

BIO 5099: Molecular Biology for Computer Scientists (et al)

Lecture 24: Pathology & Disease

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Life includes Sickness and Death

✧ Pathology is the study of mechanisms and processes of disease.

- Several thousand distinguishable human diseases
- Classified by affected organ/system or by pathological process(es) involved.

✧ Basic medical terms:

- **Symptoms** (what a patient says), **signs** (what a doctor detects on exam), **lesion** (unit of abnormality, usually anatomic), **etiology** (cause of a disease), **pathogenesis** (*how* the etiologic agent causes the disease), **prognosis** (**how the patient can reasonably expect to do**).

Basic Mechanisms

✧ Cellular & molecular aspects of injury & death

- Types of cell death
- Oxygenation, blood & free radical injuries

✧ Cellular response to injury

- Inflammation and repair
- Adaptation

✧ A sampling of important diseases

- Cancer
- Infection, sepsis and shock
- Atherosclerosis and cardiovascular disease

Cell death

✿ *Necrosis* is abnormal cell death (cf apoptosis)

✿ Proximate causes:

- Toxins, *hypoxia* (too little oxygen for cellular respiration)

✿ Ultimate causes:

- Reduction in blood supply (*ischemia*), e.g. stroke
- Too little oxygen in the blood (*hypoxemia*)
- Infective agents (producing toxins), trauma, radiation, etc.

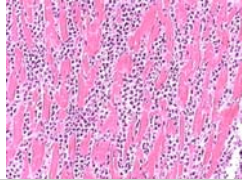
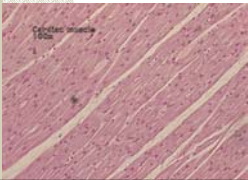
✿ Consequences:

- Cells swell and burst, spilling contents into interstitial fluid
- Strong inflammatory response, *phagocytosis*

Necrosis in heart attack

✿ Heart attack (myocardial infarction) causes ischemic necrosis in cardiac muscle

✿ Muscle cells die (no nuclei!), infiltrate of small dark inflammatory cells (*neutrophils*)



Molecular mechanisms

✿ Lack of oxygen causes:

- Depletion of ATP:
 - Na/K pump fails: Na⁺ influx, followed osmotically by water
- Reduced synthesis and increased degradation of phospholipids, particularly of cell membrane
 - Increased permeability to Ca₂⁺ (creating calpain & O₂⁻)
- Mitochondrial membrane leaks calcium (irreversibility)

✿ Reperfusion injury

- Creation of free oxygen radicals, O₂⁻, OH⁻, H₂O₂⁻
 - Very reactive, damaging nearly all biomolecules.
 - Limited detoxification capacity (e.g., superoxide dismutase)

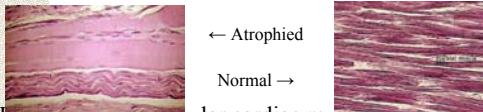
Cellular adaptation

When cells are stressed, they respond by changing their number, type or size

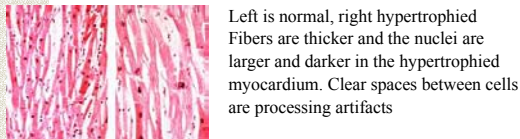
- **Atrophy:** reduction in cell (and organ) size
 - E.g. in muscles through lack of use or denervation
- **Hypertrophy:** increase in *cell size*
 - E.g. in cardiac ventricles due to high blood pressure
- **Hyperplasia:** increase in the *number of cells*
 - E.g. *excess estrogen causing endometrial hyperplasia*
- **Metaplasia:** *change in cell type (to another normal type)*
 - E.g. *columnar epithelium become squamous in smokers*
- **Dysplasia:** change to an abnormal cell type.

Adaptation pictures

Atrophy (in muscle, due to ALS denervation)



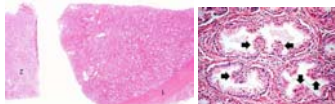
Hypertrophy (ventricular cardiac muscle)



More adaptation

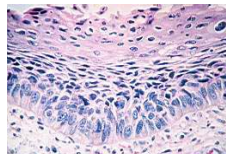
Hyperplasia (often in prostate of older men)

Left is normal
Middle is hyperplastic
Right is high mag hyperplasia



Metaplasia

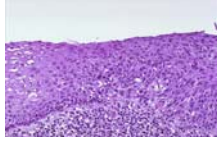
Tracheal epithelium of a smoker shows transition from (normal) columnar epithelium to squamous type normally found in skin.



