GROWTH FACTORS AND DEVELOPMENT

LLOYD GREENE

DEPARTMENT OF PATHOLOGY

February 3, 2004

PROLIFERATION

DIFFERENTIATION

MIGRATION/PATHFINDING

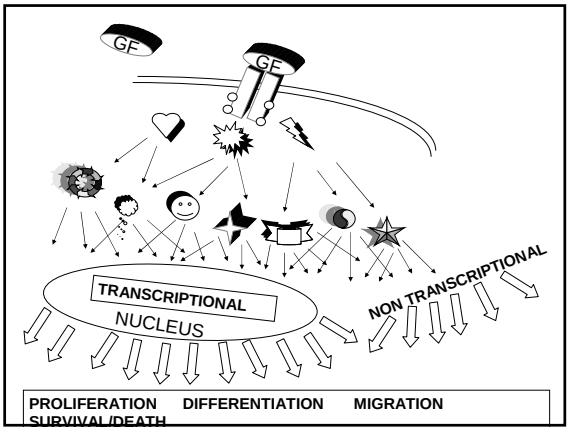
SURVIVAL AND DEATH

WHAT ARE GROWTH FACTORS?

FOR THE PURPOSES OF THIS LECTURE, WE WILL DEFINE GROWTH FACTORS AS PROTEINS THAT REACH CELLS EXTRACELLULARLY AND THAT CAUSE INTRACELLULAR CHANGES BY A TRANSDUCTION MECHANISM DEPENDEN ON TRANSMEMBRANE RECEPTORS

HOW DO GROWTH FACTORS ACT?

GROWTH FACTORS ACT THROUGH TRANSMEMBRANE RECEPTORS. THE LATTER TRANSDUCE EXTRACELLULA GROWTH FACTOR BINDING BY ACTIVATING INTRACELLUL SIGNALLING CASCADES THAT INDUCE BOTH NON-TRANSCRIPTIONAL AND TRANSCRIPTIONAL RESPON



HOW MANY GROWTH FACTORS ARE THERE?

- THERE ARE MULTIPLE SUPERFAMILIES OF GROWTH FAC COMPRISING ON THE ORDER OF SEVERAL HUNDRED DIFFE GENES

EXAMPLES OF "CLASSICAL" GROWTH FACTORS

EGF - EPIDERMAL GROWTH FACTOR

FGF - FIBROBLAST GROWTH FACTOR

NGF - NERVE GROWTH FACTOR

TGFβ - TRANSFORMING GROWTH FACTOR BETA

INSULIN & IGF'S (INSULIN-LIKE GROWTH FACTORS)

PDGF- PLATELET DERIVED GROWTH FACTOR

FGF SUPERFAMILY

22 FAMILY MEMBERS (FGF1-22) 13-71% IDENTITY

4 RECEPTORS

TGFβ SUPER FAMILY

- >35 MEMBERS
- 12 KNOWN RECEPTORS

TGFβ FAMILY (3)

BONE MORPHOGENIC PROTEINS (BMPS) (15)

GROWTH DIFFERENTIATION FACTORS (GDF) (6)

GLIAL DERIVED NEUROTROPHIC FACTORS (GDNF) (4)

ACTIVINS (4)

LEFTYS (2)

NODAL

INHIBINS

MÜLLERIAN INHIBITING SUBSTANCE

EXAMPLES OF ADDITIONAL GROWTH FACTOR FAMILIES WITH ROLES IN DEVELOPMENT

HEDGEHOG PROTEINS

WNT'S

INTERLEUKINS

SLIT'S

NETRINS

EPHRINS

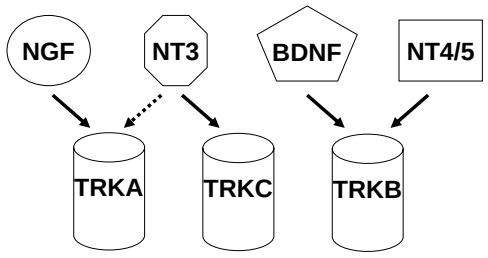
TUMOR NECROSIS α FAMILY (TNFα'S)

HOW MANY GROWTH FACTOR RECEPTORS ARE THERE AND WHAT IS THEIR DEGREE OF SPECIFIC

- THERE ARE MULTIPLE GROWTH FACTOR RECEPTORS. T ARE HIGHLY SPECIFIC BETWEEN GF FAMILIES AND EXHIBI VARIOUS DEGREES OF SPECIFICITY WITHIN GF FAMILIES (' IS, IN SOME CASES RECEPTORS ARE SHARED, IN OTHERS

