ANAT3231 - Cell Biology Lecture 12

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A Sample Signaling

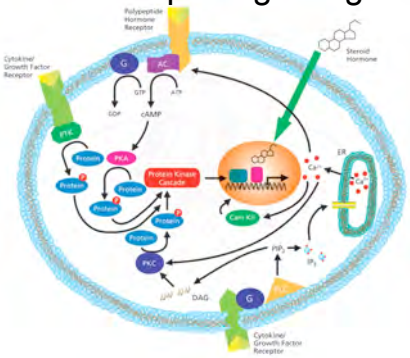


Image: Sigma Signaling

Signaling Text References

- Essential Cell Biology
  - Chapter 15
- Molecular Biology of the Cell
  - Chapter 15
- Molecular Cell Biology
  - Chapter 20
- Nature Signaling Gateway
  - http://www.signaling-gateway.org/molecule/

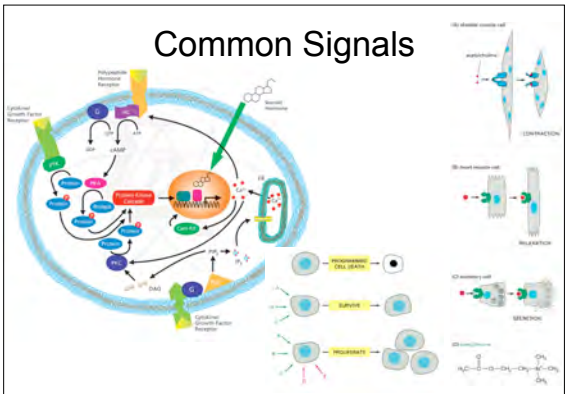
ANAT3231 Lecture 12 Signaling
–http://cellbiology.med.unsw.edu.au/units/science/lecture0512.htm

Lecture Summary

- Continuation of Lecture 11 Signaling
- Specific examples of signaling
  - Pathways
  - Mechanisms
    - Note steroid and lipid signaling covered last week

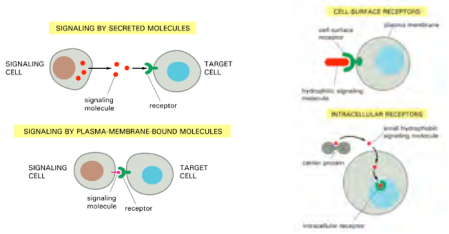
Images: MBoC and Sigma Signaling

Common Signals



Images: MBoC and Sigma Signaling

Signals and Receptors



Images: MBoC

Signaling between Tissues

- Regulation of cells and tissues
- Hormones
  - secreted by one tissue to regulate function of other cells or tissues
- Chemical Signal Types
  - water soluble
  - lipid soluble

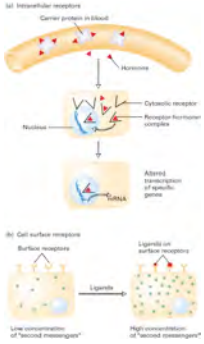


Image: Mol Cell Biol. Figure 20-2

Extracellular Signal Steps

- Signaling Molecule
  - Synthesis
  - Release by signaling cell
  - Transport to target cell
  - Detection by a specific receptor protein
- Change by receptor-signal complex (trigger)
  - Metabolism
  - Function
  - development
- Removal of the signal
  - often terminates cellular response

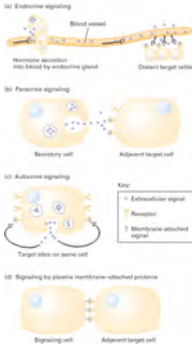
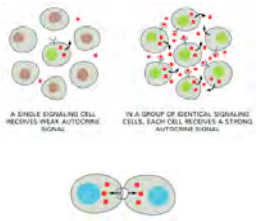


Image: Mol Cell Biol.

