Growth Factors

BIT 230
Walsh Chapter 7
3 Definitions

• **Autocrine**: a mode of hormone action in which a hormone affects the function of the cell type that produced it.

• **Paracrine**: Relating to the release of locally acting substances from endocrine cells.

• **Endocrine**: Producing secretions (especially hormones) that are distributed in the body by way of the bloodstream.
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<th>Target Cell</th>
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<td>Colony stimulating factors</td>
<td>Hemopoietic cells</td>
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<td>Insulin</td>
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<td>PDGF</td>
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Growth Factors

- Important to growing eukaryotic cells
- Can cause growth or inhibition of growth in cells
- Mitogenic effect - promotes cell growth
- Various classes
  - Cytokines: ILs, TGF-β, and CSFs
Good Drug Targets

• Pharma industry look at growth factors as good targets
• promote wound healing, etc. so can be great targets
• problem may be ubiquitous- would effect to a wide range of cells- look for specificity in potential target
Wound Healing

- Big problem in diabetics - unable to heal properly
- following tissue damage, immunological and inflammatory reactions occur
- growth factors secreted
- many types dependent on type of wound
The phases of cutaneous wound healing

Expert Reviews in Molecular Medicine ©2003 Cambridge University Press
Post-wound activation

• Fibroblasts
  – produce collagen and elastin
• Epithelial cells
  – skin cells
• Vascular and endothelial cells
• Important factors: FGFs, TGFs, PDGFs, IGF-1 and EGFs
Types of wounds

- **Acute** - healing quickly on own
- **Chronic** - slow healing; may need medication
- **Ulcers** - chronic; occur if healing process disrupted - diabetes, malnutrition, rheumatoid arthritis, ischemia (poor blood flow to affected area) (Table 7.3, page 279)
Wound site characteristics

- Bioassay or immunoassay of fluid from acute or new wound site high levels of growth factors
- Low levels of mitogens in chronic wounds
- Topical application of mitogens to wounds accelerates healing in animals
- Results mixed in humans (high proteases in chronic wounds - so topical applications causes degradation of mitogens)
Insulin-like Growth Factors (IGFs)

- 2 peptides: IGF-1 and IGF-2
- Look like proinsulin
- Infusion causes decrease in circulating insulin and better glucose uptake
- IGFs can regulate growth, activation and differentiation of cells and tissues
- Synthesized in the liver - go to the bloodstream
IGFs cont’d

• 2 types of IGF cell-surface receptors
• several IGF binding proteins
• IGF-1 on chromosome 12; 2 on chromosome 11 (adjacent to the insulin gene)
• IGF-1 is a 70 aa peptide; IGF-2 is 67 aa
IGFs cont’d

- IGF binding proteins
  - IGF 1000x times higher in serum than insulin
  - bound by IGF binding proteins (IGFBP)
  - prevent hypoglycemia
  - may protect IGF from proteolytic degradation
  - increase IGF plasma half life
IGF biological Effects

- Promote cell cycle progression
- Organogenesis in fetal development
- Longitudinal body growth and increased body weight
- Male and female reproductive tissue function
- Neuronal tissue growth and differentiation
IGF and Cancer

- Can sustain uncontrolled cell growth in cancer
- Transformed cells have high levels IGF receptors
- Growth of these cells slows when add blocking IGF-receptor antibodies - therapeutic target
Other uses for IGF

- Cachexia (wasting disease)
- Type II diabetes (helps cells uptake more glucose)
- Dwarfism (as part of GH-IGF pathway)
- Tissue repair in adults
- Reproductive disorders
- Generation of peripheral nerve damage
Epidermal Growth Factor

EGF

- One of first growth factors identified
- Skin is its major target
- Important in wound healing process
- Synthesized by monocytes, kidney and duodenal cells
- Found in milk
EGF cont’d

- EGF gene located on chromosome 4
- 1208 aa prepro-EGF
- Processing releases a 5 aa, 6kDa peptide
- very stable as mature EGF
- EGF receptor - cell surface (see Figure 7.2, page 286)
EGF cont’d