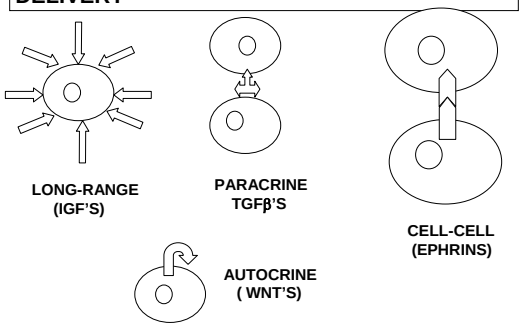
GROWTH FACTOR RECEPTOR GENES APPEAR TO NUMBE IN THE HUNDREDS IN VERTEBRATES

SPECIFICITY OF NEUROTROPHIN FAMILY RECEPTOR BIND



HOW DO GROWTH FACTORS REACH THEIR TARGET CELLS?

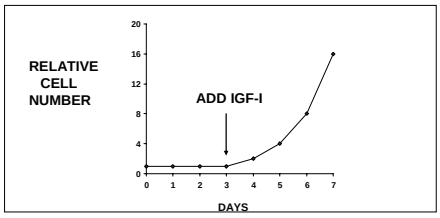
MULTIPLE MODES OF GROWTH FACTOR DELIVERY



GROWTH FACTORS AS REGULTORS OF PROLIFERATION

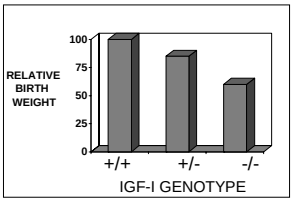
GROWTH FACTORS CAN PROMOTE CELL PROLIFERATIO

- A GOOD EXAMPLE INCLUDES MEMBERS OF THE INSULIN/INSULIN-LIKE GROWTH FACTOR (IGF) FAMILY
- 9 FAMILY MEMBERS WITH 3 RECEPTORS
- MAJOR MEMBERS INCLUDE INSULIN, IGF-I, IGF-II



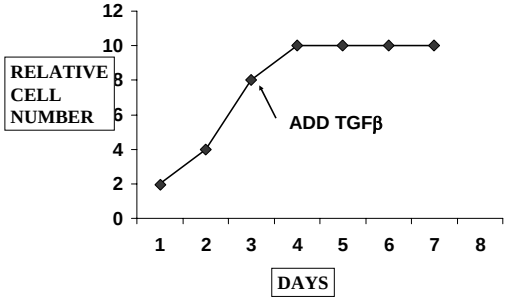
WHAT ARE THE CONSEQUENCES OF MISSING IGF'S OR INSULIN EXPRESSION DURING EMBRYOGENESIS?

IGF-I, IGF-II: GENERAL GROWTH DEFICIENCY (MUSCLE, BONE, ORGANS)



INSULIN - LEPRECHAUNISM

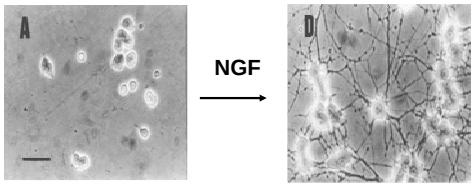
GROWTH FACTORS CAN INHIBIT CELL PROLIFERATION



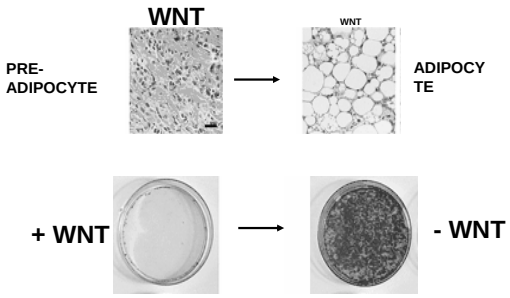
GROWTH FACTORS REGULATE CELL DIFFERENTIATION