Messenger /Receptor Interaction

- Binding of messenger (ligand) has to lead to a change in the receptor
  - like enzyme and substrate
  - Specific recognition
  - Receptor affinity
- activation
- signal transduction
  - Signal cascade
  - Secondary messengers

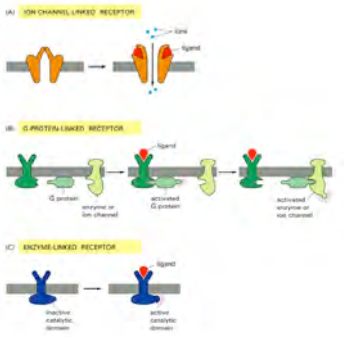


Images: MBoC

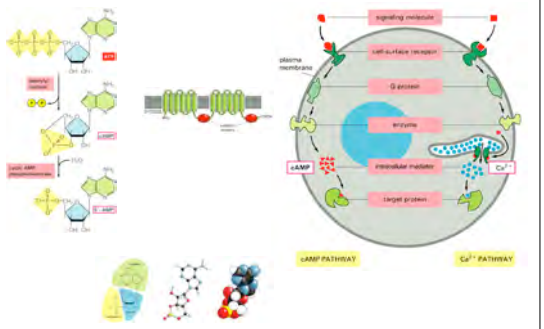
Chemical Signals

- Water Soluble
  - bind to surface receptors
- Lipid Soluble
  - bind to cytoplasmic or nuclear receptors
  - steroid hormones
    - Covered in Lecture 11

Receptor Pathways



Second Messengers



Images: MBoC

Second Messengers

- Cyclic nucleotides
  - cAMP, cGMP
- Calcium Ions
- Protein Kinase A
  - PKA, B, C
- diacylglycerol (DAG)
  - modified lipid activates PKC
- Kinase cascades
- small GTP binding proteins
  - related to RAS which is G protein family

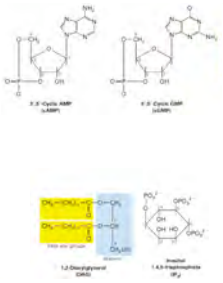
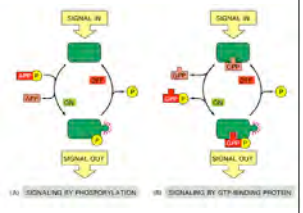


Image: Mol Cell Biol. Figure 20-4

Membrane Receptors

- embedded in plasma membrane
- ligand binding
  - leads to conformational change in receptor
  - activation of intracellular pathway
- G Protein Linked receptors



Cell Surface Receptor Types

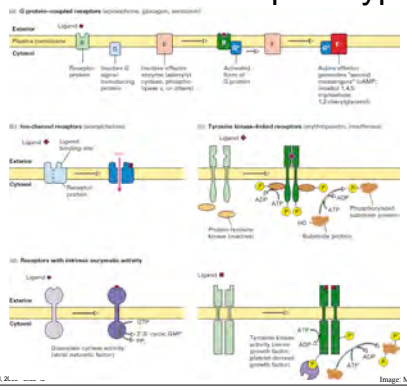
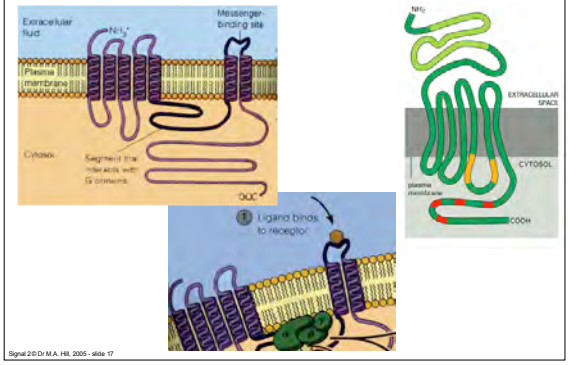


Image: Mol Cell Biol. Figure 20-3

G Protein Receptors



G Protein-Coupled Signal Pathways

- Transmembrane proteins transduce extracellular signals
  - common structural motif of 7 membrane spanning regions
- Receptor binding promotes interaction
  - between receptor
  - G protein on interior surface of membrane

