Foundations in Biomedical Sciences III:
Architecture & Dynamics of the Cell

Fall 2011
Tuesdays, Thursdays, and Fridays, 9:30 am to 11:20 am
Fridays, 12:15 pm to 1:45 pm

Course description:

The third module of the Foundations in Biomedical Sciences course will focus on the movement of proteins and membranes with the cell, the secretory process, the cytoskeletal framework of the cell and the resulting cell-cell interaction and communication with the matrix. Specific details on the content are described in the following pages. Molecular, cell biological, and biochemical experimental approaches to understanding these processes will be explored. In addition, we will discuss the possibilities of utilizing these technologies in medical treatments. The course is aimed towards first year Ph.D. students in the Division of Graduate Medical Sciences. The class will be taught by members of the Division from a variety of Departments utilizing a combination of traditional lectures and discussion sections focusing on primary research to total 7 hours of class time per week. Supplementary study materials used will be made available on blackboard to aid the students in their review of the material. Reading materials will primary be taken from the current literature but will be supplemented by handouts supplied by the faculty. Students will be evaluated on their performance on a quiz, problem set, and examination along with active participation in discussion sections.

Course Learning Objectives

By the end of this course, students should be able:

1. To understand the structural qualities and properties of biological membranes that make them ideally suited for their role in compartmentalization of the cell and movement of cellular components, such as proteins and lipids, throughout the cell.

2. To understand the structure and functions of the various subcellular compartments and to know how proteins are targeted to these compartments.

3. To understand the role of the cytoskeletal proteins in cell structure and motility, their role in the movement of organelles and their role in cell-cell interactions.

4. To understand how a cell takes up extracellular molecules, such as nutrients and how these compounds are transported through the cellular membranes.

5. To understand how a cell secretes proteins and other components.

6. To develop an understanding of how cells interact with matrix and matrix-associated proteins and the role(s) that matrix proteins have on cell function.

Course Managers:

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Dr. Robert Varelas, Assistant Professor of Biochemistry, K-620, 638-4182

Grading:

Quiz 1	20%
Final Exam	35%
Problem Set	25%
Breakout Sessions	20%
Total	100%

Recommended reference materials to supplement reading of the literature include:

1. Alberts, B., Johnson, A., Lewis, J., Raff, M., Roberts, K., Walter, P. *Molecular Biology of the Cell.* 5th ed. Garland Science, 2007.

Dates	Class	Instructor
November 15	**Introduction: Membranes & Membrane Lipids** - *Lipids –Definition* - *Fatty acids (mammalian)* - *Membrane structure - lipid bilayer – fluid mosaic model* - *Membrane components - phospholipids, cholesterol etc..* - *Membrane properties – fluidity, mobility, permeability* - *Heterogeneity, sidedness* An outlook on organization of lipids in membranes: searching for a realistic connection with the organization of biological membranes. (2010) Bagatolli LA, Ipsen JH, Simonsen AC, Mouritsen OG. Prog Lipid Res. 49:378-389	Dr. Zoeller
November 17	**Lipid Movement & Membrane-Associate Proteins** *- Intracellular lipid movement* *- Flipases* *- ABC transporters* *- Cholesterol movement* *- Membrane proteins.* *- Integral membrane proteins* o *hydrophobic alpha-helices, beta-sheets or beta barrels* *- Peripheral proteins – amphipathic α-helices,* *- Protein lipidation:* *Acylation (myristoylation, palmitoyation)* *Prenylation* *Glypiation* *- Model proteins: Bacterial rhodopsin, ABC transporters, G proteins* Protein lipid modifications in signaling and subcellular targeting. (2009) Sorek N, Bloch D, Yalovsky S. Curr Opin Plant Biol. 12:714-720.	Dr. Zoeller
November 18	**Cell-Cell Junctions** - *Structure and function of junctions* - *Tight junctions* - *Gap junctions and hemichannels* - *model tissues –astrocytes, dry eye , intestinal epi tracheal* Both sides now: multiple interactions of ATP with pannexin-1 hemichannels. Focus on "A permeant regulating its permeation pore: inhibition of pannexin 1 channels by ATP". Dubyak GR. 2009. Am J Physiol Cell Physiol. 296:C235-41.	Dr. Trinkaus-Randall