- GROWTH FACTORS EXERT BOTH POSITIVE AN NEGATIVE EFFECTS ON CELL DIFFERENTIATI

NGF PROMOTES NEURONAL DIFFERENTIATION



WNT'S CAN ACT AS NEGATIVE REGULATOR OF DIFFERENTIATION

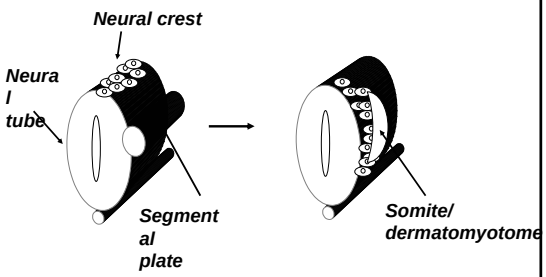


From: Ross et al., *Science* 2000, **289**:950-953

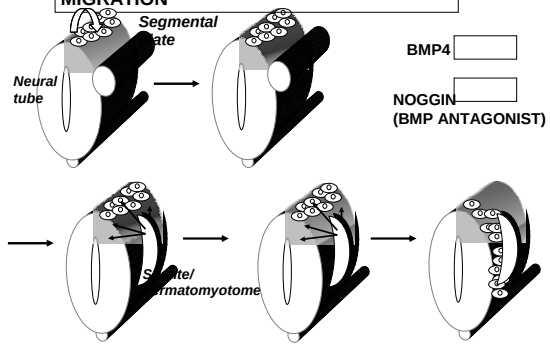
GROWTH FACTORS AS REGULATORS OF CELL MIGRATION AND MOVEMENT

- EXAMPLE OF NEURAL CREST

REGULATION OF NEURAL CREST MIGRATION



REGULATION OF NEURAL CREST MIGRATION

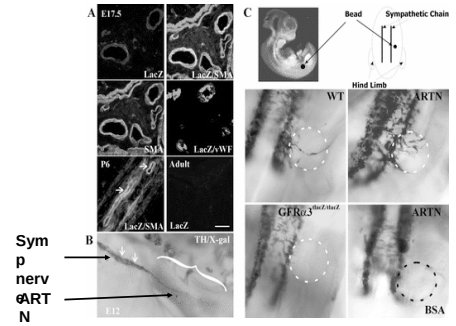


After Sela-Donenfeld and Kalcheim 2000 Development 127: 4845-4854

GROWTH FACTORS AS REGULATORS OF CELL MIGRATION AND MOVEMENT

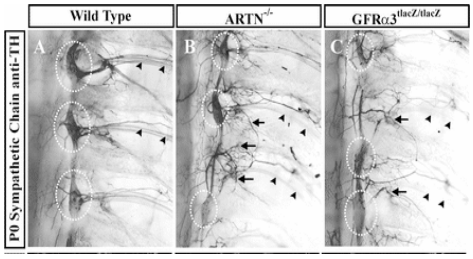
- EXAMPLE OF NEURAL CREST
  - REGULATION OF CELL MIGRATION
  - MODULATION OF GROWTH FACTOR ACTIVITY BY NATURALLY OCCURRING ANTAGONISTS
  - GROWTH FACTOR MODULATION OF ANTAGONIST EXPRESSION
- GROWTH FACTORS CAN ACT AS TROPIC GUIDANCE MOLECULES FOR NEURONAL PATHFINDING

ARTEMIN (TGFβ SUPERFAMILY) IS A TROPIC/GUIDANCE FA FOR DEVELOPING SYMPATHETIC NEURONS



From: Honma et al., 2002 Neuron 35:267-282

ARTEMIN (TGFb SUPERFAMILY) IS A TROPIC/GUIDANCE FA FOR DEVELOPING SYMPATHETIC NEURONS - 2

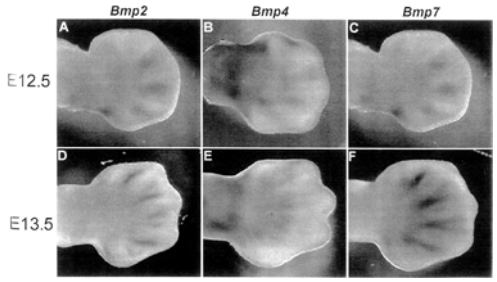


From: Honma et al., 2002 Neuron 35:267-282

GROWTH FACTORS AS REGULATORS OF CELL SURVIVAL AND DEATH

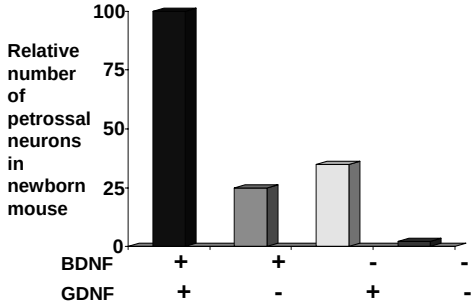
- GROWTH FACTORS CAN PROMOTE EITHER CELL SURVIVAL OR DEATH
- GROWTH FACTORS CAN ACT COORDINATELY

CELL DEATH AND FORMATION OF DIGITS 2



FROM: Chen and Zhao, J. Exp. Zool. 282:691 (1998).

