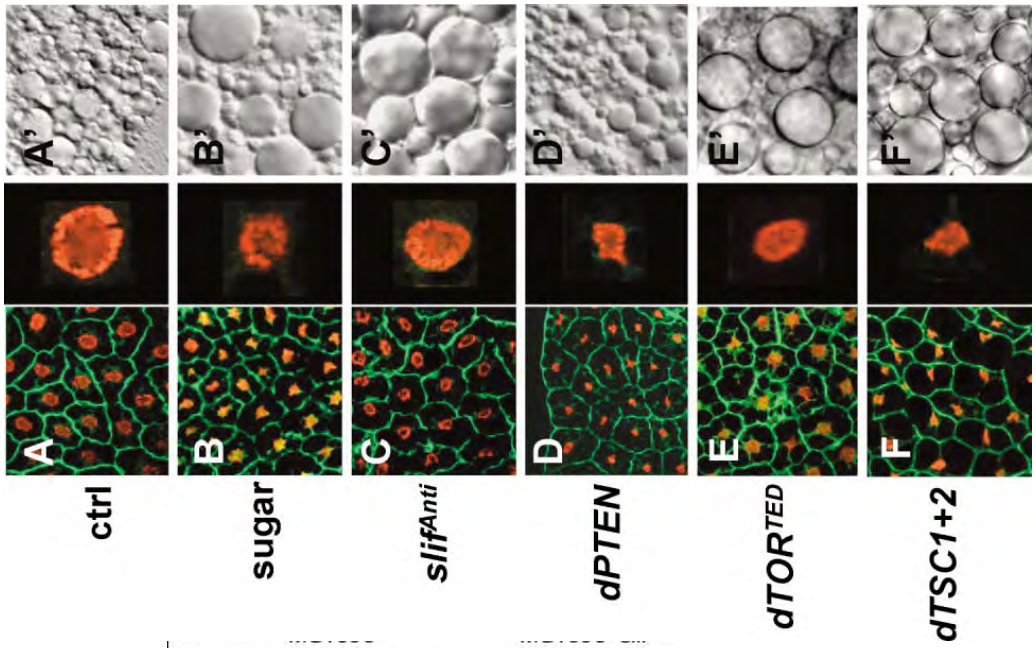
Question: Is the sensing mechanism purely cell autonomous?



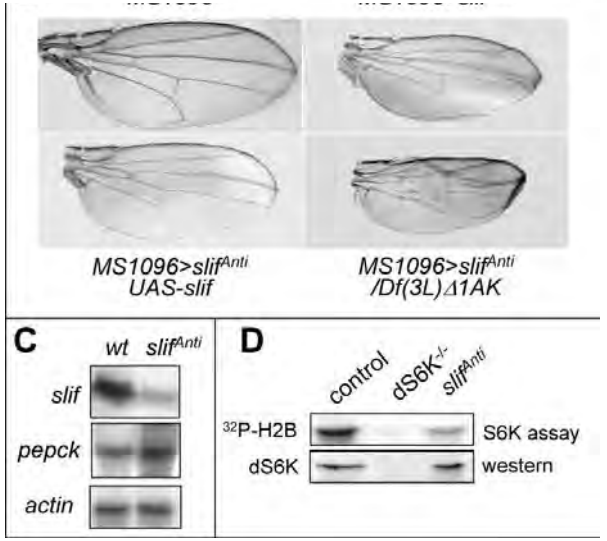
J. Colombani et al. and P. Leopold. (2003) *Cell*, Vol. 114, 739–749

• Existence of a humoral relay signal from Fat Body

- A *slif* mutant mimicks amino acid starvation:
  - Fat Body cells accumulate large storage vesicles
  - S6K activity is strongly reduced
- Inhibition of Pi3K or TOR signalling has similar effects



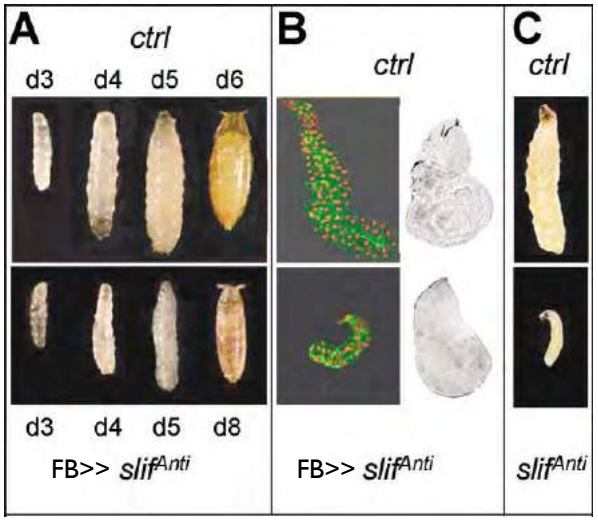
- Inhibiting Slif in developing wings reduces their size consistent with an organ autonomous requirement in addition to a cell autonomous requirement



J. Colombani et al. and P. Leopold. (2003) *Cell*, Vol. 114, 739–749

• Existence of a humoral relay signal from Fat Body

- However, inhibition of *slif* in the Fat Body (FB) alone causes non autonomous effects on adult size
- This is amplified by strong (10x) reduction of a single aa (eg. arginine).
- Similar defects are observed when TOR signalling is inhibited in the fat body.
- Therefore, the Fat Body is a bone fide organismal aa sensor responsible for a relay mechanism of tissue growth.



1/10X Arg diet

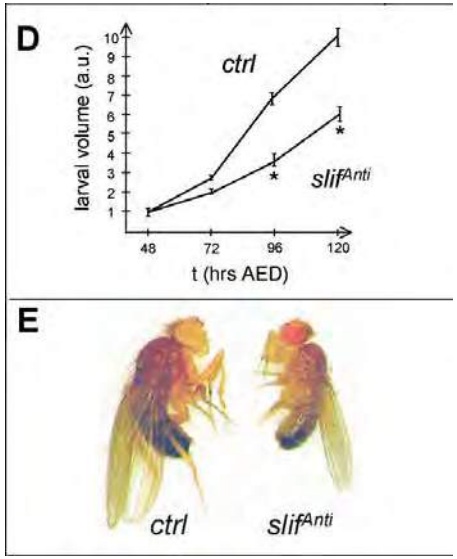


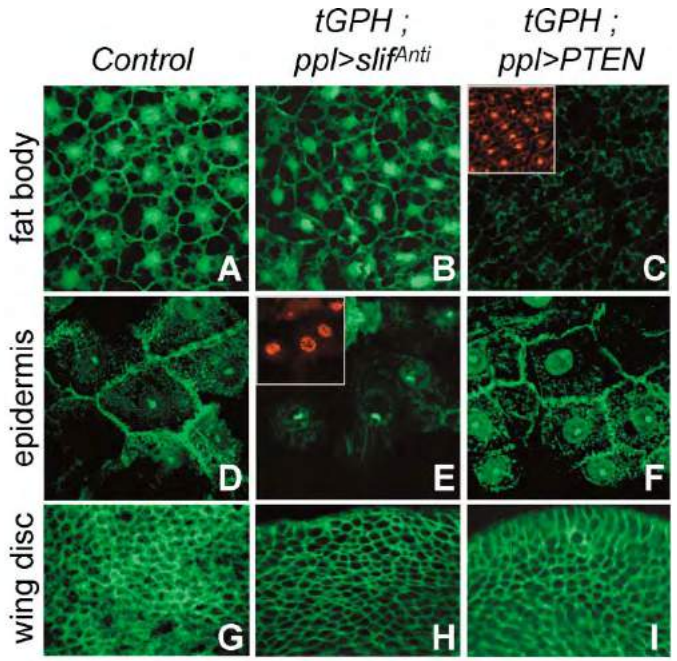
Table 1. Systemic Growth Control by the FB

	Mean Adult Emergence Time (Days)	Adult Weight (%)	FB Cell Size (%)	Nuclear Volume (%)	n
Wt	11	100	100	100	150
Sugar (PBS 20% sucrose)	–	–	69	21	–
ppl>slif^{Anti}	12.5 (18°C)	54 (18°C)	90	25	120
ppl>dPTEN	11	99	70	10	120
ppl>dTOR^{TED}	12	72	84	26	120
ppl>dTSC1 + dTSC2	12.5	82	78	19	150
ppl>slif^{Anti} + S6K-D4	12.5 (18°C)	68 (18°C)	–	–	60

J. Colombani et al. and P. Leopold. (2003) *Cell*, Vol. 114, 739–749

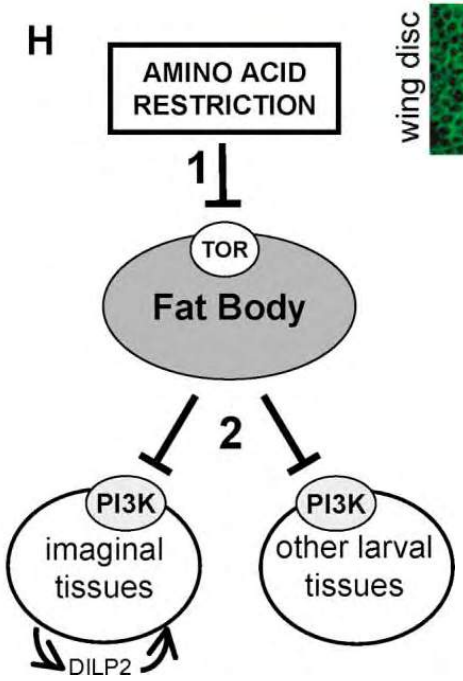
• Existence of a humoral relay signal from Fat Body

- Activation of the amino acid sensor pathway via inhibition of the aa transport Slif causes strong reduction of Pi3K signalling in encareplicating tissues (eg. epidermis), and a mild reduction in imaginal discs.



—The Fat Body is a nutrient organismal sensor that tunes TOR signalling

—A humoral relay mechanism adjusts the growth PI3K pathway in all tissues to tune cellular growth

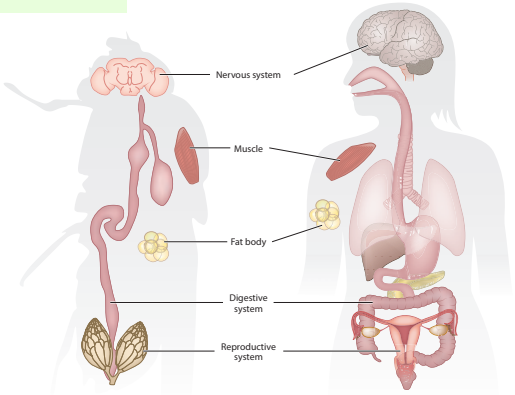


J. Colombani et al. and P. Leopold. (2003) *Cell*, Vol. 114, 739–749

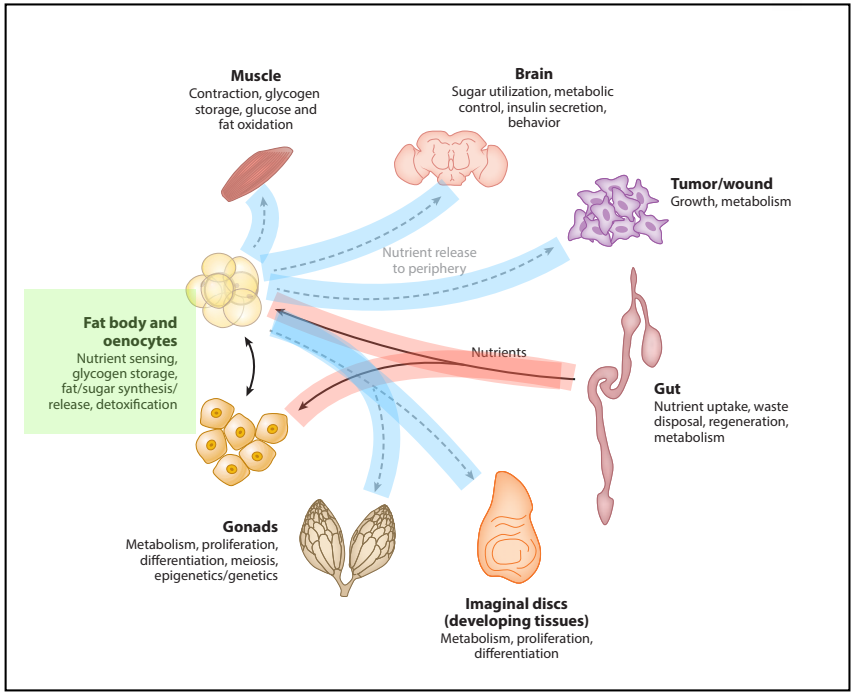
• Inter-organ communication and nutrient sensing

—Inter-organ communication tunes supply and demand

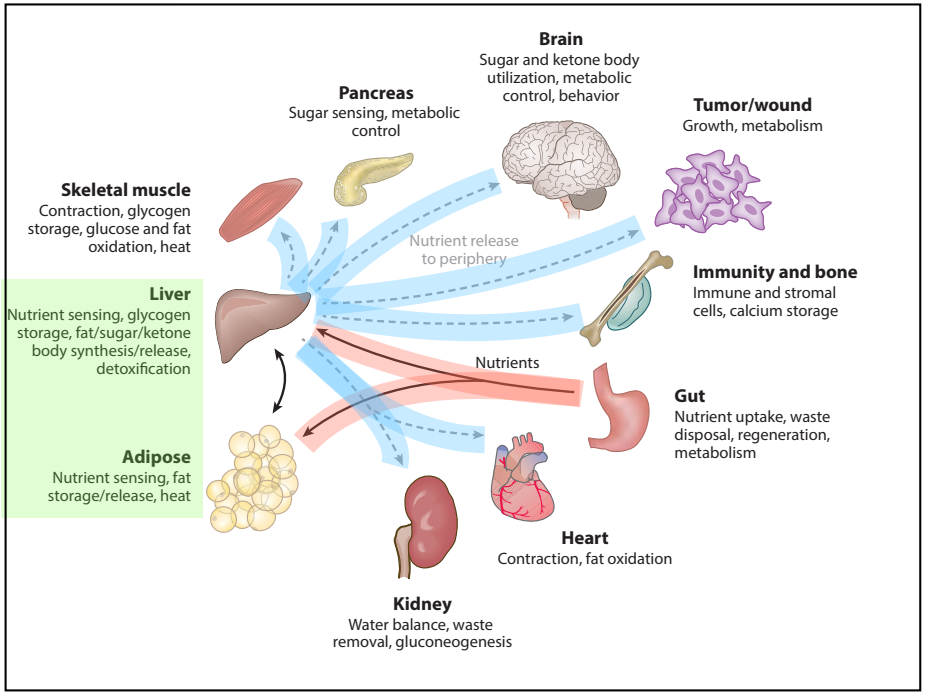
—Central sensors orchestrate such communications