- Some cancers have shortened (truncated) form of EGF
- Truncation may lead to inability of cell to cease replication
- Too much EGF transfected into cells can induce cancer
- Breast, bladder and squamous cell patients with high EGF receptor shorter life span
EGF Treatment Strategies

- Block EGF tyrosine kinase activity
- PD 153035 - can show regression of tumors
- Others to be developed
Platelet-Derived Growth Factor (PDGF)

- Synthesized by platelets
- Other cell types produce some
- Effect on fibroblasts, smooth muscle cells
- Table 7.7, page 288
- Wound healing process - released by activated platelets at the damage site (chemoattractant for cells that initiate tissue repair)
PGDF cont’d

- Normal skin devoid of PDGF
- may work as a therapy for chronic wounds
- human trials with topical PDGF showed higher healing rates (especially in some diabetic ulcers)
- Regranex - PGDF topic therapy for diabetic ulcers (www.regranex.com - Chiron Corp.)
Fibroblast Growth Factors (FGFs)

- Family of 20 proteins (FGF 1-20)
- 18-28 kDa molecular mass
- Range of responses - mitogenic, chemotactic and angiogenic
- 140 aa highly homologous central core
- Earlier ones work directly on fibroblasts (hence name), several newer members do not
FGFs cont’d

• Tightly bind heparin molecules in the extracellular matrix (ECM- An external lattice of proteins and polysaccharides that is secreted by surrounding cells in most tissues

• Secreted from their producer cells
FGFs cont’d

- Also cell-surface receptor associated
- many biological activities
- Wound repair!
- Heal myocardial tissue in some animal cells (can it work in human m.i. Cases?)
- overexpression of receptors seen in brain cancers
Transforming Growth Factors (TGFs)

• α and β forms
• Bind transmembrane glycoproteins receptors
• TGF-α
  – membrane protein
  – homologous to EGF
  – can bind the EGF receptor
  – produced by many body tissues
TGFs cont’d

- **TGF-β**
  - identified by ability to transform some fibroblast cell lines
  - 3 separate growth factors (high homologous)
  - inhibit the cell cycle (esp. hemopoietic and epithelial cells)
  - stimulate growth of other cells - connective tissue, bone and cartilage
TGFs cont’d

- **TGF-β** involved in
  - tissue remodeling
  - wound repair
  - hemopoiesis

- Make them great ideas for drug targets - for cancer, and leukemia
Neurotrophic Factors

NTs

- Regulate neuron development, maintenance and survival, in both CNS and PNS
- first member: NGF, nerve growth factor
- See Table 7.9, page 294 for types
- Neurotrophins: all belong to the same gene family (e.g., NGF, BNDF, NT-3, NT-4/5 and NT-6)
NTs cont’d

• BNDF - promotes survival of retinal ganglion cells, and other types of neurons

• NTs also interact with cell surface receptors

• receptors found on neuronal tissues only
NTs and Disease

- Death of neurons; in vitro studies show response of neurons to NTs
- Clinical trials in this area disappointing - animal and cells studies don't translate into physiological responses
- Important unmet medical need
NTs and Disease cont’d

- Amyotrophic lateral sclerosis (ALS)
- degeneration of the brainstem and spinal neurons (muscle wasting and death)
- BDNF, IGF-1, CNTF, GDNF, NT-4/5 can improve motor neuron function in vitro and in vivo (animal studies) - testing now in human trials
- IGF-1 in clinical trials by Cephalon (here in PA)
NTs and Disease cont’d

- Alzheimer’s and Parkinson’s
  - death of CNS neurons
  - blood-brain barrier complicates treatment options (can’t deliver drug via intravenous injection)
  - methods to use: direct injection of NT into brain; cranial infusion pumps; transplantation in brain of recombinant encapsulated cells (risky techniques in all cases)
NTs and Disease cont’d

- Conjugating NT to monoclonal antibodies raised against transferrin receptor.
- Transferrin transports iron across BBB
- Factors in vitro and in animals show promise of many NTs in Alzheimer’s Parkinson’s and Huntington’s

- WHAT is key issue with growth factor therapies??