MOUSE PETROSSAL NEURONS REQUIRE BOTH BDNF AND GDNF FOR SURVIVAL



After: Erickson et al., 2001 JNeurosci. 21:581-9.

THE SAME GROWTH FACTOR CAN HAVE MULTIPL ACTIONS DURING DEVELOPMENT

- DIFFERENT ACTIONS ON VARYING CELL TYPES DIFFERENT TIMES OF DEVELOPMENT
- THE SAME GROWTH FACTOR CAN AFFECT CEL PROLIFERATION, DIFFERENTIATION, SURVIVAL/DEATH AND MIGRATION

MULTIPLE DEVELOPMENTAL FUNCTIONS OF WNT FAMILY MEMBERS

Developmental functions of mouse *Wnt* genes

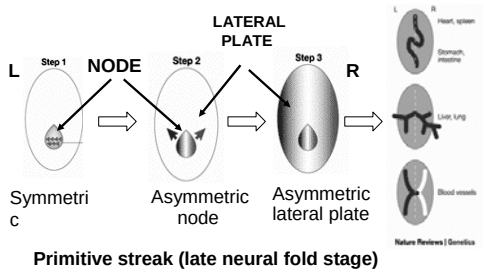
Gene	Phenotype of knockout or other functions
Wnt1	Loss of a portion of the midbrain and cerebellum
	Deficiency in dorsal neural-tube derivatives, including neural-crest cells in double knockout with *Wnt3a*
Wnt2	Placental defects
Wnt3	Defects in axis formation and gastrulation
	Defects in hair growth and structure
Wnt3a	Defects in somite and tailbud development
	Deficiency in dorsal neural-tube derivatives, including neural crest cells in double knockout with *Wnt1*
	Loss of hippocampus
Wnt4	Defects in kidney development
	Defects in female development; absence of Müllerian duct, ectopic synthesis of testosterone in females
	Defects in mammary gland morphogenesis
Wnt5a	Truncated limbs, shortened anterior-posterior axis, reduced number of proliferating cells
Wnt7a	Defects in limb polarity
	Female infertility due to failure of Müllerian duct regression
	Defects in uterine patterning
	Defects in synapse maturation in the cerebellum
Wnt7b	Placental defects
Wnt10b	Inhibition of adipogenesis

AFTER: JR Miller *Genome Biology* 2001 3(1):3001.1-3001.15

GROWTH FACTORS REGULATE MORPHOGENESIS BY INTEGRATED FEEDBACK MECHANISMS

- GENERATION OF LEFT-RIGHT ASYMMETRY

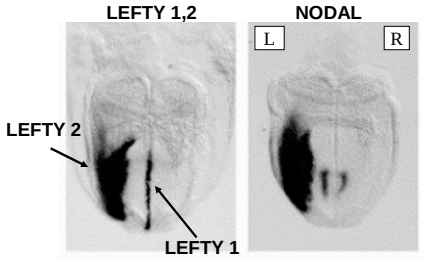
GF's AND GENERATION OF RIGHT-LEFT ASYMMET



Primitive streak (late neural fold stage)

