Analysis of Biological Networks

Professors

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Systems Approach to Biological Problems

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Retinopathy

- Diabetic retinopathy, Macular degenration and 10 other indications
- Over 500,000 patients per year
- Unmet medical condition
- Current treatment - laser surgery and this procedure has > 60%relapse < 3 months

Central Dogma of Molecular Biology

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Proteins

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Post-genomic challenges

- Newer tools and more sophisticated technology to push the field forward in the post genomic age
- Genomics, proteomics, glycomics and others
- ….enter cell, tissue organ level mechanisms
- A 'systems approach' to understand the complex biological system

Linking molecular & cellular events

with physiological function

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Please see:

Figure 2a in Hunter, Peter J. and Borg, Thomas K. "Integration from proteins to organs: The Physiome Project." *Nature Reviews*, vol. 4, March 2003, pp. 237-243.

Protein Post-translational Modification
Signal Transduction

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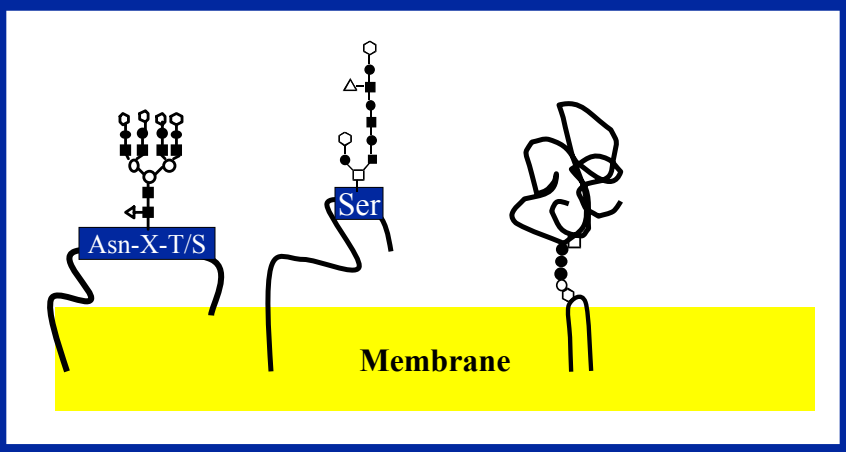
Protein Post-translational Modification
Glycoprotein



Scale and components

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Example I


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Retina and fine structure

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Please see:

http://www.arts.uwaterloo.ca/~bfleming/psych261/image19.gif

Circulatory system

- Unicellular - multicellular transition
- Supply of oxygen and nutrients
- Major Constraints on growth: surface to volume ratio
- Area changes as $L^2 \alpha(4\pi r^2)$ and volume as L^3 ($4/3\pi r^3$)
- Diffusion from outside versus inside- solutions: flat, hollow tubes and invagination
- Circulation: problem of size: effective transport (large) diffusion small vessels, also, decrease size increase resistance

Hierarchical View

- Tissue level: endothelium/ECM/pericytes
- Cellular level: endothelial cells
- Cellular and molecular level: signal transduction and growth factors
- Molecular level

Angiogenesis

Matrix degradation

Release of transient molecules

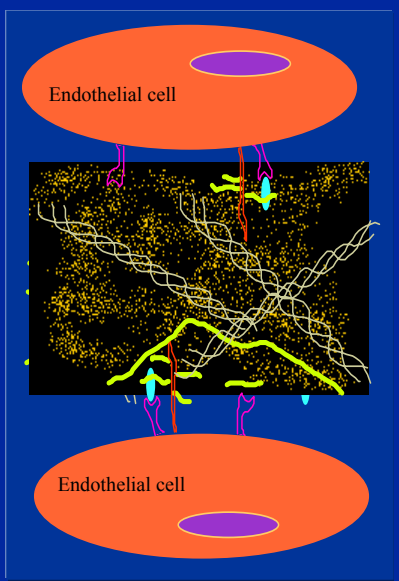
Cell migration

Promotion by angiogenic factors

Cell proliferation

Other matrix molecules

Capillary formation



Single Cell

- Basic house keeping
  - energy,
  - multiplication
- Cell cycle
- Genotype – phenotype
- Signaling pathways

Division, Differentiation or Death

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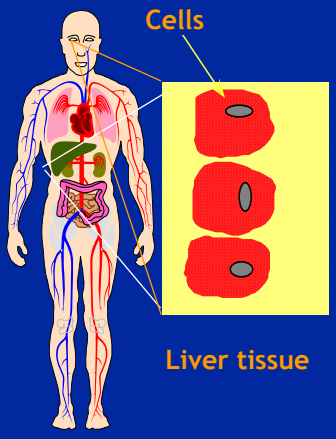
Extracellular Matrix



