Cell biological mechanisms of neurodegenerative disease

Facilitators: Lars Dreier and Alex van der Bliek

Course content
In this course, we will examine the effects of mitochondrial turnover and more in general of proteostasis on apoptosis, autophagy and necrotic cell death. These processes play prominent roles in major diseases, such as heart disease and the neurodegenerative diseases Alzheimer's and Parkinson's. New insights into the underlying cellular causes of these diseases hold promises for therapeutic developments. We will touch on those promises in our discussions of some key papers from recent literature.

Course format
Students will meet separately to prepare for the class, and they will meet with facilitators in two sessions per week. For each session, one primary research paper will be assigned. Students are expected to have read this paper thoroughly before class and obtain appropriate background information to adequately discuss the research paper and topic (standard cell biology textbooks like *Molecular Biology of the Cell, Alberts et al.* or *Molecular Cell Biology, Lodish et al.* can provide excellent background). During the session, students will be called on randomly to present figures of the papers.

Things to consider when reading the paper for the session:
1. What are the important findings that lead to this work?
2. What is the main question addressed by this paper?
3. What experiments were done to answer this question? What are the main findings and conclusions?
4. Do the findings support the conclusions? Are there additional experiments that could strengthen the conclusions? What are the next crucial questions that would advance our understanding of the topic?

Things to go over when examining or presenting a figure or a panel of a figure:
1. What question does the experiment of this panel address?
2. How was the experiment done and what is the result?
3. What is the conclusion of the experiment?
4. Does the result of the experiment support the authors' conclusion? Are there alternative interpretations? Are there additional critical control experiments? Are there technical concerns? Are there additional experiments that would strengthen the conclusion?
5. Based on the result, what is the next question (this can lead to the next figure)?

Written assignment
During the last week of the course, students are to hand in a written assignment in which they critically evaluate one of the assigned papers and propose follow-up experiments. Be sure to use complete sentences, critically assess the main conclusions and use citations for any literature you use. The report should be no more than 3 pages, 11-12 point font and 1.5 spacing. It should focus on one of the discussion papers and cover the following points:

(1) Summarize the main question(s) addressed in this paper (10%).
(2) Summarize the relevant finding(s) that lead to the work (10%).
(3) Describe the key finding(s) supporting the major conclusion(s) of the paper (40%). Mention approaches.
(4) Propose follow-up experiments that could strengthen key conclusions or would investigate crucial open questions to advance our understanding of the findings reported in the paper (40%).

The report should be emailed to us (AVan@mednet.ucla.edu; larsdreier@ucla.edu).

Evaluation
254B should be considered a priority and attendance at all meetings is required. Students will be evaluated based on class participation (50%) and the written assignment (50%).

Practical info
Students should divide themselves up in groups to prepare the Powerpoint presentations (cut and pasted copies of the Figure panels from the papers).
Time for faculty meetings: 10:00am – 12:00N on Tuesdays & Fridays
Room for faculty meetings: Zoom meetings.
Time for Students-only meetings: 10:00am – 12:00 on Mondays & Thursdays (starting Mon. 11/9/20)
Room for Students-only meetings: Zoom meeting.

Papers

1. Hsieh et al. (2016). Functional Impairment in Miro Degradation and Mitophagy Is a Shared Feature in Familial and Sporadic Parkinson's Disease. Cell Stem Cell 19, 1-16.
http://www.sciencedirect.com/science/article/pii/S1934590916302491

2. Wall et al. (2019). PPEF2 Opposes PINK1-Mediated Mitochondrial Quality Control by Dephosphorylating Ubiquitin. Cell Reports 29, 3280–3292.
https://pubmed.ncbi.nlm.nih.gov/31801089/

3. Fujioka et al. (2020). Phase separation organizes the site of autophagosome formation. Nature 578:301-305.
https://www.nature.com/articles/s41586-020-1977-6

4. D'Amico et al. (2019). The RNA-Binding Protein PUM2 Impairs Mitochondrial Dynamics and Mitophagy During Aging. Molecular Cell 73, 775–787.
https://pubmed.ncbi.nlm.nih.gov/30642763/

5. Tang et al. (2014). Loss of mTOR-Dependent Macroautophagy Causes Autistic-like Synaptic Pruning Deficits. Neuron 83, 1131–1143.
http://www.sciencedirect.com/science/article/pii/S0896627314006515

6. Gassen et al. (2019). SKP2 attenuates autophagy through Beclin1-ubiquitination and its inhibition reduces MERS-Coronavirus infection. Nat. Commun. 10, 5770.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6920372/

7. Dhir et al. (2018). Mitochondrial double-stranded RNA triggers antiviral signalling in humans. Nature 560, 238-242.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6570621/

8. Chouchani et al. (2014). Ischaemic accumulation of succinate controls reperfusion injury through mitochondrial ROS. Nature 515, 431-435.
http://www.nature.com/nature/journal/v515/n7527/full/nature13909.html

9. Bell et al. (2012). Apolipoprotein E controls cerebrovascular integrity via cyclophilin A. Nature 485, 512-6.
http://www.nature.com/nature/journal/v485/n7399/full/nature11087.html

10. Xie et al. (2013). Sleep drives metabolite clearance from the adult brain. Science 342, 373-7.
http://science.sciencemag.org/content/342/6156/373.full