After: Hamada et al., Nature Reviews Genetics 2002 3: 102-113

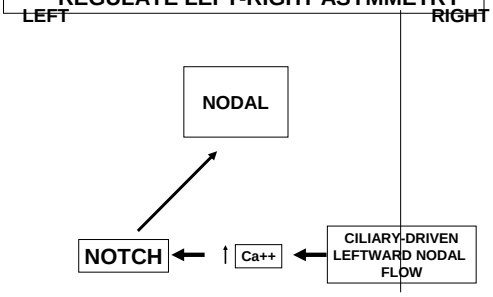
TGFb FAMILY MEMBERS LEFTY AND NODAL REGULATE LEFT-RIGHT ASYMMETRY



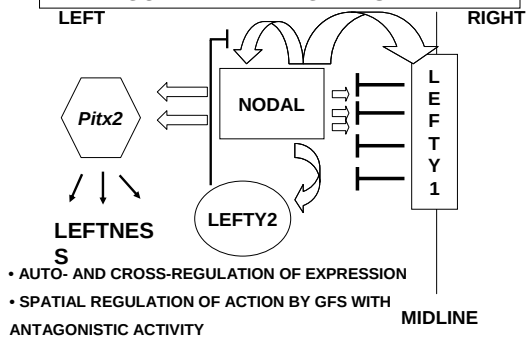
LATERAL PLATE MESODERM

After: Hamada et al., Nature Reviews Genetics 2002 3: 102-113

NODAL AND NODAL ANTAGONISTS LEFTY1/2 REGULATE LEFT-RIGHT ASYMMETRY



NODAL AND NODAL ANTAGONISTS LEFTY1/2 REGULATE LEFT-RIGHT ASYMMETRY

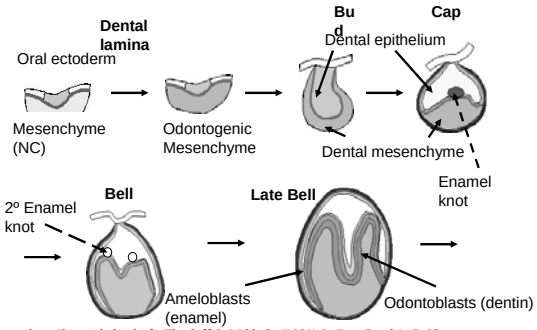


- AUTO- AND CROSS-REGULATION OF EXPRESSION
- SPATIAL REGULATION OF ACTION BY GFS WITH ANTAGONISTIC ACTIVITY

GROWTH FACTORS REGULATE MORPHOGENESIS BY INTEGRATED FEEDBACK MECHANISMS

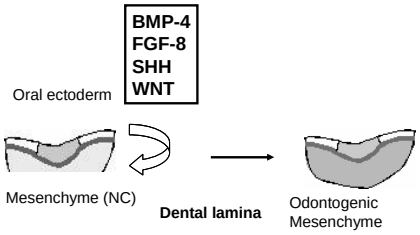
- GENERATION OF ASYMMETRY
- INITIATION OF TOOTH DEVELOPMENT

EARLY TOOTH DEVELOPMENT



From: http://bite-it.helsinki.fi; Thesleff & Mikkola (2002) In Rev Cytol 217: 93-135

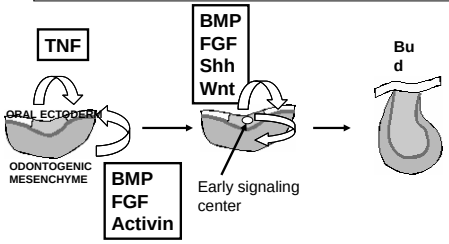
INITIATION OF EARLY TOOTH DEVELOPMENT



- Epithelial-Mesenchymal inductive interactions mediated by growth factors
- Actions mediated by multiple growth factor types of different families

From: http://bite-it.helsinki.fi; Thesleff & Mikkola (2002) In Rev Cytol 217: 93-135\

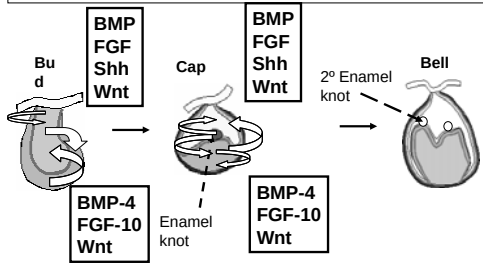
GROWTH FACTORS IN EARLY TOOTH DEVELOPMENT



- Sequential actions of growth factors
- Reciprocal actions of growth factors
- Formation of signaling centers with localized synthesis of growth factors

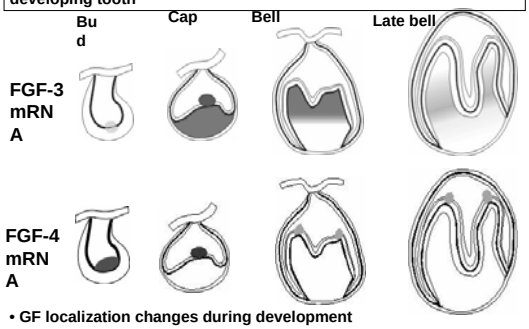
From: http://bite-it.helsinki.fi; Thesleff & Mikkola (2002) In Rev Cytol 217: 93-135

GROWTH FACTORS AND EARLY TOOTH CYTODIFFERENTIATION



- Reiterative use of growth factors
- Growth factor actions on proliferation, differentiation, morphogenesis