	Metabolic autocrine regulation of neurons involves cooperation among pannexin hemichannels, adenosine receptors, and KATP channels. 2010. Kawamura M Jr, Ruskin DN, Masino SA. J Neurosci. 30:3886-95. Pannexin 1: the molecular substrate of astrocyte "hemichannels". 2009. Iglesias R, Dahl G, Qiu F, Spray DC, Scemes E. J Neurosci.29:7092-7.	
November 18	**Discussion Session #III-1** *1. Methods used to study membranes and membrane proteins.* *- Structural analyses – predictions using sequence analysis* *- Hydropathy maps to predict transbilayer segments* *- Examine structures, sequences to predict pore-forming proteins.* *- FRAP & FLIP (for both lipids & membrane proteins)* *2. Inherited diseases of membrane dysregulation* Large-scale profiling of protein palmitoylation in mammalian cells. 2009. Martin BR, Cravatt BF. Nat Methods. 6:135-8. Functional genomic screen reveals genes involved in lipid-droplet formation and utilization. 2008. Guo Y, Walther TC, Rao M, Stuurman N, Goshima G, Terayama K, Wong JS, Vale RD, Walter P, Farese RV. Nature 453:657-61.	Discussion facilitators
November 22	**Compartmentalization of Eukaryotic Cells** - *Plasma membrane organization-lipid rafts* - *Organelles Intro – Golgi, peroxisomes, mitochondria, nucleus…..* - *Biochemical and morphological approach to identifying and studying organelles* - *Targeting of proteins to intracellular compartments (sorting signals)* - *Gated transport, transmembrane transport, vesicular transport*	Dr. Pilch
November 29	**Intracellular transport pathways** *- Endocytic Transport Types* *- Receptor mediated endocytosis* *- Phagocytosis* *- Pinocytosis* *- Mechanisms of Membrane Transport* *- Coat and tethering proteins* *- Rab proteins, SNARES* *- Mechanistic steps of vesicular transport* *- Vesicle formation, targeting and fission* New insights into membrane trafficking and protein sorting. Derby MC, Gleeson PA. Int Rev Cytol. 2007;261:47-116. Review.	Dr. Pilch

	Signals for sorting of transmembrane proteins to endosomes and lysosomes. Bonifacino JS, Traub LM. Annu Rev Biochem. 2003;72:395-447. Epub 2003 Mar 6. Review.	
December 1	**Protein maturation and processing** *-ER-golgi transition and movement of proteins (single-pass and multi-pass TM proteins)* *-Techniques used to mark state of protein folding* *Improperly folded proteins and degradation* *- Protein degradation* *- Heat shock proteins, UPR, proteasome, lysosome* The unfolded protein response: a pathway that links insulin demand with beta-cell failure and diabetes. Scheuner D, Kaufman RJ. Endocr Rev. 2008;29:317-333.	Dr. Pilch
December 2	**Mitochondria and Peroxisomes** *- Mitochondrial function & diseases* *- Mitochondrial protein targeting (Tom & Tim complexes)* *- Peroxisomal function and protein targeting (Pex system)*	Dr. Zoeller
December 2	**Discussion Session #III-2** *- QUIZ #1* *- Inherited diseases of mitochondrial, peroxisomal, lysosomal function* *- Techniques to study protein targeting to subcellular compartments* *- Confocal microscopy* *- Immunofluorescence* *- Subcellular fractionation* The N-terminal peptide of the syntaxin Tlg2p modulates binding of its closed conformation to Vps45p. 2009. Furgason ML, MacDonald C, Shanks SG, Ryder SP, Bryant NJ, Munson M. Proc Natl Acad Sci U S A. 106:14303-8.	Discussion facilitators
December 6	**Actin and tubulin** *-On off rates* *-Nucleation* *-Polymerization* *-Plus and minus ends* *-Nucleotide hydrolysis* *-Treadmilling* *-Dynamic instability and role in cytoskeletal rearrangement*	Dr. McKnight
December 8	**Actin and tubulin accessory proteins** *-Association with actin subunits – formins – actin*	Dr. McKnight