Drosophila — Insects



Human — Mammals



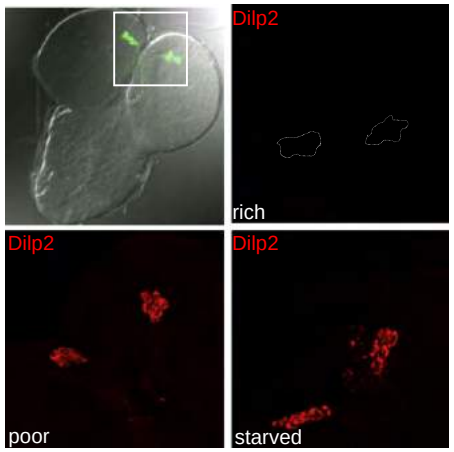
I. A. Droujinine and N.Perrimon (2016)
Annu. Rev. Genet. 50:539–70
0.1146/annurev-genet-121415–122024

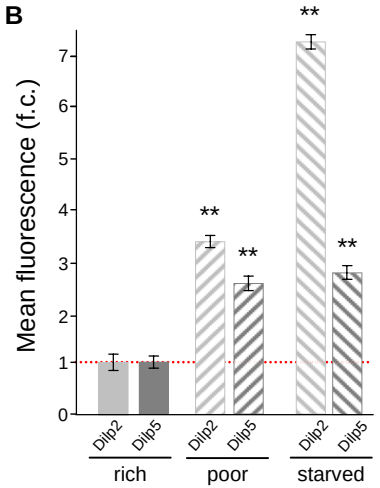
• Inter-organ communication and nutrient sensing

Diet controls Insulin production in neurosecretory cells in the brain

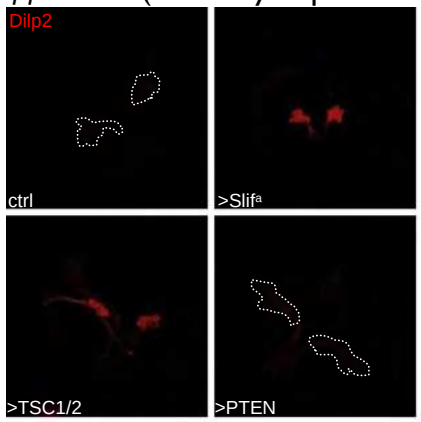
The brain insulin producing cells integrates fat body derived signals to control growth via insulin secretion

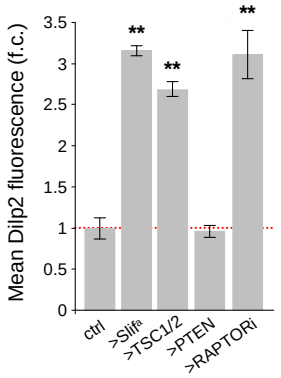
- dILP2 is expressed and secreted by a small group of neurons in the brain
- dILP2 secretion is blocked when animals are starved
- dILP2 secretion is also blocked when aa transport in the Fat Body or when TOR signalling is inhibited





ppl-Gal4 (Fat Body expression)



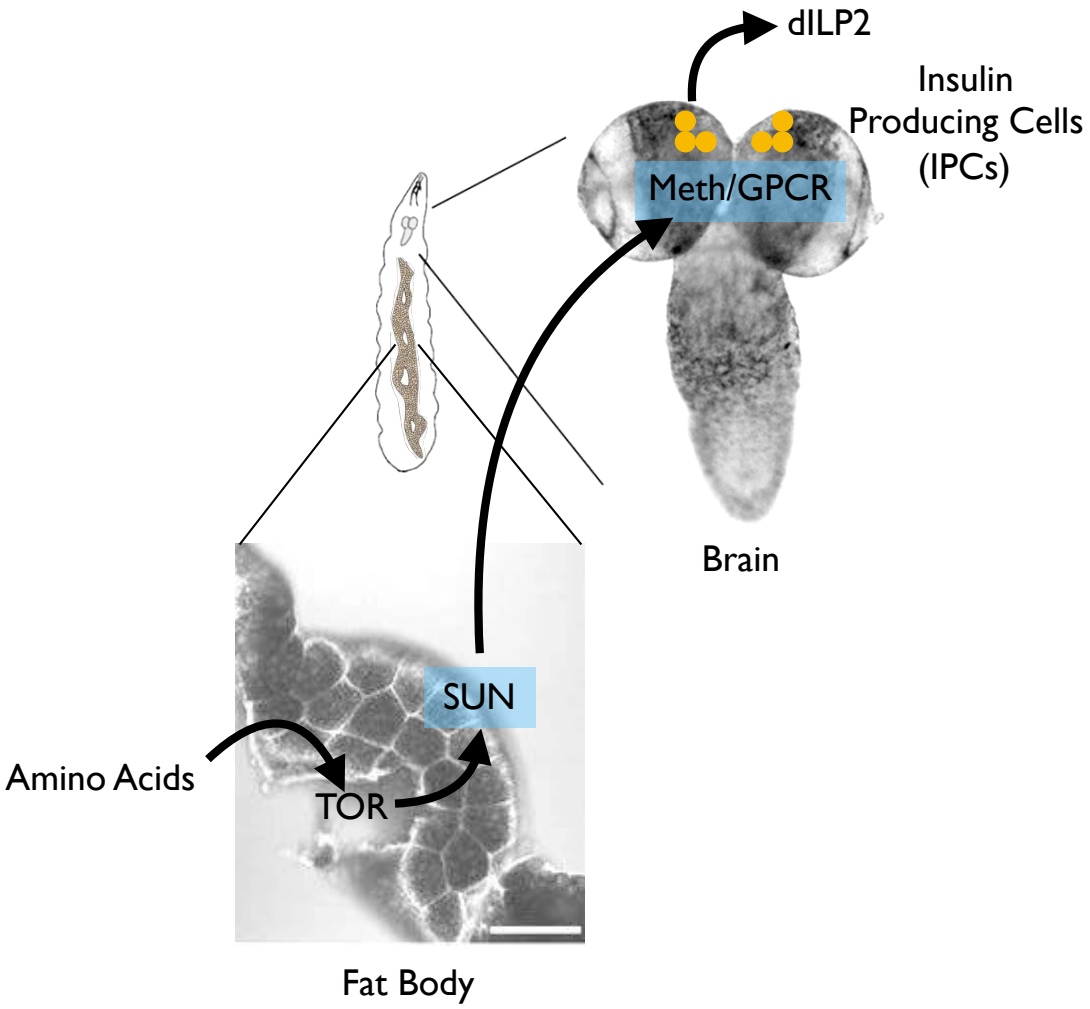


C. Geminard, E. Rulifson and P. Leopold. (2009) *Cell Metabolism 10*, 199–207,

• Nature of humoral the relay signals

—Positive signal:

Sun/Mth promote insulin secretion in response to protein-rich diet



doi.org/10.1101/704734
doi:10.1371/journal.pone.0077953.g001

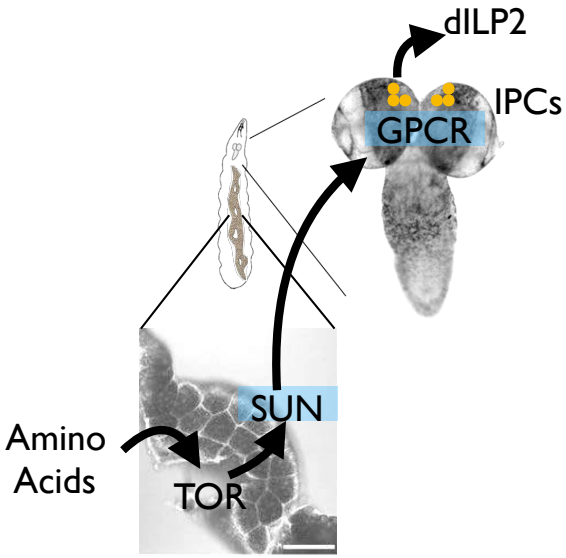
• Nature of humoral the relay signals

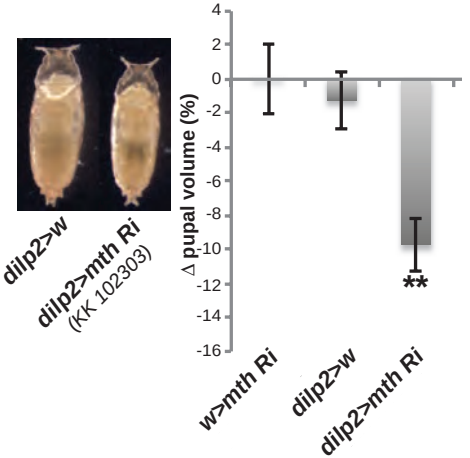
—Positive signal:

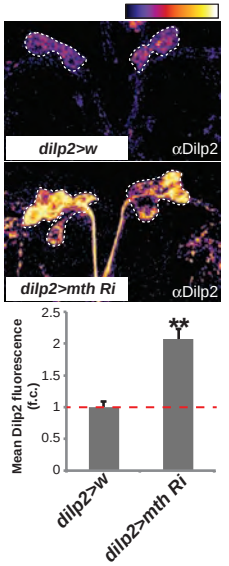
Sun/Mth promote insulin secretion in response to protein-rich diet

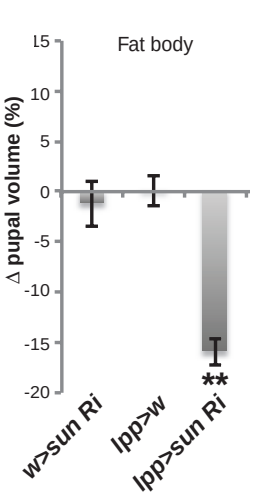
The GPCR Meth is required specifically in dILP2 producing neurons to control organismal growth and dILP2 secretion

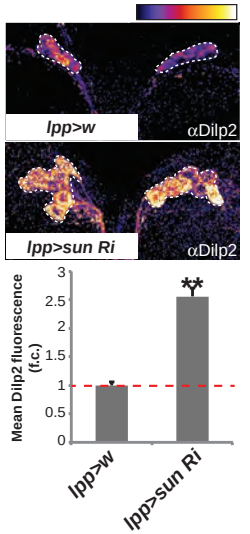
Sun is required in the Fat Body to control organismal growth and insulin secretion









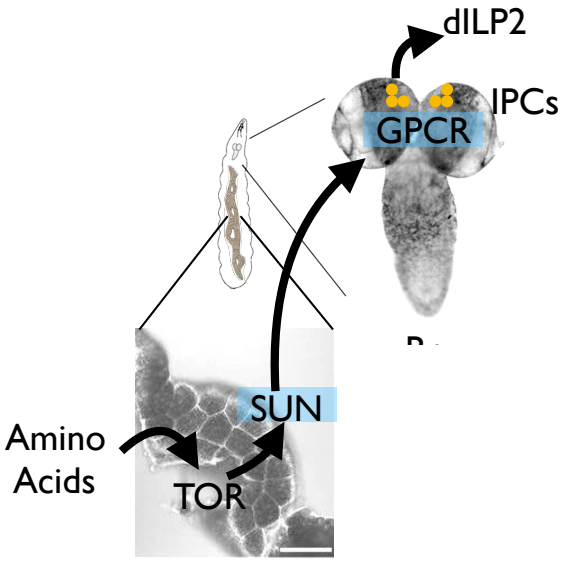


R. Delanoue et al. and P. Leopold. (2016) *Science* **353** (6307), 1553-1556. DOI: 10.1126/science.aaf8430

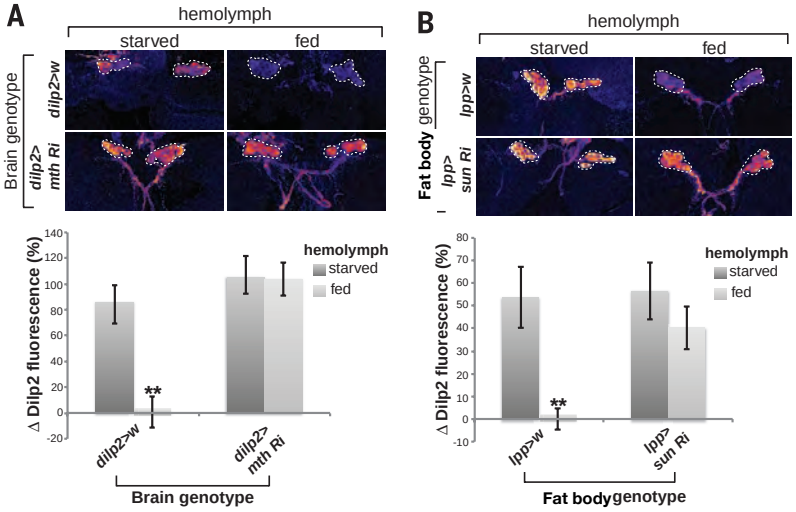
• Nature of humoral the relay signals

—Positive signal:

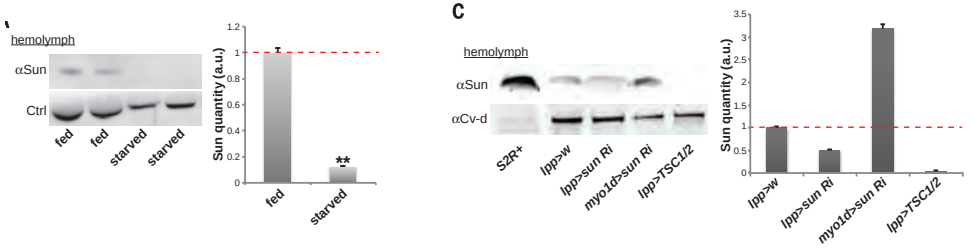
Sun/Mth promote insulin secretion in response to protein-rich diet



Sun is a Fat Body derived factor that promotes insuline secretion in the brain
(collect of hemolymph and incubation with brain)



Sun levels in the home lymph requires Feeding and TOR signalling in the Fat Body

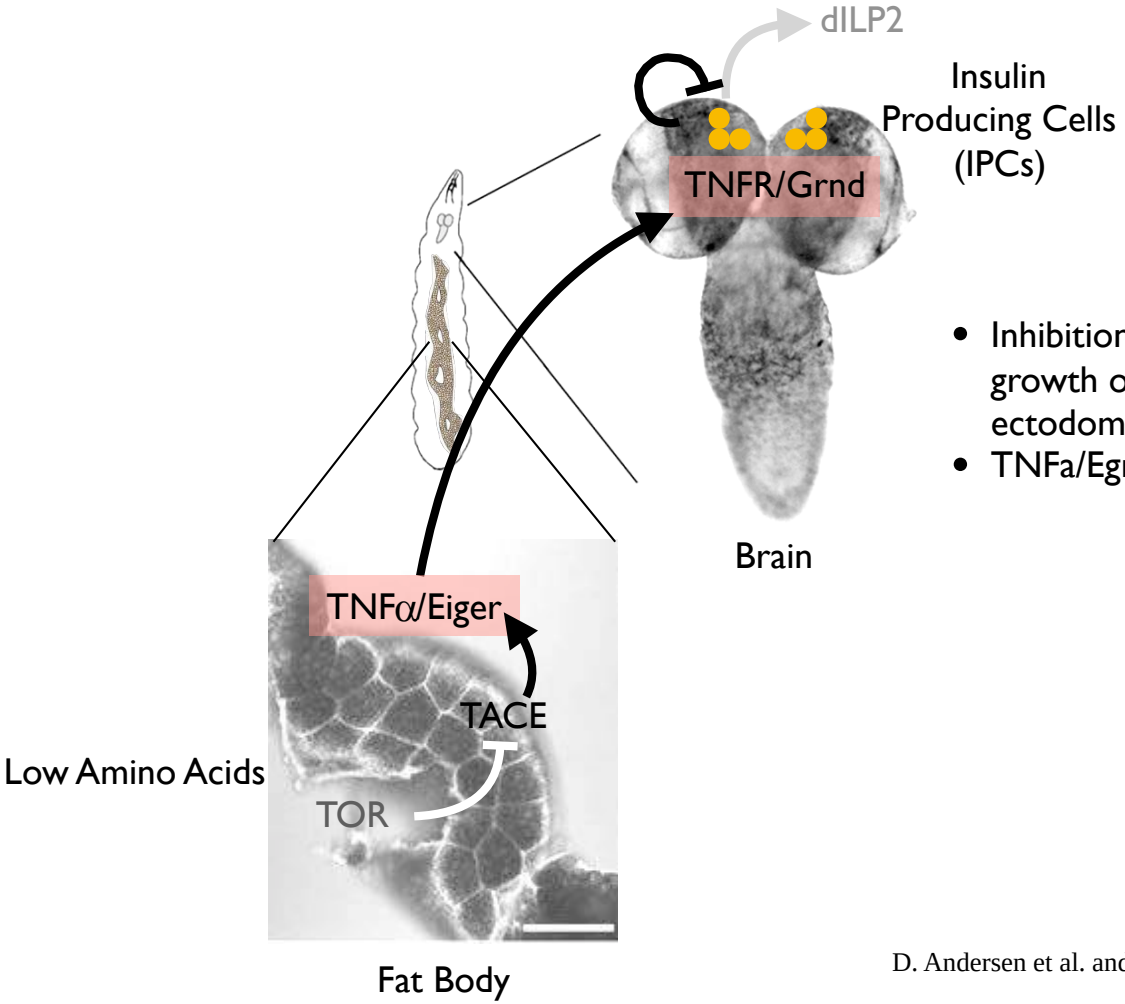


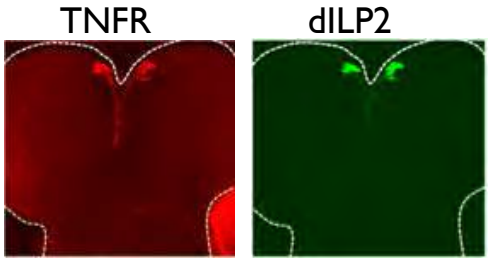
R. Delanoue et al. and P. Leopold. (2016) *Science* **353** (6307), 1553-1556. DOI: 10.1126/science.aaf8430

• Nature of humoral the relay signals

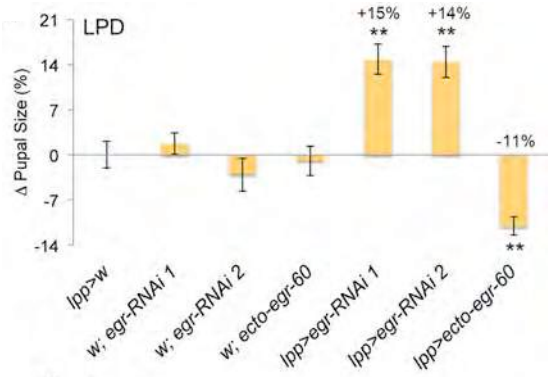
—Negative signal:

TNF/egr signalling limits growth in low nutrient conditions





- Inhibition of TNF/egr in the Fat body increases the growth of starved animals and over expression of the ectodomain further reduces growth
- TNFa/Egr inhibits growth in starved animals

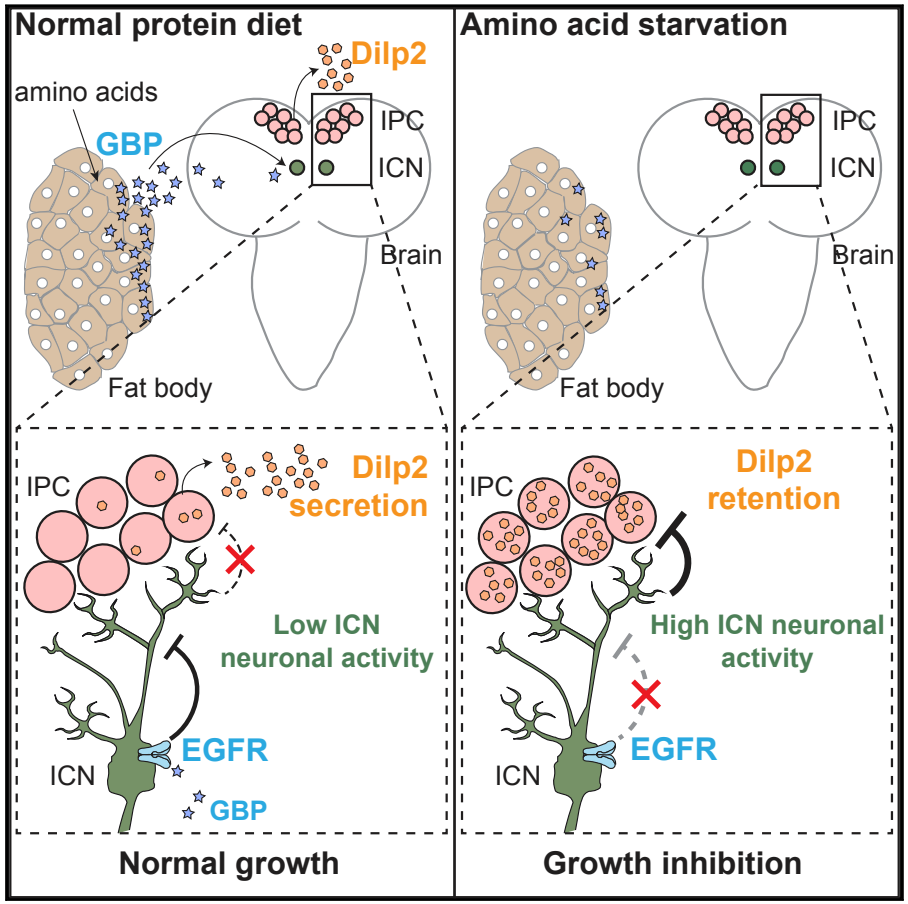


D. Andersen et al. and P. Léopold. (2016) *Nature*. 522: 482-486—doi:10.1038/nature14298

N. Agrawal et al. and P. Léopold. (2016) *Cell Metab*. 2016 Apr 12;23(4):675-84. doi: 10.1016/j.cmet.2016.03.003.

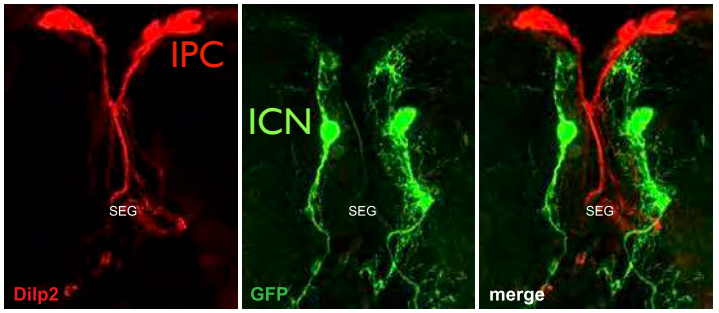
• Nature of humoral the relay signals

A neuronal circuit that couples nutrition, Insulin secretion and growth.



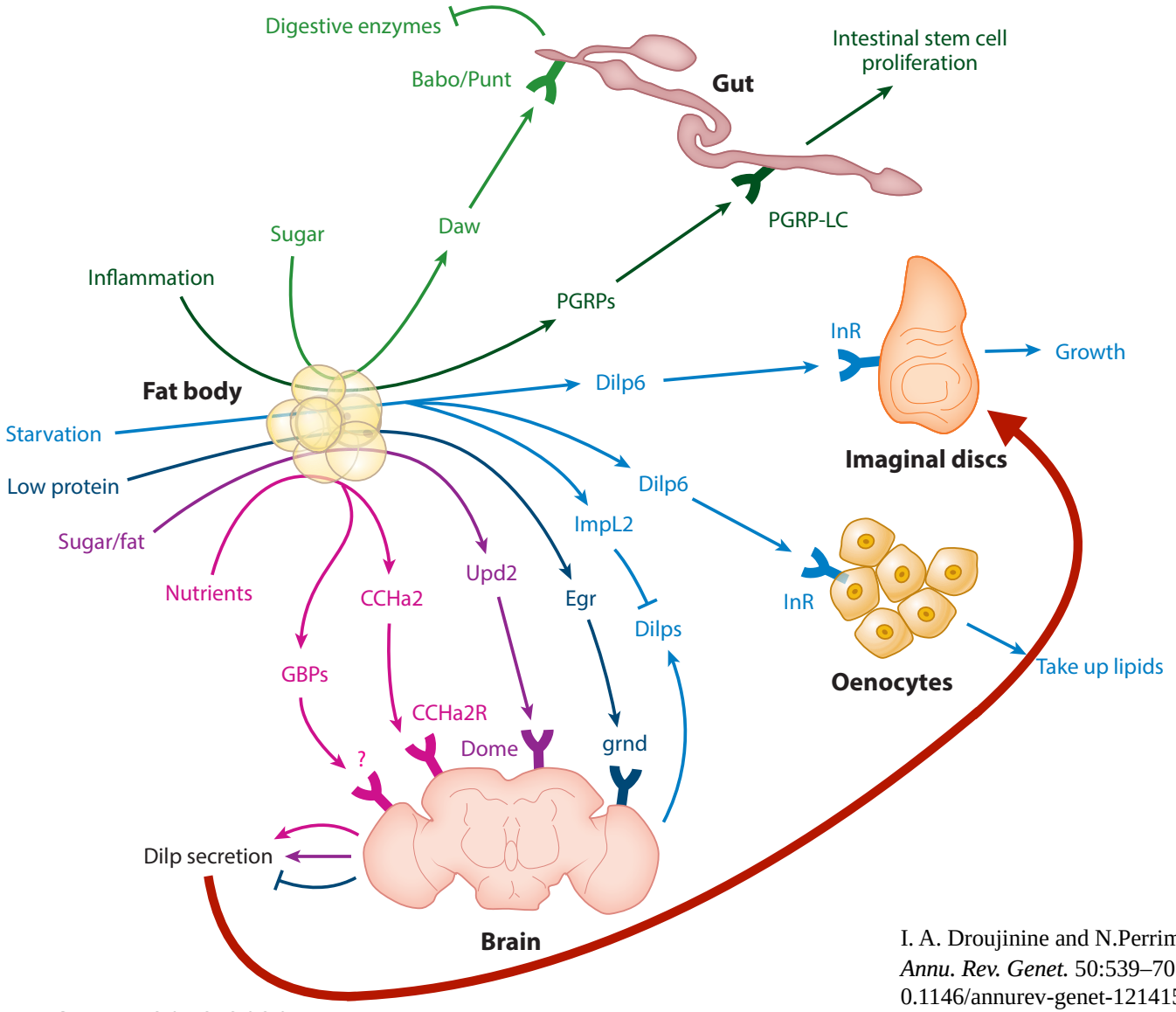
GBP: growth blocking peptide

ICN: intermediate neurons that repress Insulin Producing neurons (IPC)



E. Meschi, P. Leopold and R. Delanoue,(2019), *Developmental Cell* 48, 1–11
https://doi.org/10.1016/j.devcel.2018.11.029

- The complexity of humoral the relay signals coordinating nutrition, metabolism and growth