Comparison of FGF-3 and FGF-4 mRNA localization in developing tooth



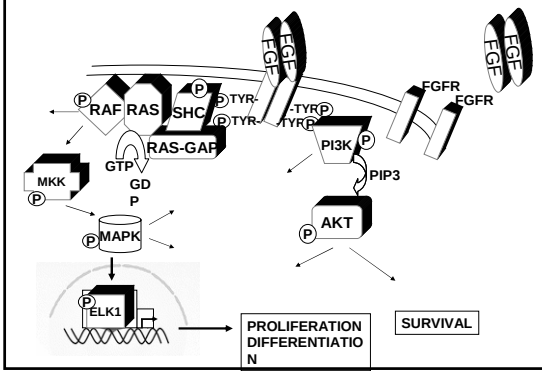
- GF localization changes during development
- Differential localization of different GFs

From: http://bite-it.helsinki.fi

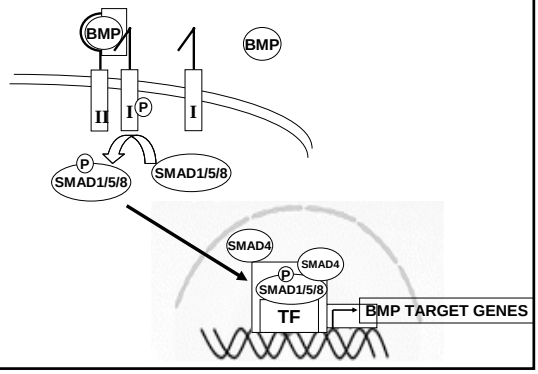
HOW DO GROWTH FACTORS SIGNAL?

- FGF - RECEPTOR TYROSINE KINASE SIGNALING
- BMP - SER/THR KINASE - SMAD SIGNALING
- WNT - INACTIVATION SIGNALING

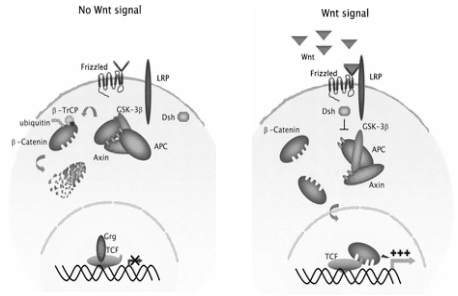
GROWTH FACTOR SIGNALING - FGF



GROWTH FACTOR SIGNALING - BMP'S



GROWTH FACTOR SIGNALING - WNT'S



From: van de Wetering et al., 2002 Cell 109: S13-S19.

BMP-5 (*short ear*)1 Viable; skeletal and cartilage abnormalities; role in allantois development and fusion with the chorion along with BMP-7

BMP-6 Viable; slight delay in ossification of sternum; role in cardiac cushion formation and septation along with BMP-7

BMP-7 Perinatal lethal; kidney dysgenesis and anophthalmia; skeletal patterning defects; role in cardiac cushion formation and septation along with BMP-6; role in allantois development and fusion with the

TGF-ß2 Perinatal lethal; various craniofacial defects, axial and appendicular skeletal defects; retinal hyperplasia; heart defects; renal defects in a majority of females 169

TGF-ß3 Perinatal lethal; cleft palate; delayed lung development

Endocr Rev 2002 Dec 1;23(6):787-823 Related Articles, Links

Genetic Analysis of the Mammalian Transforming Growth Factor-beta Superfamily.
Chang H, Brown CW, Matzuk MM.

THERE ARE MULTIPLE SUPERFAMILIES OF GROWTH FACTO

THERE ARE MULTIPLE GROWTH FACTOR RECEPTORS WITH VARIOUS DEGREES OF SPECIFICITY

GF RECEPTORS TRANSDUCE EXTRACELLULAR GROWTH FAC BINDING BY ACTIVATING INTRACELLULAR SIGNALLING CASCADES THAT INDUCE BOTH NON-TRANSCRIPTIONAL ANI TRANSCRIPTIONAL RESPONSES

GF'S ARE REQUIRED FOR BOTH SPECIFIC AND OVERALL GR DURING DEVELOPMENT

GROWTH FACTORS CAN EXERT BOTH POSITIVE AND NEGA EFFECTS ON CELL DIFFERNTIATION, SURVIVAL, MIGRATIO PROLIFERATION

GFS GUIDE REGULATE CELL MIGRATION AND SERVE AS TROPIC GUIDANCE MOLECULES FOR NEURONAL PATHFIN

IN SOME CASES (I.E. BMPS) ANTAGONISTS PLAY AN IMPORTANT ROLE IN REGULATING DEVELOPMENT

GF'S REGULATE BOTH CELL SURVIVAL AND DEATH