	elongation *-Association with actin filament – ARP complex* *-Association with microtubules – severin proteins* *-Length and kinetic behavior of actin and MT* *-MAPs* Control of cell membrane tension by myosin-I." 2009. Rajalakshmi Nambiar, Russell E. McConnell, and Matthew J. Tyska1. PNAS. 106(29): 11972–11977.	
December 9	**Molecular Motors** *-Characteristics of filament, directionality* *-Myosin superfamily* *-MT motor proteins – kinesin and dyneins* *-Generation of force by motor proteins* *-Motor proteins mediate intracellular transport* *motor proteins carry membrane-enclosed organelles (mitochondria, golgi or secretory vesicles)* *-Motor proteins cause cytoskeletal filaments to exert tension generating force that drives contraction, ciliary beating, division* Switches, Latches and Amplifiers:Common themes of G proteins and molecular motors." 1996. Vale,R.D.. J Cell Biol. 135(2):291-302.	Dr. Moore
December 9	**Discussion Session #III-3** - *Paper: Actin or microtubule-dependent organelle transport – discussion from both sides (4 and 4)* - *Imaging Technology: Cell shape changes then move to quantitative assessment* Nonlinear elasticity and an 8-nm workingstroke of single myosin molecules in myofilaments. 2010. Motoshi Kaya, et al. Science 329, 686	Discussion facilitators
December 13	**Cell Polarity** *-The cytoskeleton during changes in cell shape* *-Filament assembly and disassembly to reshape cytoskeleton* *- Characteristics of different cell types including polarity* *- Examples (Fibroblasts, endothelial, neuronal etc…)* *- Morphological specialization of neuron depends on cytoskeleton* *-Reorganization of cytoskeleton in response to external stimuli* Reversal of cell polarity and actin-myosin cytoskeleton reorganization under mechanical and chemical stimulation.2008. Dalous J, Burghardt E, Müller-Taubenberger A, Bruckert F, Gerisch G, Bretschneider T.Biophys J. 2008 Feb 1;94(3):1063-74. Epub	Dr. Varelas

	2007 Sep 28.	
December 15	**Cell Motility** *-Examples of different actin arrays in a cell (contractile/gel- like/tight bundle)* *-Cellular examples* *- neutrophil* *- leukocyte rolling and extravasation* *- pathogenic example candida albicans forming a rod* *- wound healing –, change in stress filaments* *- Cell-cell and cell-matrix interactions using actin and MT structures* *- Focal adhesions and associated proteins* *- Proteins that comprise actin and MT based structures* *Integrins* The Tail of Integrins, Talin, and Kindlins". 2009. Markus Moser, Kyle R. Legate, Roy Zent and Reinhard Fässler. Scinece. 324 (5929):895-899. "The integrin-growth factor receptor duet".2007. Naved Alam, Hira Lal Goel, Matthew J. Zarif, Julie E. Butterfield, Hillary M. Perkins, Brian G. Sansoucy, Thomas K. Sawyer, Lucia R. Languino. J Cell Physiol 213 (3):649–653.	Dr. Trinkaus-Randall
December 16	**Matrix Proteins** *- Structure and composition* *- Different structures, functions of matrix and composition of matrix proteins in different tissues* *- Stability and turnover of the matrix* *- Examples of Matrix proteins* *-Collagens* *-Glycoproteins (Laminins and Fibronectins)* "The RGD motif in fibronectin is essential for development but dispensable for fibril assembly. "Takahashi S, Leiss M, Moser M, Ohashi T, Kitao T, Heckmann D, Pfeifer A, Kessler H, Takagi J, Erickson HP, Fässler R. J Cell Biol. 178(1):167-78.	Dr. Trinkaus-Randall
December 16	**Discussion Session #III-4** *In class summaries by students on topics – divide by groups*	Discussion facilitators
December 20	**MODULE III FINAL EXAM**	