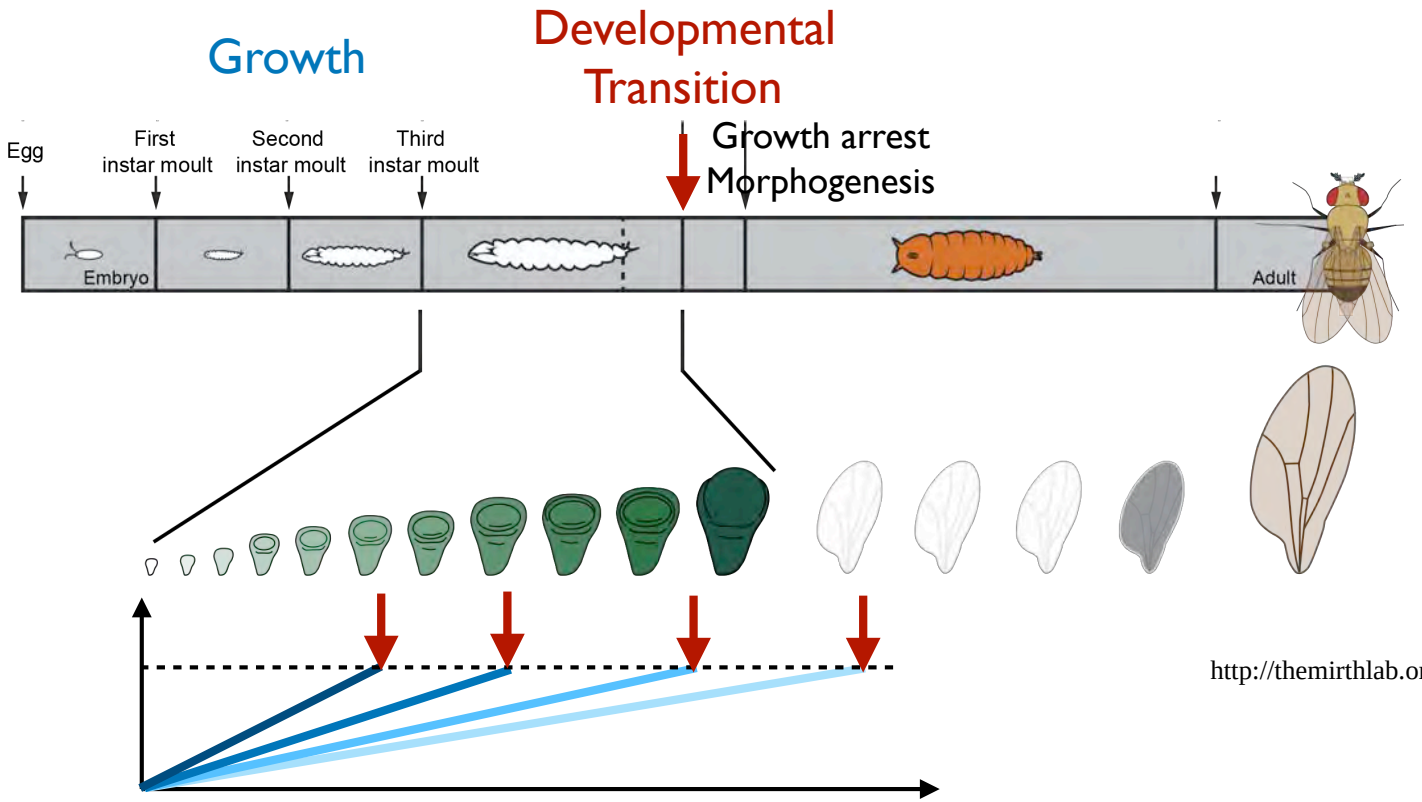


I. A. Droujinine and N.Perrimon (2016)
Annu. Rev. Genet. 50:539–70
0.1146/annurev-genet-121415–122024

• Link between Growth and developmental transition: Timing

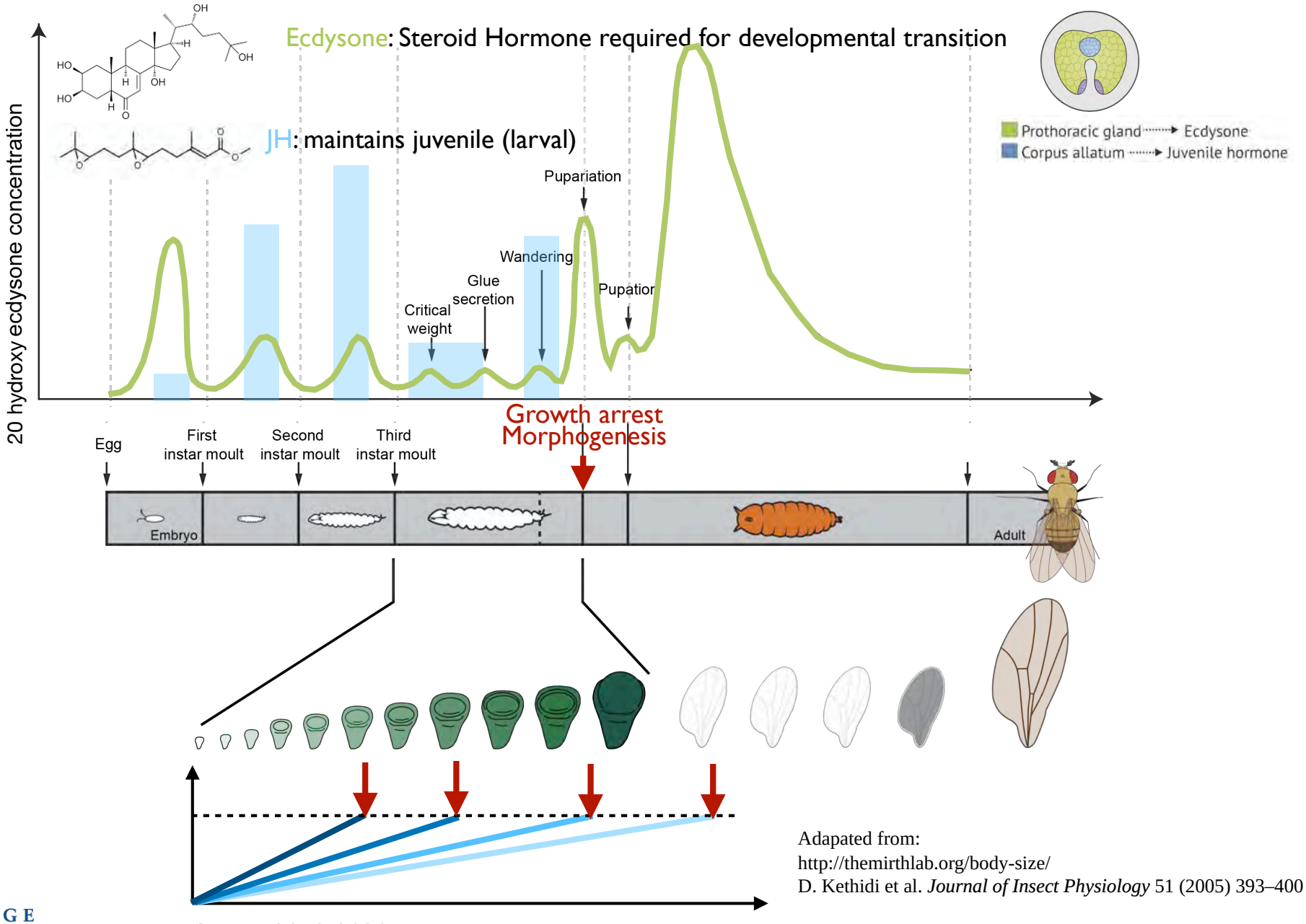
—Metamorphosis: a key developmental transition must be properly timed with respect to growth/size.

- Organ intrinsic growth arrest mechanisms could induce developmental transition
- As a consequence: if growth is delayed, metamorphosis is delayed until proper organ size is reached.
- And/Or Feedback interactions between Developmental Timing and Growth?



http://themirthlab.org/body-size/

• Link between Growth and developmental transition: Timing



Adapted from:
http://themirthlab.org/body-size/
D. Kethidi et al. *Journal of Insect Physiology* 51 (2005) 393–400

• Link between Growth and developmental transition: Timing

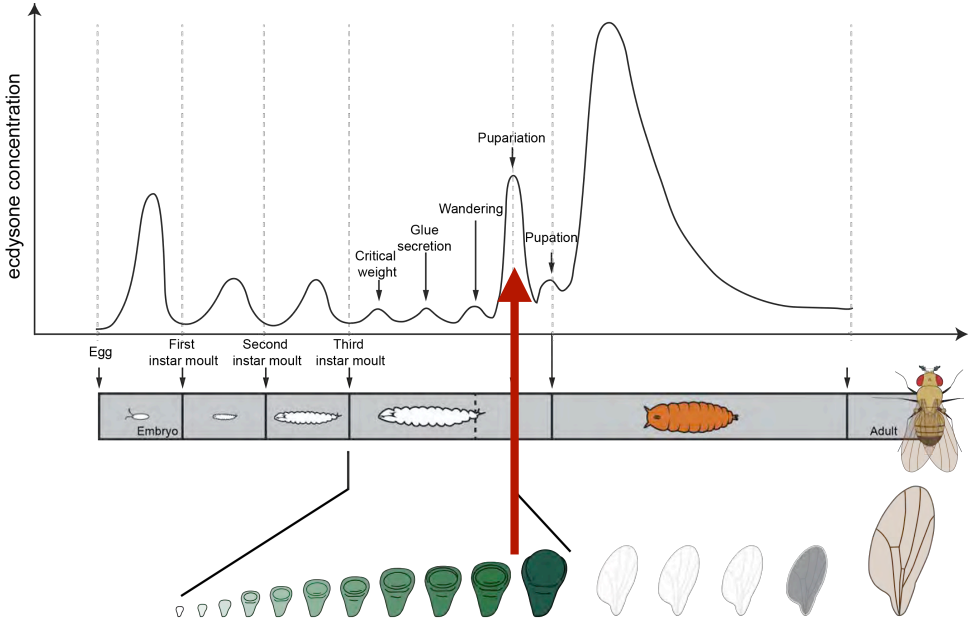
J. Embryol. exp. Morph. Vol. 57, pp. 155–165, 1980
Printed in Great Britain © Company of Biologists Limited 1980

The initiation of pupariation in *Drosophila*: dependence on growth of the imaginal discs

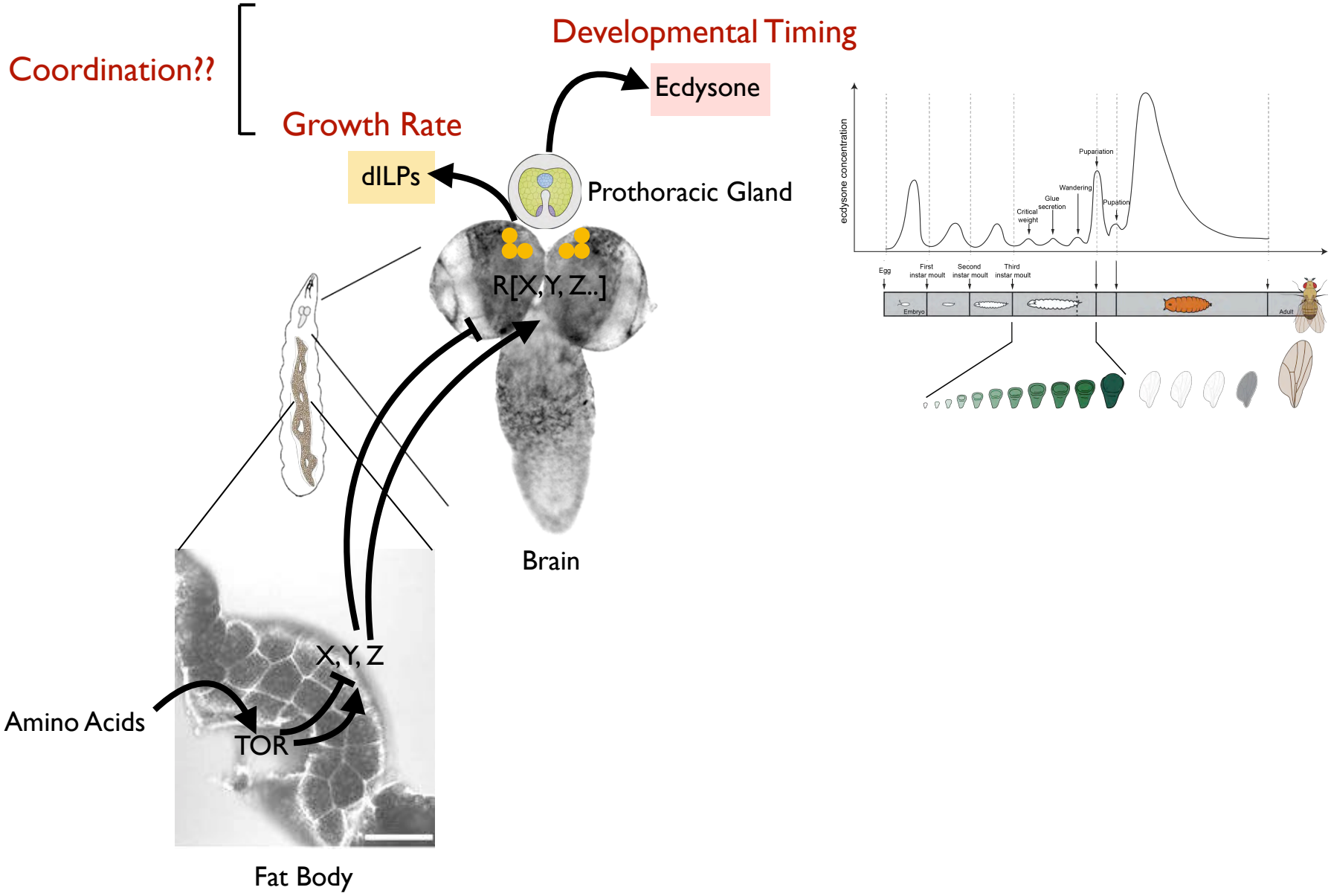
By P. SIMPSON,[1] P. BERREUR[2] AND J. BERREUR-BONNENFANT[2]
From the Centre de Génétique Moléculaire, Gif-sur-Yvette, France

