Cell Cycle and Growth Control (2024)

Course Coordinator: Drs. Jim Dennis and Ran Kafri
Course Time and Date: Feb 21 - March 27th

Course Overview:

The course will serve as an in depth exploration of mechanisms that program and maintain homeostasis of growth (hypertrophy) and cell division (hyperplasia) in metazoan biology. Different animal cell types, or cells from different animal tissues, display marked differences in cell size. Pancreatic acinar cells, for example, are over four times larger than their neighboring pancreatic beta cells. In proliferating cells, maintenance of cell size reflects a coordination of cell growth with rates of cell division. By contrast, in non-proliferating and terminally differentiated cells, size homeostasis exclusively depends on mechanisms that coordinate biosynthesis with turnover. To add to this complexity, both growth and cell division are exquisitely tuned to the balance of mitogenic (proliferative) signals, energy status and nutrient availability.

What is the nature of the molecular program that coordinates growth, division and turnover to maintain homeostasis? While the answer to this question is not yet realized, many new and exciting mechanistic details pertaining to these processes are continuously reported. Science is a union of observations and story-telling. Driven by curiosity, we seek a narrative that weaves disparate observations into a coherent narrative.

In this course, will rely on an in-depth exploration of literature to derive novel, experimentally testable, narratives on the subject of growth homeostasis. Particular emphasis will be placed on cell cycle checkpoints, cell size checkpoints and sensing mechanisms that respond to changes in metabolic status and nutrient availability.

Course Objectives:

The course will encourage students to think outside the box and present new hypotheses and new narrative concerning questions that remain conflicted in the literature. The course will open with two presentations given by the instructors, a presentation on growth and cell cycle (Dr. Kafri) and a presentation on metabolism and energy homeostasis (Dr. Dennis). The instructors will then present a list of open questions and literature that pertains to those questions. The students will then assemble into small “research groups” (2-4 students per group) and rely on literature as a research tool to investigate these questions. Particular emphasis will be placed on trying to derive experimentally testable narratives that may untangle apparently contradictory observations found in literature.

Class Format:

Students will present selected research papers (see list below), 20 min, pointing out the novelty as well as a critique noting shortcoming (~ 8-10 ppt figures). You should set-up the paper briefly then select the key figures, and distill them down to the critical points. Formulate 2 or 3 questions that arise from the research in the paper that are worth further investigation. We will have questions and a short discussion after you present. Active participation from listening students is also graded. Slides should be submitted to Dropbox or emailed to Jim & Ran 24h before the class.

Written assignment:

You will write a ~1500 word grant (single space), on any of the topics of the papers discussed in the classes (other than your own graduate research project). Please introduce why the question is important, state a hypothesis and aims, experimental approaches and possible outcomes. Include what techniques, animals and cells etc will be needed. Keep in mind the limitations of time (5 years) and money where a grant is ~ $250K per year. The suggested structure is: Abstract, background paragraph to set-up the problem, hypothesis, main goals, 3 specific aims, experimental section and the overall significance in one sentence. References and any figures you wish to include can be added in a 1 page appendix to be submitted on or before May 8.

Evaluation:

Paper presentation and class participation is 50%, and 50% for your grant proposal.

If you anticipate missing a class you must let the instructor know in advance, given the weight on participation and the fact that there are only six classes. Providing that you had a legitimate reason for missing the class, you will provided with an assignment based on the reading for that week that you can use to make up for the lost class.

Syllabus

Section I: From the molecules to quantitative information: mass-action and signals driving the cell cycle.

Classic papers:

1. The biochemical basis of an all-or-none cell fate switch in Xenopus oocytes.[1]

2. Network motifs in the transcriptional regulation network of Escherichia coli [2].
3. Design principles of cell circuits with paradoxical components.[3]

Reviews:

1. Models in biology: lessons from modeling regulation of the eukaryotic cell cycle.[4]
2. Dennis JW. Many Light Touches Convey the Message. [5]
3. Simplicity in biology.[6]
4. SnapShot: network motifs.[7]
5. Ultrasensitivity parts I, II, III: cascades, bistable switches, and oscillators. [8]

Section II: Cell cycle coordination with protein synthesis and metabolism.