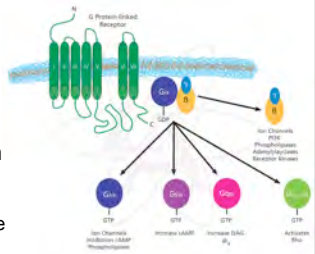


Image and modified text: Sigma Signaling

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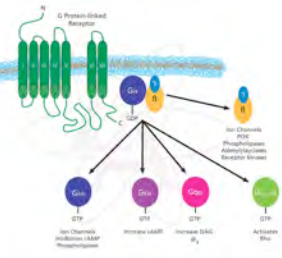
G Protein-Coupled Signal Pathways

- induces an exchange of GDP for GTP on G protein α subunit and dissociation of the α subunit from the βγ heterodimer
- Depending on isoform, GTP-α subunit complex mediates intracellular signaling either
  - **indirectly** by acting on effector molecules
    - adenylyl cyclase (AC)
    - phospholipase C (PLC)
  - **directly** by regulating ion channel or kinase function



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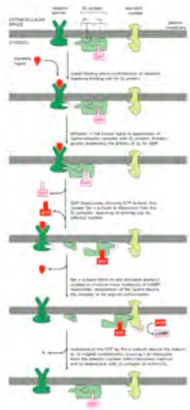
G Protein Linked



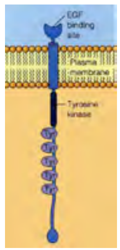
Growth Factors

Factor	Principal Source	Primary Activity	Comments
PDGF	platelets, endothelial cells, placenta	promotes proliferation of connective tissue, glial and smooth muscle cells	two different protein chains form 3 distinct dimer forms; AA, AB and BB
EGF	submaxillary gland, Brunners gland	promotes proliferation of mesenchymal, glial and epithelial cells	
TGF-α	common in transformed cells	may be important for normal wound healing	related to EGF
FGF	wide range of cells; protein is associated with the ECM	promotes proliferation of many cells; inhibits some stem cells; induces mesoderm to form in early embryos	at least 19 family members, 4 distinct receptors
NGF		promotes neurite outgrowth and neural cell survival	several related proteins first identified as proto-oncogenes; trkA (trackA), trkB, trkC
Erythropoietin	kidney	promotes proliferation and differentiation of erythrocytes	
TGF-β	activated T_H1 cells (T-helper) and natural killer (NK) cells	anti-inflammatory (suppresses cytokine production and class II MHC expression), promotes wound healing, inhibits macrophage and lymphocyte proliferation	at least 100 different family members
IGF-I	primarily liver	promotes proliferation of many cell types	related to IGF-II and proinsulin, also called Somatomedin C
IGF-II	variety of cells	promotes proliferation of many cell types primarily of fetal origin	related to IGF-I and proinsulin

Source: http://web.indstate.edu/thcme/mwking/growth-factors.html

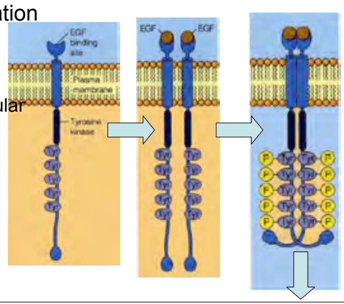
Receptor associated with Kinase

- Many growth factors use this pathway
  - Vascular Endothelial Growth Factor
  - Epidermal Growth Factor
  - Nerve Growth Factor
  - Bone Morphogenic Protein
  - Transforming Growth Factor-beta



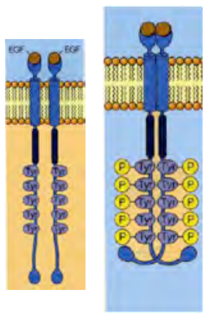
Receptor Kinase Pathway

- Ligand binding
- Receptor association
- Phosphorylation
- Kinase cascade
  - Multiple intracellular tagets



Proto-oncogenes

- proto-oncogenes
  - Normal cell proteins that have potential to cause uncontrolled growth when mutated
- loss of receptor regulation
- cells grow out of control
- mutation in TK Receptor
  - receptor always activated
- mutation of activating protein
  - always active
- Oncogenes
  - Ras
  - mutants detected in 30% cervical cancers



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Fibroblast Growth Factors

- 19 FGF family of growth factors
- 2 originally characterized FGFs were identified by biological assay
  - FGF1 (acidic-FGF, aFGF)
  - FGF2 (basic-FGF, bFGF)