- Lesions of cells in imaginal discs delay pupariation
- The amount of lesion correlates with the extent of developmental delay

- Hypothesis: a signal produced by growing tissues induce hormones required for pupariation



- Link between Growth and developmental transition: Timing



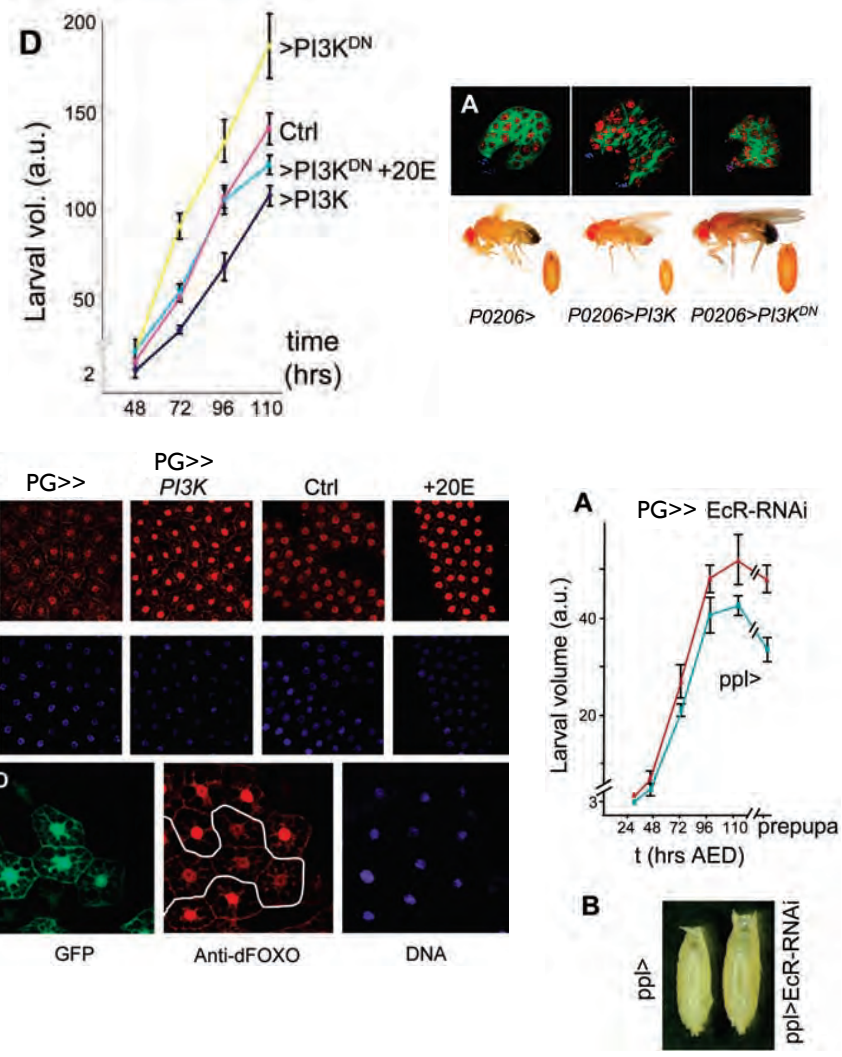
• Link with developmental transition: Timing

—Systemic Negative Feedback of Developmental Timing on Growth

- Surprisingly, overgrowth of the Prothoracic Gland (PG) with activation of the Pi3K pathway causes a reduction of animal size. And conversely, a smaller PG is associated with animal overgrowth.
- 20Ecdyzone suppresses this effect arguing that it represses growth

- FOXO is inhibited by Pi3K signalling.
- Activation of Pi3K in the prothoracic gland (PG) or feeding with Ecdysone induces FOXO and inhibits Pi3K signalling in the Fat Body (FB)
- Conversely clones that inhibit Ecdysone signalling (mutant receptor EcR) in Fat Body cells activate Pi3K.
- Inhibition of EcR in the Fat Body increases animal size

- Production of Ecdysone by the Prothoracic Gland induces a negative feedback on growth via the Fat Body

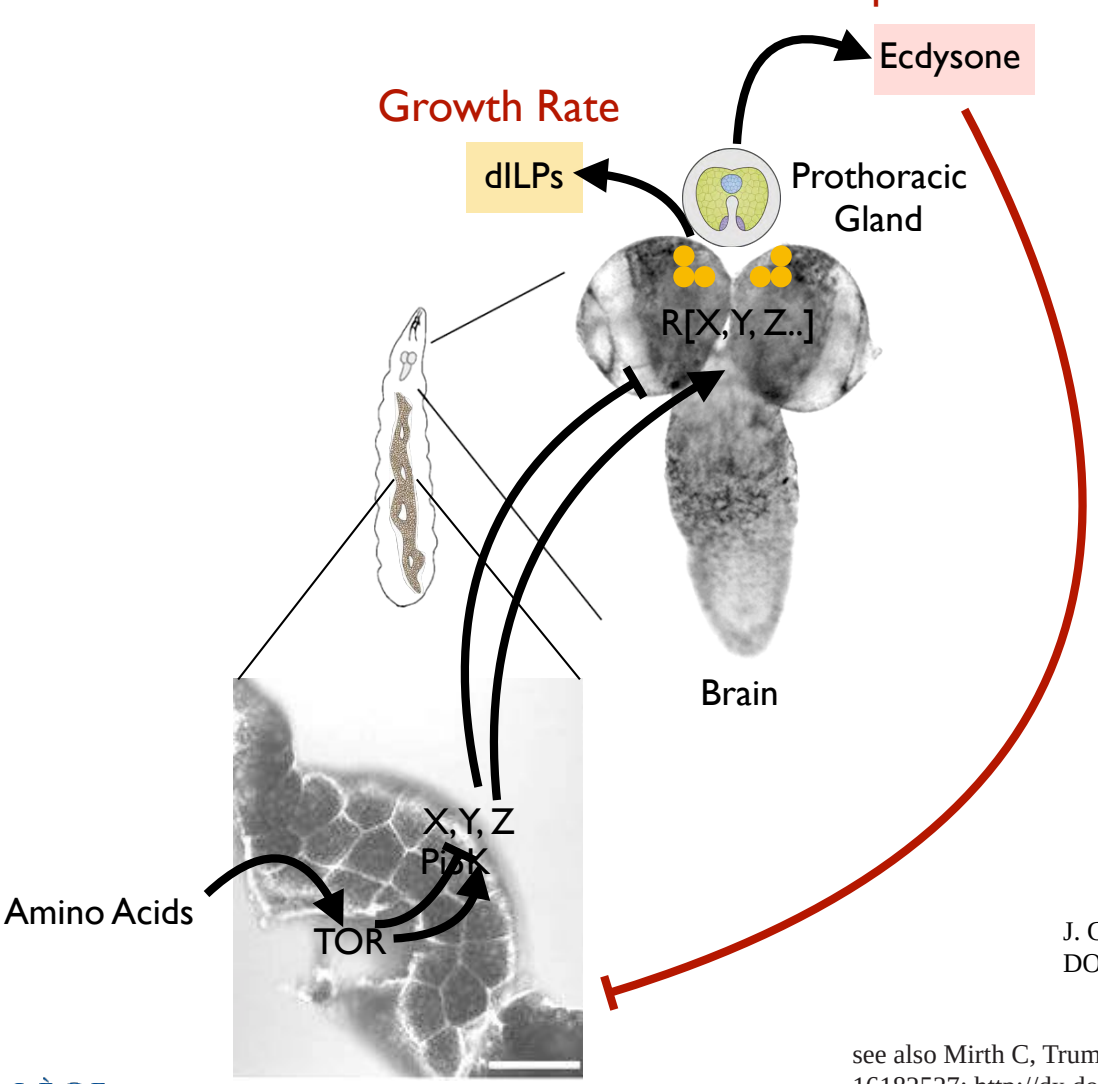


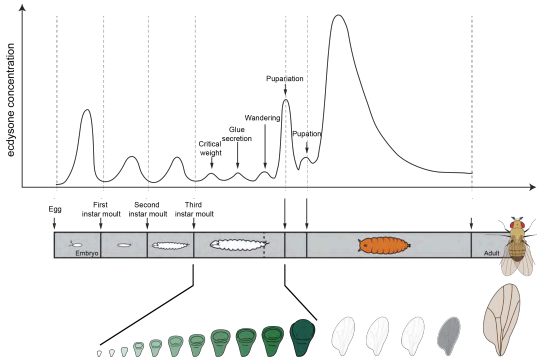
J. Colombani et al. and P. Léopold. (2005) *Science* 310 (5748), 667-670. DOI: 10.1126/science.1119432

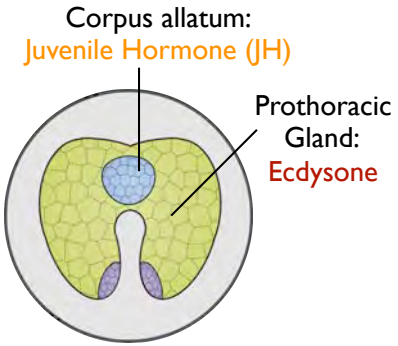
• Link between Growth and Developmental transition: Timing

—Systemic Negative Feedback of Developmental Timing on Growth

Growth induced signalling in the prothoracic gland accelerates developmental transition via Ecdysone signalling





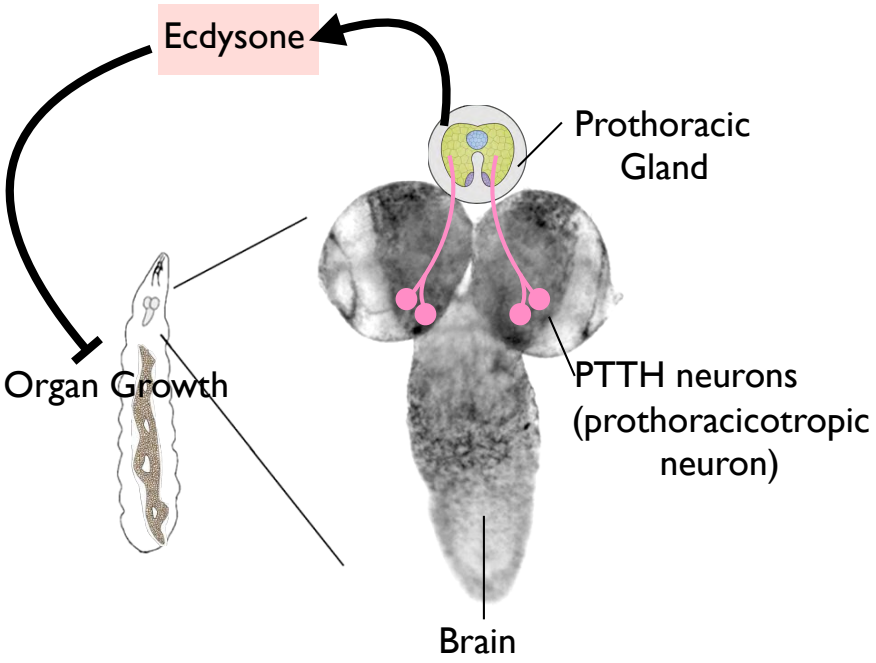


J. Colombani et al. and P. Léopold. (2005) *Science* 310 (5748), 667-670. DOI: 10.1126/science.1119432

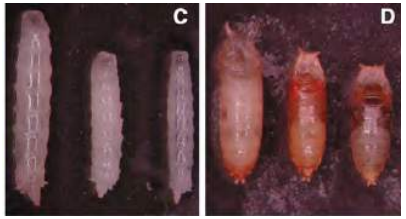
see also Mirth C, Truman JW, Riddiford LM. *Curr Biol* 2005; 15:1796-807; PMID: 16182527; http://dx.doi. org/10.1016/j.cub.2005.09.017