Dysplasia (and on to Neoplasm)

✿ Cervical dysplasia

- Normal squamous epithelium on left shades into disordered dysplastic cells on the right



✿ Dysplasia is a step toward cancer.

✿ Neoplasm (tumor) is a mass of new tissue

- Develops its own blood supply
- Benign (stay in place) or malignant (invades other tissues)

✿ Dysplasias grow into malignant neoplasms

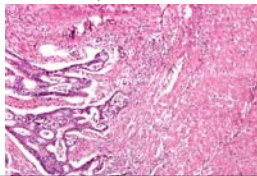
Cancer

✿ Breakdown of the deal of multicellularity

- Abnormally proliferating, invasive somatic cells

✿ Cancer cells

- Grow very quickly (although often not as quickly as embryonic or bone marrow or intestinal epithelial cells)
- Tend to de-differentiate, but exhibit some of the characteristics of their cell type of origin, e.g. make glands
- Cancer when cells invade past a basement membrane



Molecular Biology of Cancer

✿ Large-scale rearrangements of chromosomes common in cancer; sometimes specific



✿ Oncogenes are genes whose mutations or expression (or lack) is associated with cancer

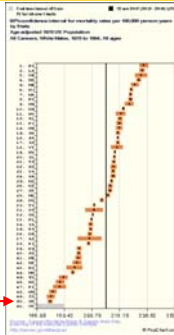
- **Bcl2**: component of transduction of apoptosis signal. Cells with mutated Bcl-2 do not respond to apoptosis signals.
- **p53**: inhibits reproduction of cells with damaged DNA. Many human tumors have a p53 defect.
- **PTEN**: mutation or loss found in many advanced (metastatic) tumors; possible role in cell adhesion

Cancer Incidence

- ✿ Lung cancer (from tobacco) dominates cancer deaths.
- ✿ Breast cancer worst killer for women, but lung accelerating
- ✿ Colorado has lowest incidence in US for all cancers (and 3rd lowest tobacco use)



cancer mortality rates per 100,000 person years (>5) for white women in CO



Cancer Research Directions

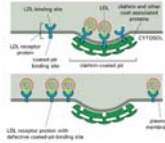
- ✿ Current regimes based on agents that are toxic to all rapidly dividing cells
 - Horrendous side effects, poor efficacy.
- ✿ More specific therapies require finding “molecular signatures” of tumor cells
 - From signatures come diagnostics and drug targets
- ✿ Focus on *interaction* between genes, environment and lifestyle
 - Familial cancer predispositions (e.g. BRCA1) are very rare
- ✿ Many disappointments (anti-angiogenesis?)

Infectious disease

- ✿ Caused (in part, at least) by an external agent
 - Bacteria (e.g. chlamydia, rickettsia, streptococcus, TB)
 - Virus (e.g. AIDS, common cold, smallpox, West Nile, etc.)
 - Fungus (e.g. yeast infections, thrush, athlete's foot)
 - Parasite (e.g. malaria, Giardia, trypanosomes, worms)
 - Prion (e.g. Crutzfeld-Jakob, Kuru)
- ✿ Infectious diseases are usually opportunistic
 - Malnutrition, alcohol, wound foreign bodies, etc. play a role
- ✿ Largely treatable, but kill tens of millions of people a year internationally.

Molecular Biology of Atherosclerosis

- Eukaryotic cells regularly ingest regions of membrane by *endocytosis*.
- Process happens at specific regions of membrane, *clatherin-coated pits*
 - Receptor-mediated endocytosis preferentially takes up particular external molecules.
 - Cells use this to take up cholesterol, a lipid required for membrane synthesis, from the blood.
- Excess cholesterol is deposited on arteries as plaque.



Causes of Death in the US

– Cardiovascular disease, cancer & trauma

Figure 23. Death rates for leading causes of death among persons 25–44 years of age and over: United States, 1950–99

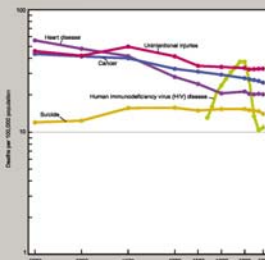
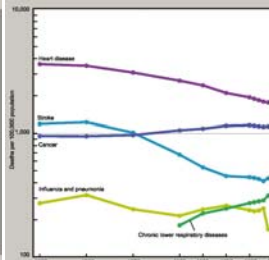


Figure 27. Death rates due to leading causes of death among persons 65 years of age and over: United States, 1950–99



Economics and Disease

- Many risk factors for disease correlate with economic status
 - Malnutrition with poverty
 - Obesity/Inactivity with wealth