FGF Receptors

- family of related tyrosine kinase receptors
  - FGFR1, FGFR2, FGFR3, FGFR4
- Protein structure
  - 3 extracellular immunoglobulin-like domains
  - 1 membrane spanning segment
  - cytoplasmic tyrosine kinase domain

FGF Receptors

- transmembrane receptors with tyrosine kinase activity
  - Like EGF and PDGF receptors
  - immediate response to FGF binding is receptor autophosphorylation
  - Following activation numerous signal-transducing proteins associate with receptor and become tyrosine-phosphorylated
  - Example: expressed in developing bone
    - autosomal dominant disorders of bone growth result from mutations in FGFR genes
    - FGFR3 (mutant in achondroplasia)

Nerve Growth Factor

- polypeptide involved in regulation of growth and differentiation of sympathetic and certain sensory neurons
  - Levi-Montalcini, R. The nerve growth factor thirty-five years later. *Science* 237: 1154-1162, 1987

Nerve Growth Factor Receptor

- p75 (NTR)
  - molecular mass and ability to bind at low affinity not only NGF but also other neurotrophins
    - brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NTF3), and neurotrophin-4/5 (NTF5)
- tumor necrosis factor receptors share overall structure of NGFR
  - 4 extracellular ligand-binding, cysteine-rich repeats (CRs), and signaling through association with, or disassociation from, cytoplasmic interactors
- Associated with nuclear factor kappa-B (NFKB) and apoptosis pathways

Nerve Growth Factor Receptor

- Low affinity
  - monomer NGFR binds NGF
- High affinity binding
  - by association with low-affinity neurotrophin receptors (tropomyosin receptor kinases- TRK)
    - TRKA (NTRK1), TRKB (NTRK2), and TRKC (NTRK3)
  - Specificity
    - TRKA - NGF
    - TRKB - NTF5 and BDNF
    - TRKC - NTF3
      - NTF3 also binds to TRKA and TRKB with significantly lower affinity

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TrkA Receptor

- Trk proto-oncogenes
  - TrkA, TrkB, TrkC, TrkE
- variably expressed in CNS and PNS
- TrkA binds to nerve growth factor (NGF) and autophosphorylates
  - leading to activation of multiple downstream effector proteins

Image: Sigma Signaling

VEGF Receptor and Ligands

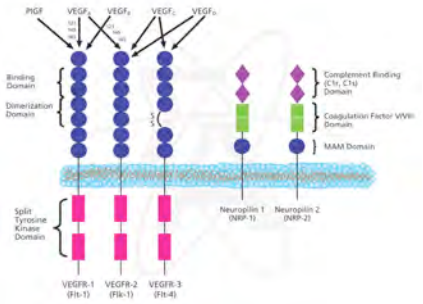


Image: Sigma Signaling

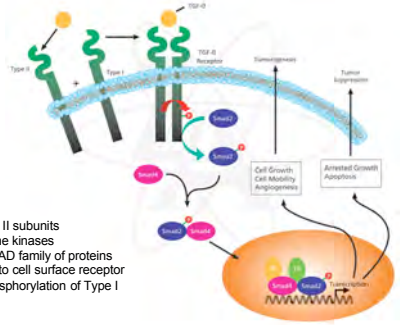
EGF Receptor Transduction Pathway

EGF = Epidermal Growth Factor
Image: Sigma Signaling

Transforming Growth Factors

- are a family of biologically active polypeptides that reversibly confer transformed phenotype on cultured cells
  - TGFA (alpha)
    - shows homology (40%) with epidermal growth factor (EGF) and competes with EGF for binding to the EGF receptor stimulating its phosphorylation and producing a mitogenic response
  - TGFB (beta)
    - acts synergistically with TGFA in inducing transformation

Signaling Pathway of TGF-β



TGF-β receptor

- include Type I and II subunits
- are serine-threonine kinases
- signal through SMAD family of proteins
- binding of TGF-β) to cell surface receptor Type II leads to phosphorylation of Type I receptor by Type II.