• Link with developmental transition: Timing

—Systemic Negative Feedback of Developmental Timing on Growth



- ablation of PTTH neurons increases size



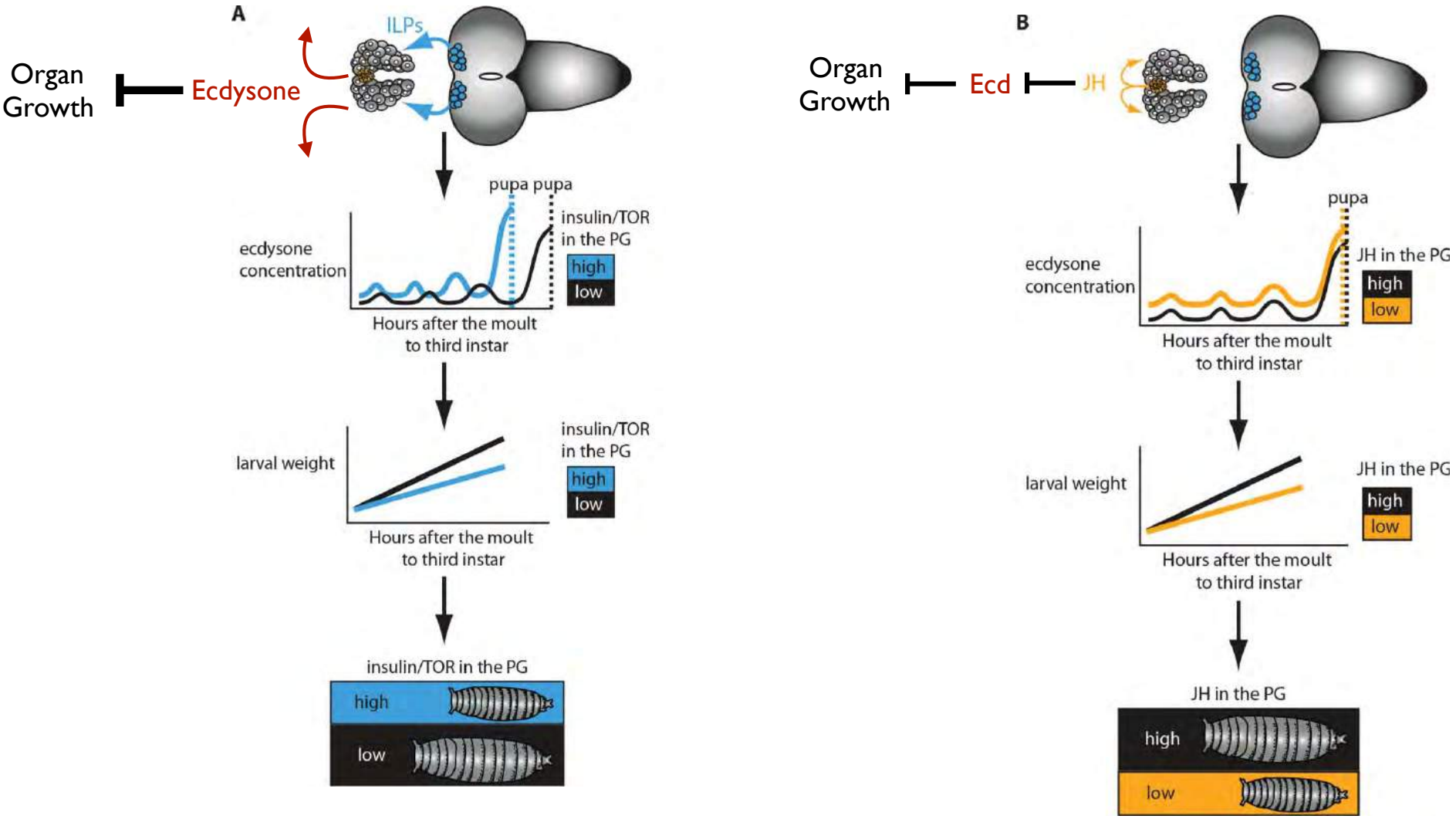
ablated ablated

ablated controls

Z. McBrayer et al. M. O'Connor. (2007) *Developmental Cell* 13, 857–871

• Link with developmental transition: Timing

—Integration of size sensing inputs

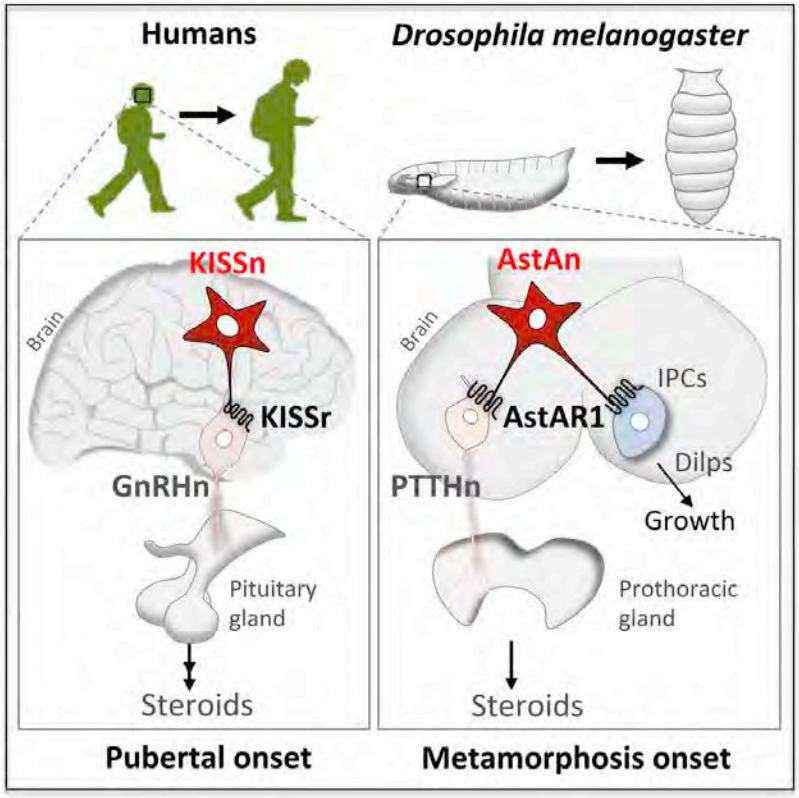


C. M. Mirth & A.W. Shingleton (2014) *Communicative & Integrative Biology,* 7:5, e971568, DOI: 10.4161/cib.29240

Mirth CK, et al. Shingleton AW. Juvenile hormone regulates body size and perturbs insulin signaling in Drosophila. (2014) *PNAS*; 111:7018-23;

• Link with developmental transition: Timing

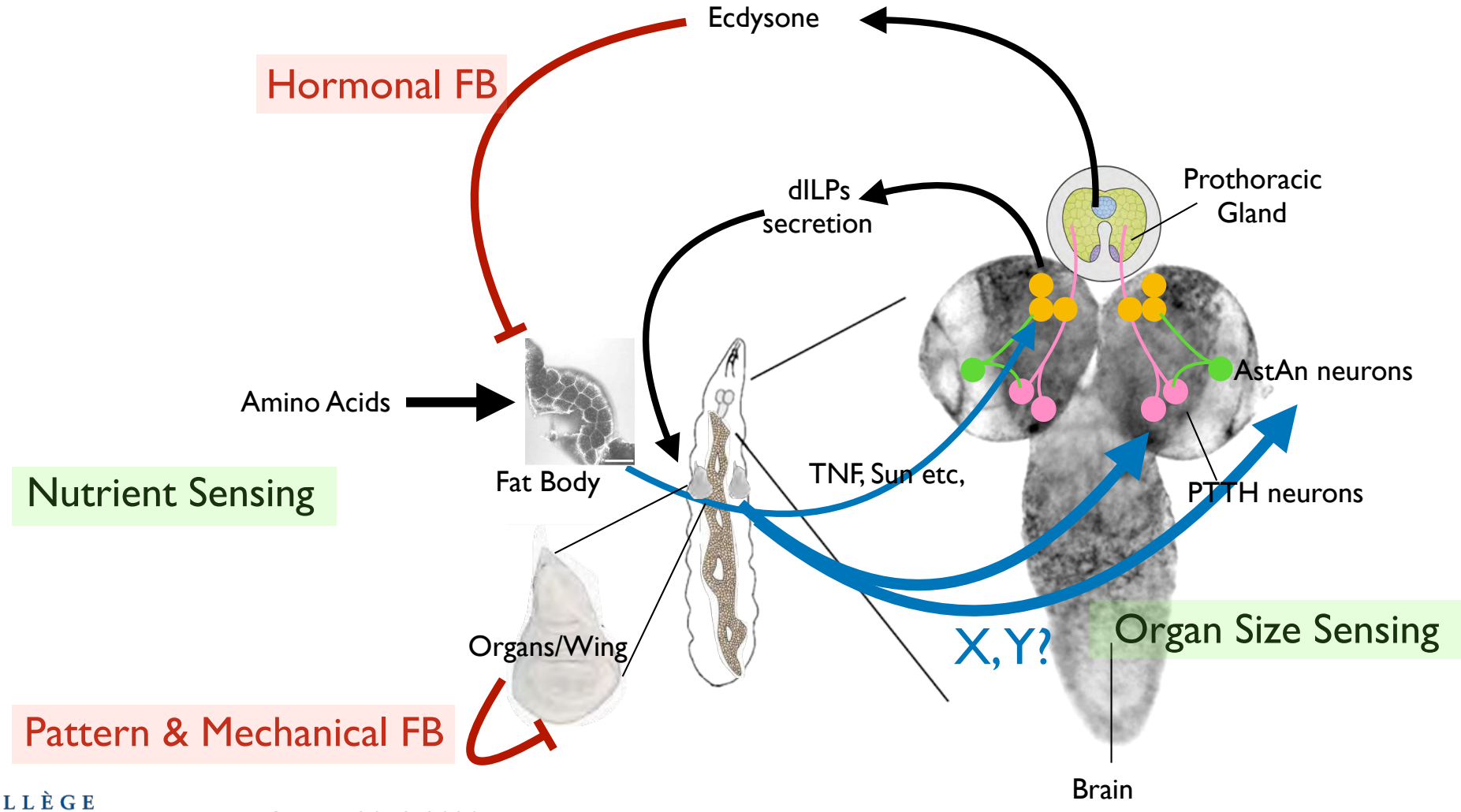
—Orchestration of growth signalling and metamorphosis (adult transition) by Allostatins



Deveci et al., and P. Léopold. (2019), *Current Biology* 29, 1–10 https://doi.org/10.1016/j.cub.2019.01.053

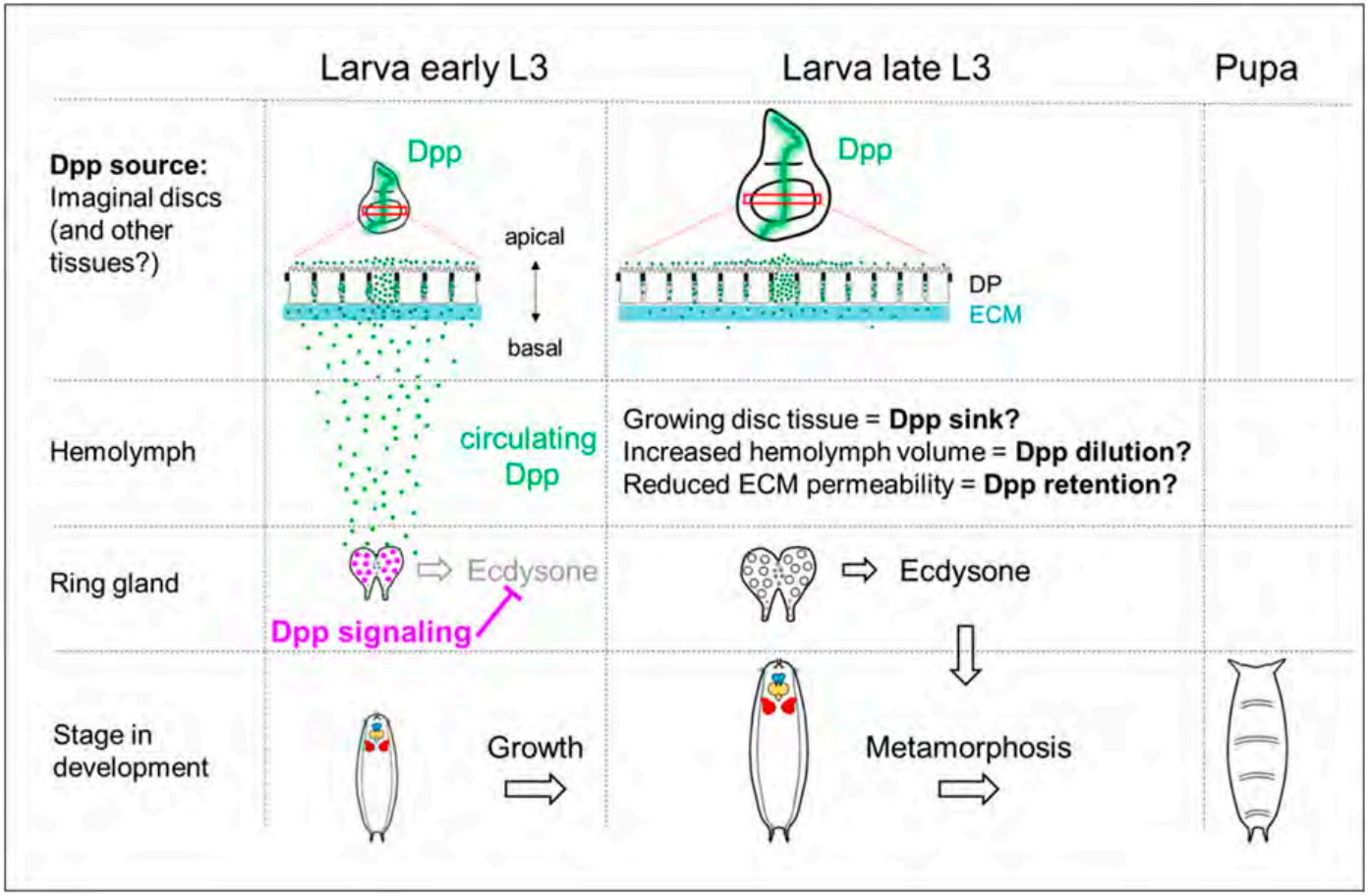
• Summary: Sensors and Feedbacks

—Energy (nutrient) sensing and Organ Size-sensing
—Nested organ-scale and systemic negative feedbacks
define growth arrest and tissue size



- How does the neuroendocrine central system senses organ size?

—Hypothesis: Dpp as a coupling mechanism and size-dependent sequestration?



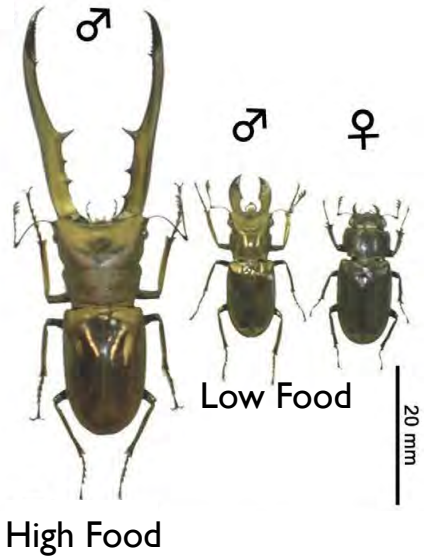
L. Setiawan et al and M. O'Connor and I. Hariharan. *Life Sci Alliance.* (2018);1(6):e201800216. doi: 10.26508/lsa.201800216.