Classic papers:

1. Coordination between cell growth and cell cycle transit in animal cells[9]

Reviews:

1. Interconnection between Metabolism and Cell Cycle in Cancer[10]
2. Control of cell growth by the SCF and APC/C ubiquitin ligases [11]

Section III: Growth regulators and cell cycle. The influence of protein synthesis, ribosomal biogenesis or metabolism on cell cycle progression.

Reviews:

1. Gatekeepers of chromatin: Small metabolites elicit big changes in gene expression.[12]

Section IV: Cell Competition and fitness. From hypertrophy (cell size) and hyperplasia (cell division) to organ size and organ homeostasis.

Reviews:

1. Cell competition: Emerging mechanisms to eliminate neighbors. [13]
2. Cell Competition During Growth and Regeneration. [14]

Section V: Adapting the cell surface with metabolic states: N-glycosylation interacts with nutrient conditions to regulates receptors, cell fate and aging?

Reviews:

1. Stanley P. Golgi glycosylation. Cold Spring Harb Perspect Biol. 2011[15]
2. Essentials of Glycobiology, 3rd edition, complete text is online

Books of interest:

- Why size matters: from Bacteria to Blue whales – John Tyler Bonner
- Probably approximately correct – Leslie Valiant
- Why Information grows - Cesar Hidalgo

References

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3. Hart, Y., Antebi, Y. E., Mayo, A. E., Friedman, N. & Alon, U. Design principles of cell circuits with paradoxical components. *Proceedings of the National Academy of Sciences* vol. 109 8346–8351 Preprint at https://doi.org/10.1073/pnas.1117475109 (2012).
4. Tyson, J. J. & Novák, B. Models in biology: lessons from modeling regulation of the eukaryotic cell cycle. *BMC Biol.* **13**, 46 (2015).
5. Dennis, J. W. Many Light Touches Convey the Message. *Trends Biochem. Sci.* **40**, 673–686 (2015).
6. Alon, U. Simplicity in biology. *Nature* **446**, 497 (2007).
7. Shoval, O. & Alon, U. SnapShot: network motifs. *Cell* **143**, 326-e1 (2010).
8. Ferrell, J. E. & Ha, S. H. Ultrasensitivity part III: cascades, bistable switches, and oscillators. *Trends in Biochemical Sciences* vol. 39 612–618 Preprint at https://doi.org/10.1016/j.tibs.2014.10.002 (2014).
9. Baker, D. J. *et al.* Clearance of p16Ink4a-positive senescent cells delays ageing-associated disorders. *Nature* **479**, 232–236 (2011).

10. Icard, P., Fournel, L., Wu, Z., Alifano, M. & Lincet, H. Interconnection between Metabolism and Cell Cycle in Cancer. *Trends Biochem. Sci.* (2019) doi:10.1016/j.tibs.2018.12.007.
11. Skaar, J. R. & Pagano, M. Control of cell growth by the SCF and APC/C ubiquitin ligases. *Curr. Opin. Cell Biol.* **21**, 816–824 (2009).
12. Kaochar, S. & Tu, B. P. Gatekeepers of chromatin: Small metabolites elicit big changes in gene expression. *Trends Biochem. Sci.* **37**, 477–483 (2012).
13. Nagata, R. & Igaki, T. Cell competition: Emerging mechanisms to eliminate neighbors. *Dev. Growth Differ.* **60**, 522–530 (2018).
14. Gogna, R., Shee, K. & Moreno, E. Cell Competition During Growth and Regeneration. *Annual Review of Genetics* vol. 49 697–718 Preprint at https://doi.org/10.1146/annurev-genet-112414-055214 (2015).
15. Stanley, P. Golgi glycosylation. *Cold Spring Harb. Perspect. Biol.* **3**, (2011).