TGF-β = transforming growth factor ß
Image: Sigma Signaling

Transforming Growth Factor- beta

- Transforming growth factors (TGFs) are biologically active polypeptides that reversibly confer the transformed phenotype on cultured cells
  - Many cells synthesize TGFB and also have specific receptors for this peptide
- Function
  - controls proliferation, differentiation, and other functions in many cell types
  - TGFB acts synergistically with TGFA in inducing transformation
  - acts as a negative autocrine growth factor
  - Dysregulation of TGFB activation and signaling may result in apoptosis
  - TGFB1, TGFB2 and TGFB3 all function through same receptor signaling systems

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Insulin-like Growth Factors

- Insulin-like growth factors I and II
  - also known as somatomedin C and A
  - polypeptides which share an amino acid sequence homology with insulin (47%) and relaxin (31%) insulin family of polypeptide growth factors.
- Functions
  - mediation of growth hormone action, stimulation of growth of cultured cells, stimulation of insulin action, and involvement in development and growth
  - autocrine regulators of cell proliferation

Erythropoietin

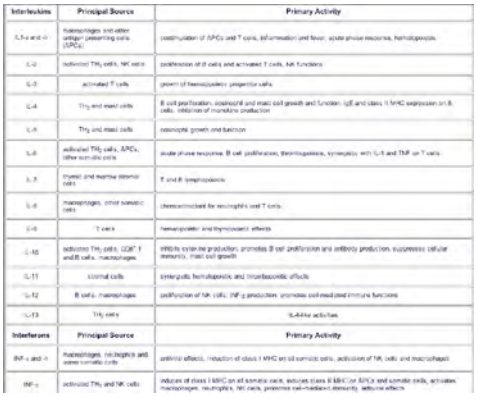
- Main regulator of red cell production
  - synthesized and released by the kidney
  - circulates to the bone marrow where it stimulates resident erythroid progenitors via a specific receptor
- acidic glycoprotein hormone (Mr 34 kD)
- Receptor
  - Related to cytokine receptors
  - protein phosphorylation an early component of transmembrane signaling

Cytokines

- Secreted by leukocytes
  - stimulate humoral and cellular immune responses
  - activation of phagocytic cells
    - lymphokines secreted by lymphocytes
    - monokines secreted by monocytes or macrophages
- produced by other cells of the body
- lymphokines also known as interleukins (ILs)
  - not only secreted by leukocytes also able to affect cellular responses of leukocytes

Interleukins

- growth factors targeted to cells of hematopoietic origin
- now 22 identified interleukins
  - Number still growing with individual activities



Interleukins	Principal Source	Primary Activity
IL-1α and -β	Macrophages and other antigen presenting cells (APCs)	costimulation of APCs and T cells, inflammation and fever, acute phase response, hematopoiesis
IL-2	activated TH_1 cells, NK cells	proliferation of B cells and activated T cells, NK functions
IL-3	activated T cells	growth of hematopoietic progenitor cells
IL-4	TH_2 and mast cells	B cell proliferation, isotype/IgE and mast cell growth and function, IgE and class II MHC expression on B cells, inhibition of monokine production
IL-5	TH_2 and mast cells	eosinophil growth and function
IL-6	activated TH_2 cells, APCs, other somatic cells	acute phase response, B cell proliferation, thrombopoiesis, synergistic with IL-3 and TNF on T cells
IL-7	thymic and marrow stromal cells	T and B lymphopoiesis
IL-8	macrophages, other somatic cells	chemoattractant for neutrophils and T cells
IL-9	T cells	hematopoietic and thymocytic effects
IL-10	activated TH_2 cells, CD8+ T and B cells, macrophages	inhibits cytokine production, promotes B cell proliferation and antibody production, suppresses cellular immunity, mast cell growth
IL-11	stromal cells	synergistic hematopoietic and thrombocytic effects
IL-12	B cells, macrophages	proliferation of NK cells, INF-γ production, promotes cell-mediated immune functions
IL-13	TH_2 cells	IL-4-like activities
Interferons	**Principal Source**	**Primary Activity**
INF-α and -β	macrophages, neutrophils and some somatic cells	antiviral effects, induction of class I MHC on all somatic cells, activation of NK cells and macrophages
INF-γ	activated TH_1 and NK cells	induces of class I MHC on all somatic cells, induces class II MHC on APCs and somatic cells, activates macrophages, neutrophils, NK cells, promotes cell-mediated immunity, antiviral effects