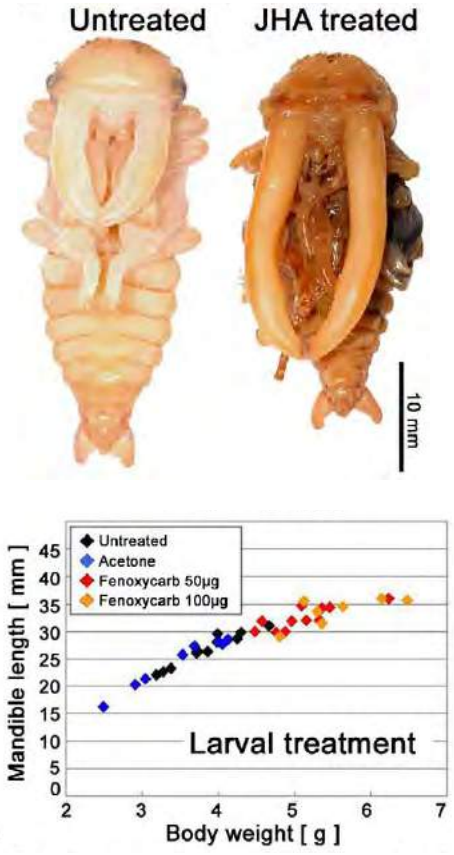
Dpp secretion and sequestration hypothesis: not straightforward un light of:

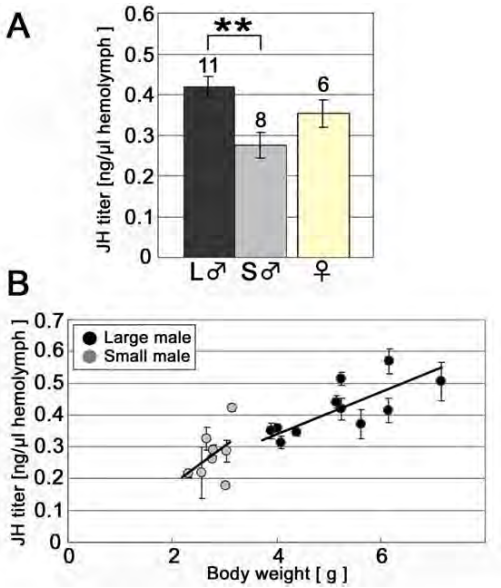
O. Wartlick *et al.* F. Jülicher and M. Gonzalez-Gaitan (2011) *Science* 331:: 1154; doi: 10.1126/science.1200037

• Differential (allometric) growth mediated by Nutrient and Hormonal relay

—Hormonal relay of food impacts growth of organs and whole organism





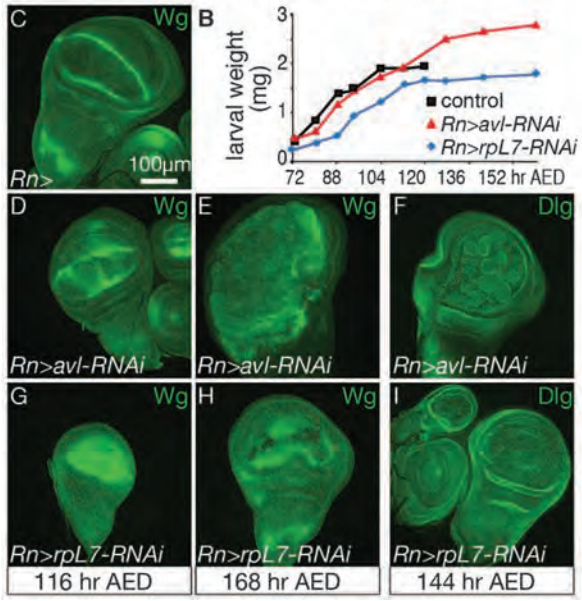


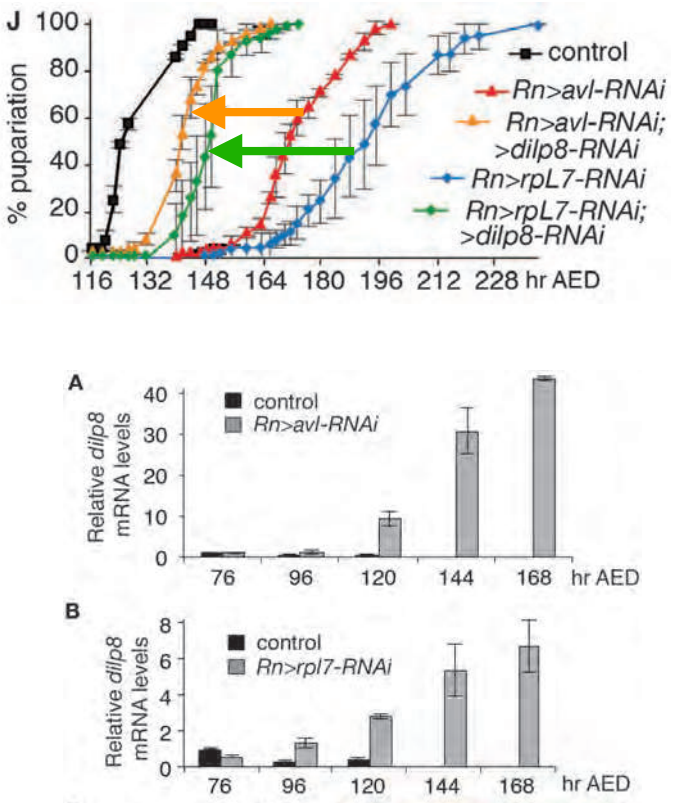
Gotoh H, Cornette R, Koshikawa S, Okada Y, Lavine LC, et al. (2011) *PLoS ONE* 6(6): e21139. doi:10.1371/journal.pone.0021139

• Systems' response to perturbations

—Genetic lesions in growing tissues (minute mutation or tissue integrity) cause delay of developmental transition

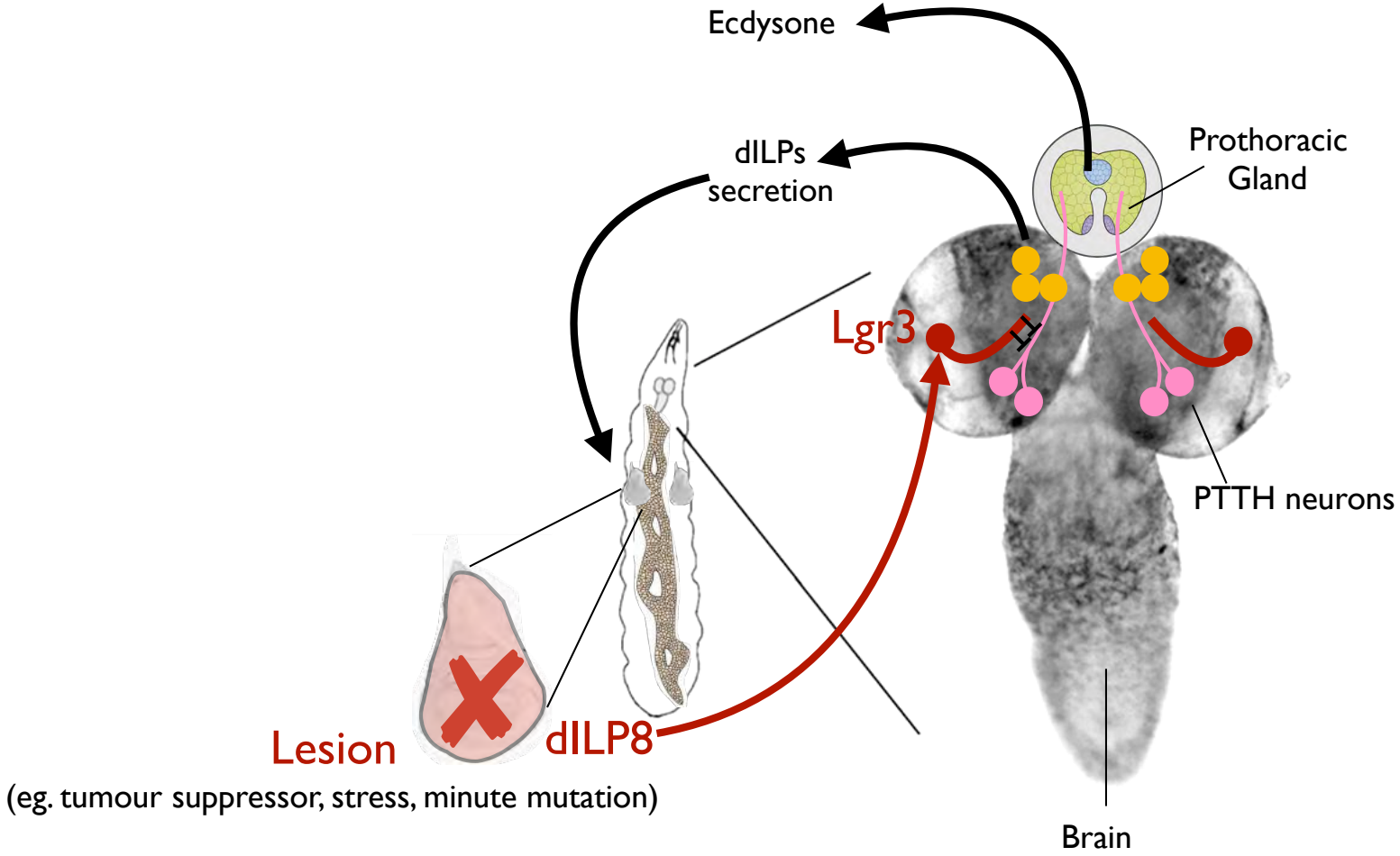
—Discs produce an Insuline like peptide that triggers developmental delay





Julien Colombani *et al.* and P. Léopold
Science 336, 582 (2012); DOI: 10.1126/science.1216689

• Systems' response to perturbations



Julien Colombani *et al.* and P. Léopold (2012) *Science* 336, 582

A. Garelli et al. and M. Dominguez. (2012) *Science*. 336(6081):579-82

DM. Vallejo et al. and M. Dominguez. *Science*. (2015) 350(6262)

Colombani et al., and P. Léopold (2015), *Current Biology* 25, 2723–2729

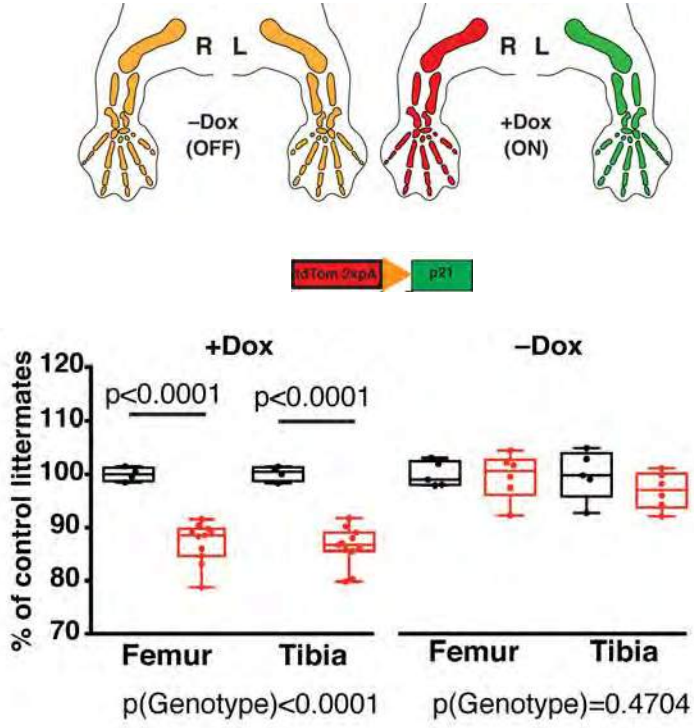
• System's response to perturbations

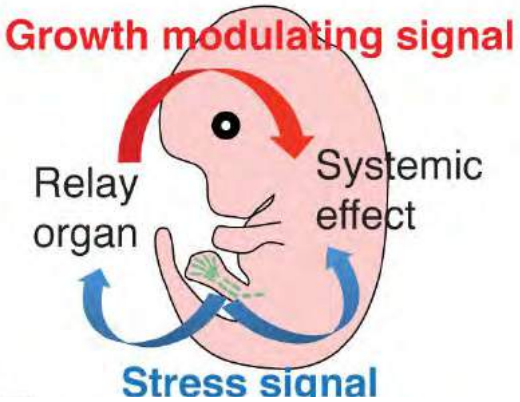
RESEARCH ARTICLE

Cell-nonautonomous local and systemic responses to cell arrest enable long-bone catch-up growth in developing mice

Alberto Roselló-Díez[1¤a]*, Linda Madisen[2], Sébastien Bastide[1¤b], Hongkui Zeng[2], Alexandra L. Joyner[1,3]*

- Mosaic local proliferation blockade in chondrocytes of the left limb results in systemic growth reduction
- Most likely involves the nervous system (*a priori* no role for dILP8/Relaxin)





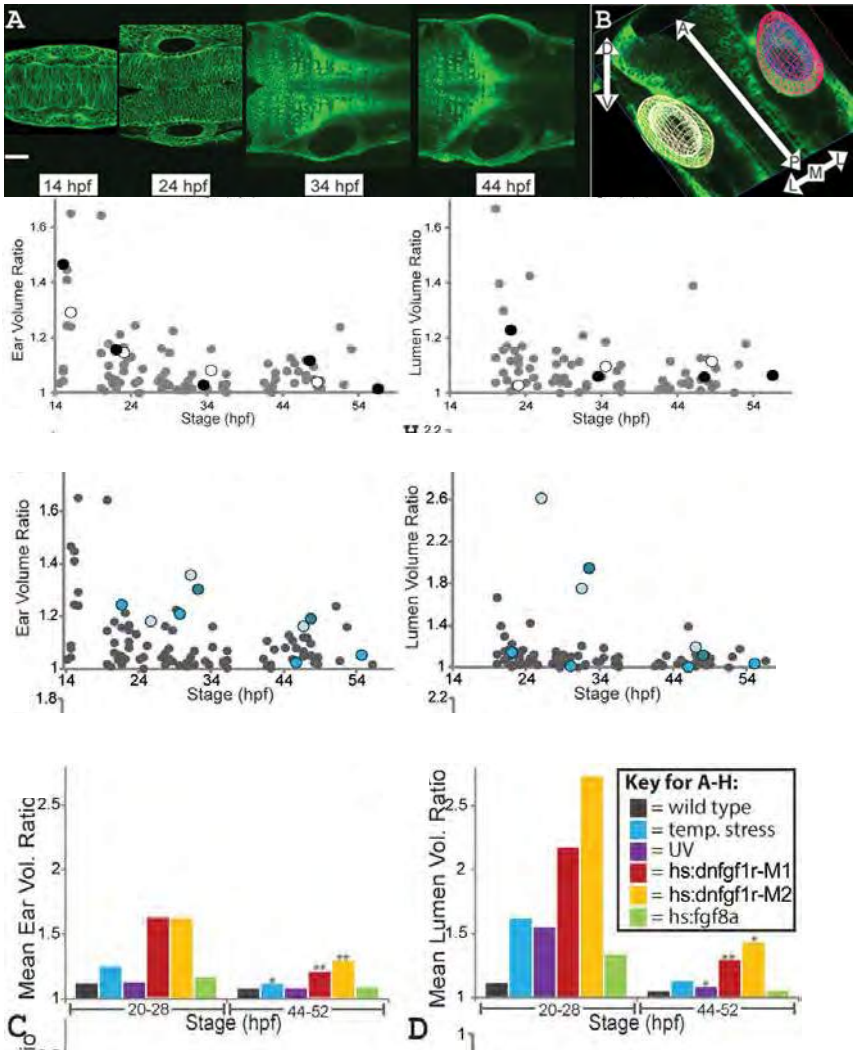
A. Rosello-Diez et al. and A. Joyner. (2018) *PLoS Biol* 16(6): e2005086. https://doi.org/ 10.1371/journal.pbio.2005086