ECM critical path between cell and outside

Cell volume 3-5 % in tissue, rest is ECM

ECM
- Water (~ 70-80 %)
- Protein (~ 20-10 %)
- Polysaccharide (~ 8-10 %)

Scaffold for cells to form tissue

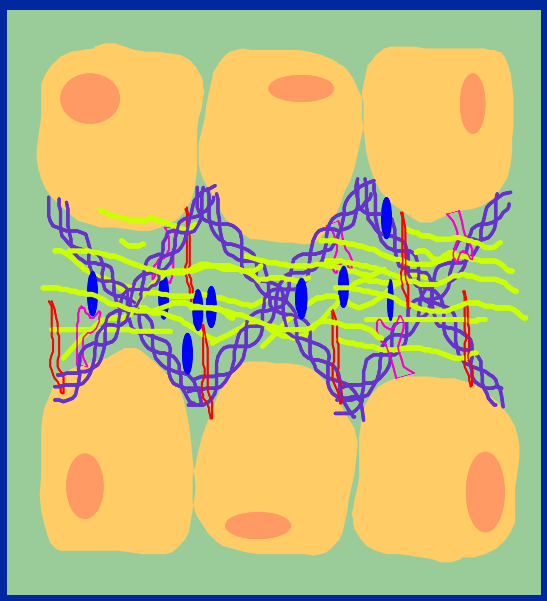
Sponge bringing water and food to cells

ECM

collagen

polysaccharide

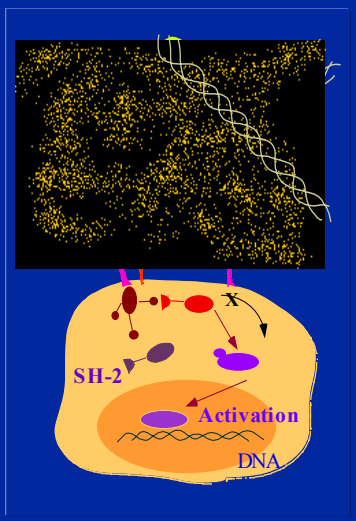
cytokines



Properties of ECM

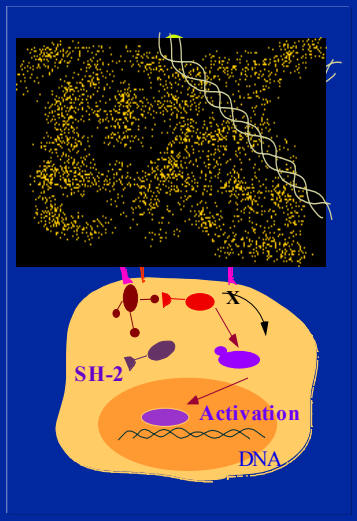
- ECM is bi-phasic
  - insoluble (mechanical)
  - soluble (chemical)
- ECM influences
  - hydration and ionic strength
  - permeability, diffusion and transport
  - mechanical strength
- Passive physico-chemical properties
  - binding (enthalpic)
  - excluded volume (entropic)
- ECM highly heterogeneous (varying ratios and chemical composition)

Cell- ECM Interactions



- Cells make the matrix - matrix tells cells what to do
- Cells can rapidly change matrix components
- Matrix is the signature of cellular phenotype or states
- Direct link between ECM-Cell surface- Nucleus
- Generation of signal versus signal processing
- Stored, latent and activation
- Signal amplification

Signal Transduction



Extracellular signal sensor

↓

Protein phosphorylation

↓

transcriptional activator

- Signal amplification and regulation
- Transmembrane G protein
- Tyrosine or Ser/Thr kinases
- many second messengers
- Transcriptional regulation

Cell-ECM Interactions

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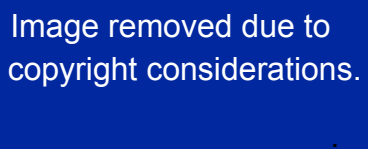
- Integrin clustering
- multiple pathways

Coupled-signaling



Important Principles

- **Signal processing rather than signal generation**
- **Information flow between cells and the ECM is both dynamic and reciprocal**
- **Physical connections between ECM - cell surface - cytoskeleton-nucleus occur along a structural continuum**
- **Architectural scaffold upon which biochemical pathways overlaid**
- **ECM context, accessory factors, and the milieu impinge a template**