http://web.indstate.edu/thcme/mwking/growth-factors.html

Online References

- ANAT3231 Lectures
  - http://cellbiology.med.unsw.edu.au/units/science/lectures.htm
- Molecular Biology of the Cell (Ch15)
  - http://www.ncbi.nlm.nih.gov:80/books/bv.fcgi?call=bv.View..ShowSection&rid=cell.section.3834
- Developmental Biology (Ch6)
  - http://www.ncbi.nlm.nih.gov:80/books/bv.fcgi?call=bv.View..ShowSection&rid=.TWQLjiW2xLXyWUOVemh0sDWJf2YbG1QHJC-
- Molecular Cell Biology (Ch20)
  - http://www.ncbi.nlm.nih.gov:80/books/bv.fcgi?call=bv.View..ShowSection&rid=mcb.chapter.5687
- The Cell- A molecular approach (Ch13)
  - http://www.ncbi.nlm.nih.gov:80/books/bv.fcgi?tool=bookshelf&call=bv.View..ShowSection&searchterm=cell&rid=cooper.chapter.2198
- Sigma Apoptosis Brochure
  - http://www.sigmaaldrich.com/Area_of_Interest/Life_Science/Cell_Signaling.html
- Growth factors
  - http://web.indstate.edu/thcme/mwking/growth-factors.html

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Legend

* Site has data (figures, images or movies)
# Site has protocols
Main Organism(s) of Study:
B = bacterial sp.
C = Caenorhabditis elegans
Di = Dicytostelium discoideum
Dr = Drosophila melanogaster
E = echinoderm sp.
H = Homo sapiens
I = intracellular pathogens, e.g. Listeria, Shigella
M = mouse
MI = misc. invertebrate sp., e.g. Aplysia, Ascaris
MV = misc. verlebrate sp., e.g. fish, newt, chick, rabbit, rat, dog, aardvark
P = plant sp.
U = unicellular eukaryotic Acanthamoeba, Chlamydomonas
X = Xenopus laevis and tropicalis
Y = yeast sp.
Z = no one species in particular

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Reference: Molecular Biology of Cell

- III. Internal Organization of the Cell
  - 15. Cell Signaling
    - Introduction
    - General Principles of Cell Signaling
    - Signaling via G-Protein-linked Cell-Surface Receptors
    - Signaling via Enzyme-linked Cell-Surface Receptors
    - Target-Cell Adaptation
    - The Logic of Intracellular Signaling: Lessons from Computer-based "Neural Networks"
    - References

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Reference: Molecular Cell Biology

- 20. Cell-to-Cell Signaling: Hormones and Receptors
  - 20.1 Overview of Extracellular Signaling
  - 20.2 Identification and Purification of Cell-Surface Receptors
  - 20.3 G Protein –Coupled Receptors and Their Effectors
  - 20.4 Receptor Tyrosine Kinases and Ras
  - 20.5 MAP Kinase Pathways
  - 20.6 Second Messengers
  - 20.7 Interaction and Regulation of Signaling Pathways
  - 20.8 From Plasma Membrane to Nucleus
  - PERSPECTIVES
    - Future
    - Literature

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Reference: The Cell

- IV. Cell Regulation
  - 13. Cell Signaling
    - Signaling Molecules and Their Receptors
    - Functions of Cell Surface Receptors
    - Pathways of Intracellular Signal Transduction
    - Signal Transduction and the Cytoskeleton
    - Signaling in Development and Differentiation
    - Regulation of Programmed Cell Death
    - Summary
    - Questions
    - References and Further Reading

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Reference: Developmental Biology

- Part 1. Principles of development in biology
  - 6. Cell-cell communication in development
    - Induction and Competence
    - Paracrine Factors
    - Cell Surface Receptors and Their Signal Transduction Pathways
    - The Cell Death Pathways
    - Juxtacrine Signaling
    - Cross-Talk between Pathways
    - Coda
    - Principles of Development:Cell-Cell Communication
    - References

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