• Developmental noise and robustness of growth

—Feedback interactions between organs correct for developmental noise and confer robustness to growth

—Left/Right growth fluctuations

- Inner ear of zebrafish embryos
- Left-right fluctuations in volume of ear (total or lumen) occur early on during development and are corrected subsequently.
- Induced perturbation using external (UV, temperature) cues also enhances L/R asymmetries which are later corrected.
- Internal genetic perturbations are also corrected during development



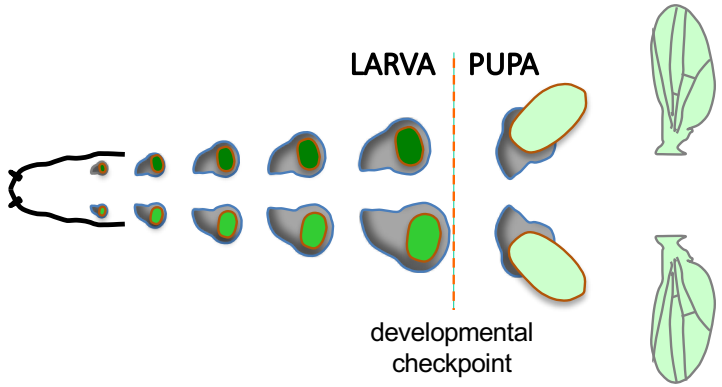
A. Green et al. and S. Megason. (2017) *Developmental Dynamics* 246:451–465

• Developmental noise and robustness of growth

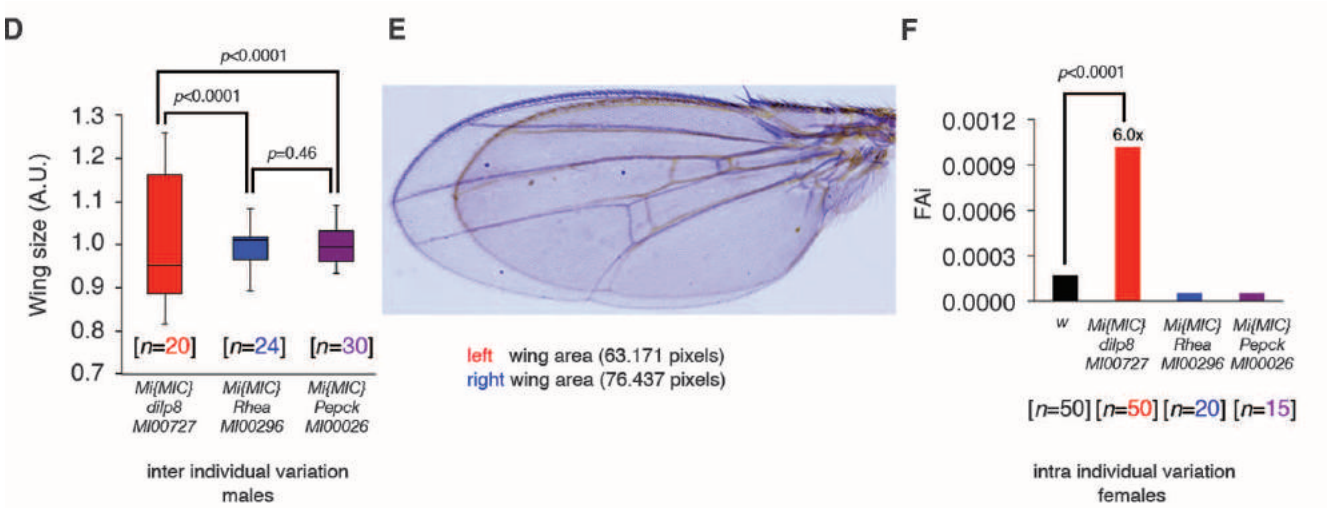
—Feedback interactions between organs correct for developmental noise and confer robustness to growth

—Left/Right growth fluctuations

- In *dILP8* mutants, left-right developmental fluctuations are enhanced.



P. Léopold



$FAi = Var(A_L - A_R)$

A. Garelli et al. and M. Dominguez. (2012) *Science.* 336(6081):579-82

• Amplification and stabilisation of growth asymmetry

Fiddler crabs

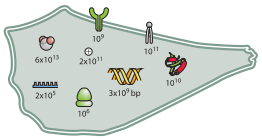
Huxley, J. S. 1924. *Nature* 114:895–896.

• Motor, Constraints and Regulation of Growth

Energy supply

carbohydrates
amino-acids
oxygen

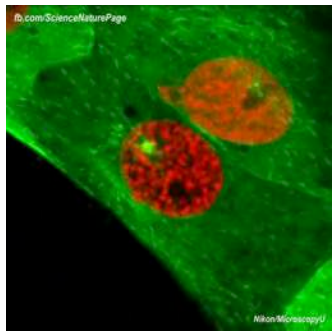
Metabolism



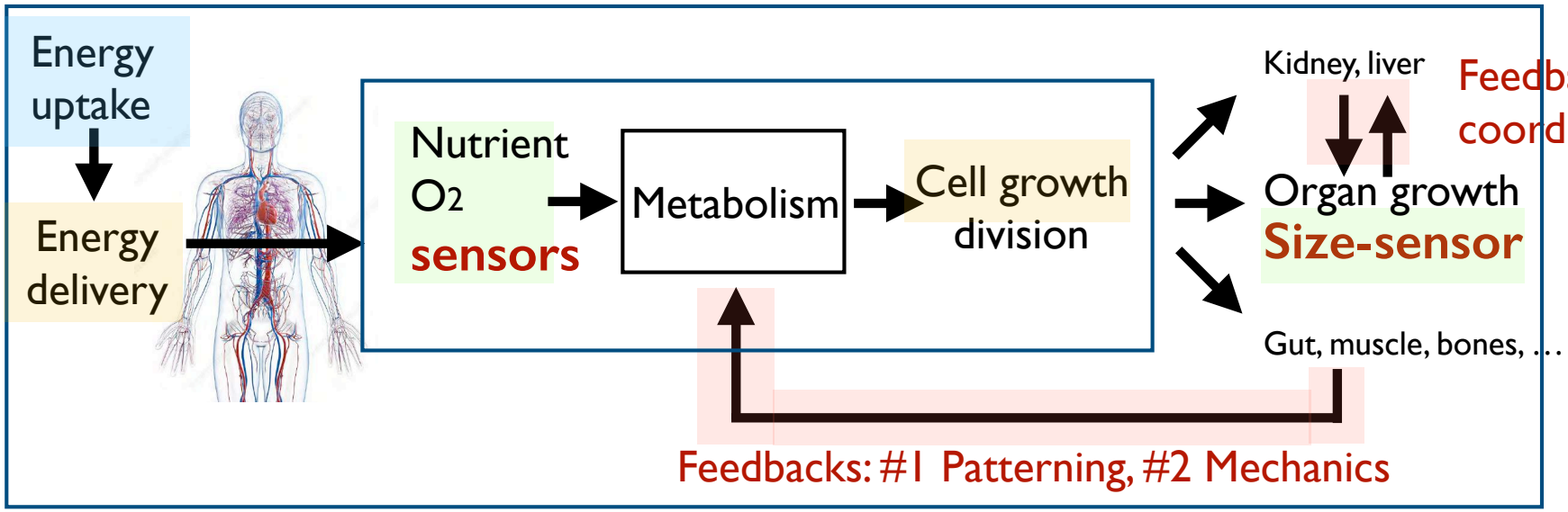
Synthesis:
ATP, amino-acids, proteins, lipids, carbohydrates, etc

H_2O flux

Cell growth, division

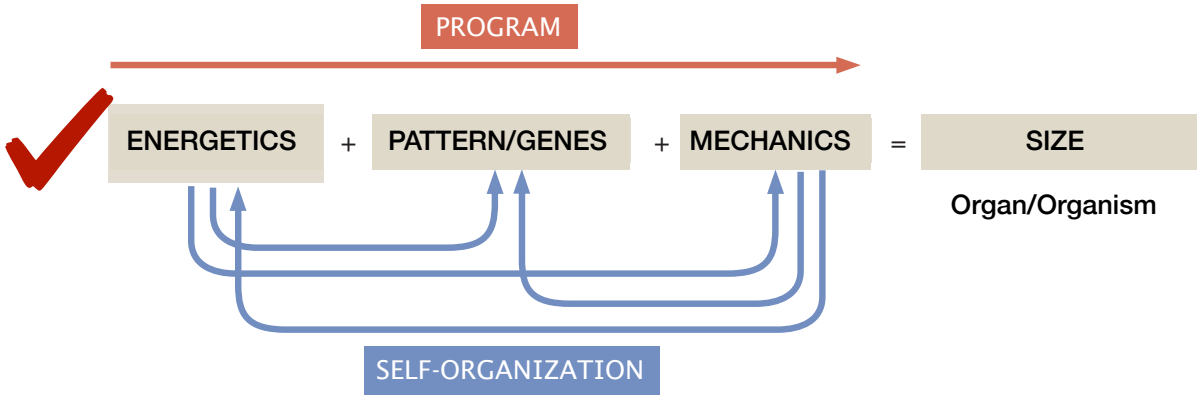


kidney cell



How to encode Size?

- hierarchical
- modular
- deterministic rules (ie. genetically encoded)

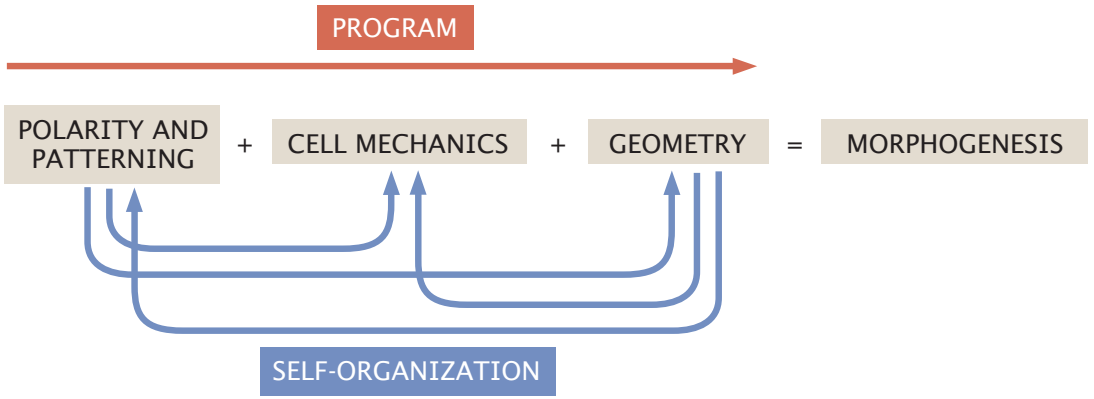


- no hierarchy
- feedbacks
- statistical rules/fluctuations

How to encode Shape?

2017 and 2018

- hierarchical
- modular
- deterministic rules (ie. genetically encoded)



- no hierarchy
- feedbacks
- statistical rules/fluctuations

COLLÈGE DE FRANCE
1530

chaire Dynamiques du Vivant

Colloque :

Constraints and plasticity in Development and Evolution

(avec Denis Duboule, chaire Évolution des génomes et développement)

Le mardi 30 juin et le mercredi 1er juillet, de 9h à 18h
Amphithéâtre Maurice Halbwachs

Detlev Arendt (EMBL Heidelberg)
Virginie Courtier-Orgogozo (Paris)
Stanislas Dehaene (Collège de France)
Claude Desplan (NYU)
Caroline Dean (John Innes Center)
Liam Dolan (Oxford)
Hopi Hoekstra (Harvard)
Laurent Keller (Univ. Lausanne)
Natacha Kurpios (Cornell Ithaca)
Shigeru Kuratani (Kobe)
L. Mahadevan (Harvard)
Marie Manceau (Collège de France)
Nipam Patel (Woods Hole)
Olivier Pourquié (Harvard)
Luis Quitana-Murci (Pasteur & Collège de France)
Eric Siggia (Rockefeller University)
Vikas Tervidi (EMBL Barcelona)
Elly Tanaka (IMP Vienna)
Günter Wagner (Yale Univ.)

Rob Phillips

Professeur, California Institute of Technology

Invité par l'Assemblée des professeurs,
sur proposition du professeur Thomas LECUIT

Biology by the Numbers

Conférences à 17 heures
Le 27 avril et les 4, 11 et 18 mai
Salle 2

Lecture 1: Biology by the Numbers
Lecture 2: Case Studies in Biological Theory: Predicting Transcription
Lecture 3: Molecular Vitalism: Nonequilibrium Effects in Living Matter
Lecture 4: The Great Human Experiment by the Numbers: Sizing up the Anthropocene