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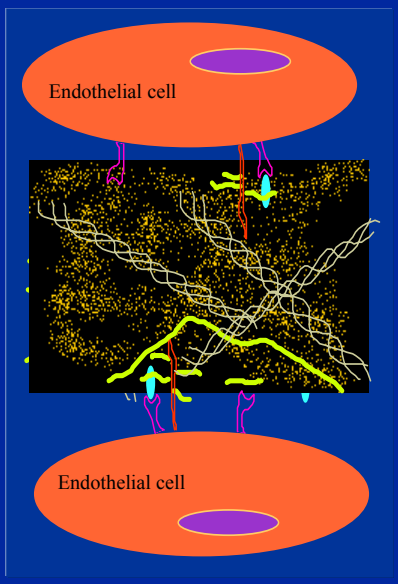

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Example II

Cellular - Molecular II

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Please see:

Figure 2 in Hanahan D, Weinberg RA.
"The hallmarks of cancer." *Cell.* 2000 Jan 7;100(1):57-70.

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Please see:

Figure 1 in H. Jeong, S. P. Mason, A.-L. Barabssi, Z. N. Oltvai. "Lethality and centrality in protein networks." *Nature* 411, 41 - 42 (03 May 2001).

Molecular/Cellular System as a "Circuit"

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Map of Boston

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Map of Boston with all hotels

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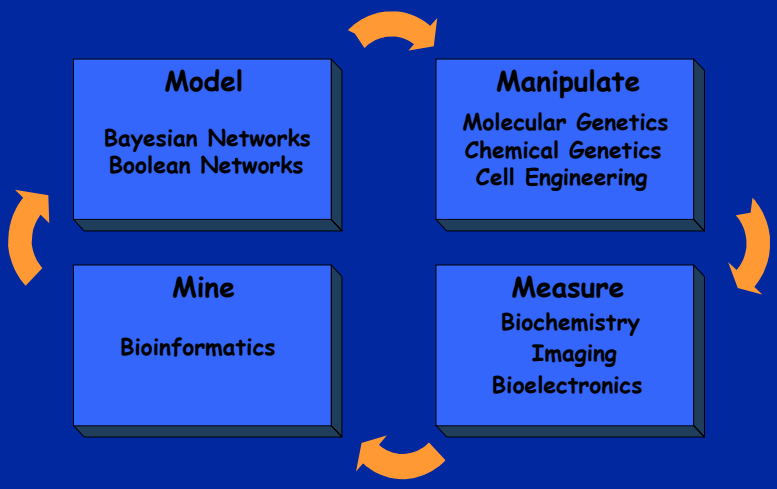
Systems Biology

Large 'Glue' Programs

Systems Biology



New Research Models for Post Genomics Science
- the Glue Grants

- **Alliance for Cellular Signaling (AfCS):** To understand as completely as possible the relationships between sets of inputs and outputs in signaling cells that vary both temporally and spatially, *i.e.* how cells interpret signals in a context-dependent manner
- **Cell Migration Consortium:** To accelerate progress in cell migration-related research by fostering interdisciplinary research activities and producing novel reagents and information
- **Consoritum for Functional Glycomics:** Define the paradigms by which carbohydrate binding proteins function in cellular communication
- **Inflammation and Host Response Consortium:** It is designed to acquire new scientific knowledge about the biological basis for different outcomes in injured patients.

Consortium for Functional Glycomics

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Highlights of CFG

- Data Acquisition Interface
  - Core D: 251 Synthetic Glycan Structures have been deposited
  - Core E: 20 Experiments and 260 Samples deposited
  - Core F: Information on all 24 mouse strains in web site have been uploaded in database
  - Core G: Database of over 5000 mice have been transferred to Core B and is being updated on monthly basis; 73 Experiments from 4 SubCores, for 7 Strains deposited
- Data Dissemination Interface for Consortium Database
  - List, View, Search and Download features implemented for all Core data
- GBP and Glycoenzyme Molecule Page Interface
  - Prototype Interfaces for 160 GBPs have been implemented
- Glycan Structures Database and Interfaces
  - Created seed database of 1751 glycan structures (1500[Glycominds] + 251 from Core D and Glycan Array)

Molecule Page Interface

Automated Acquisition

Data from Public databases, links to Public resources

Data from Cores

Links to Resource and Data IDs for viewing Consortium resources

PI entry

Filling out fields as experts on the molecule

Integration of data from different components

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