Cell death or survival:
->Interactions between signaling pathways
-> Survival factors: classical and alternative pathways

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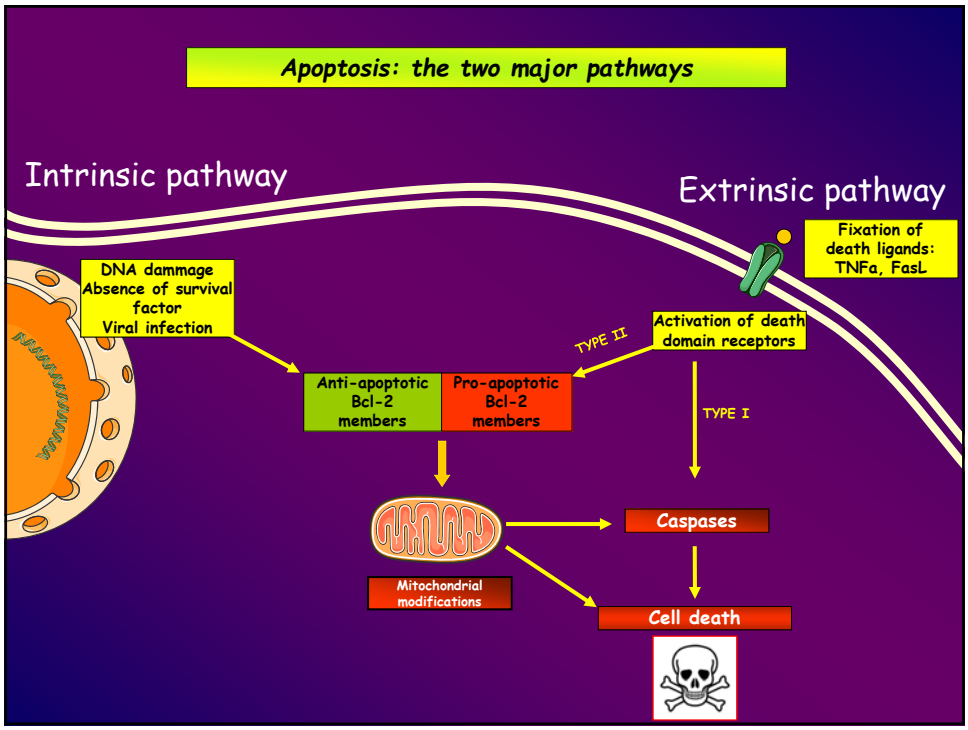
Apoptosis: the two major pathways



The BCL-2 family: regulation of apoptosis

Anti-apoptotic members

BCL-2
BCL-X_L
BCL-W
MCL-1
A1/Bfl1

BH4 BH3 BH1 BH2 TM

Bcl-2-like Survival Factors

Pro-apoptotic members

BAX
BAK
BOK/Mtd

BH3 BH1 BH2 TM

Bax-like Death Factors

BIK
HRK
BIM
BAD, BID
PUMA
BMF
NOXA

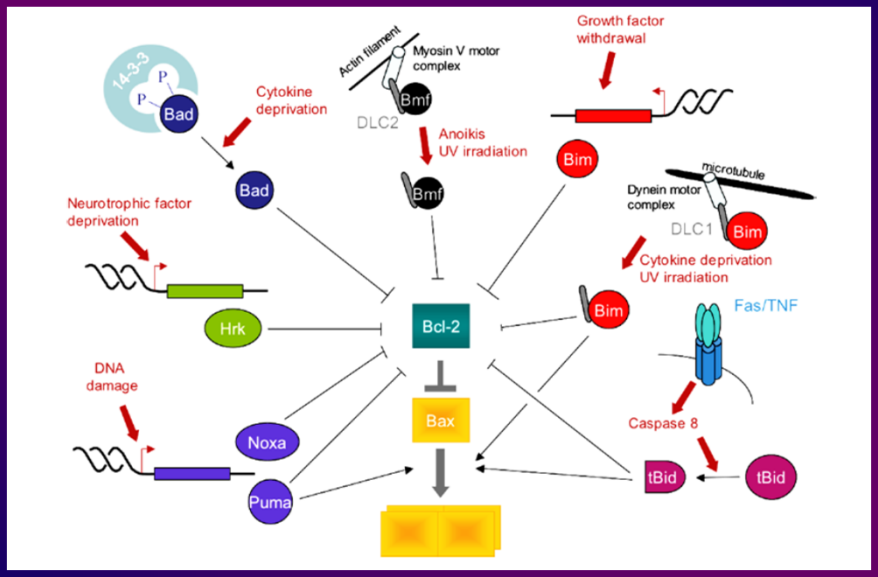
BH3-only Death Factors

Stress → BH3 only → BCL-2 ⊣ BAX → Mitochondria → Caspases

BH 1-4 Protein interaction

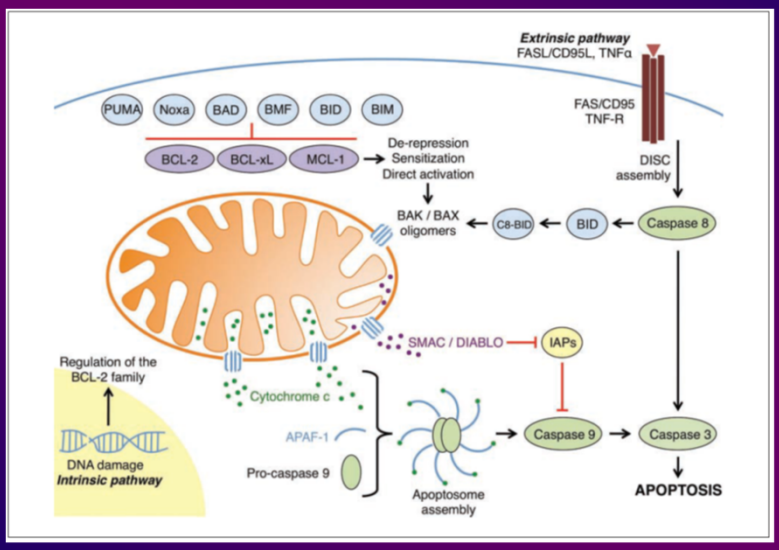
TM Membrane translocation

The BH3-only death factors activation



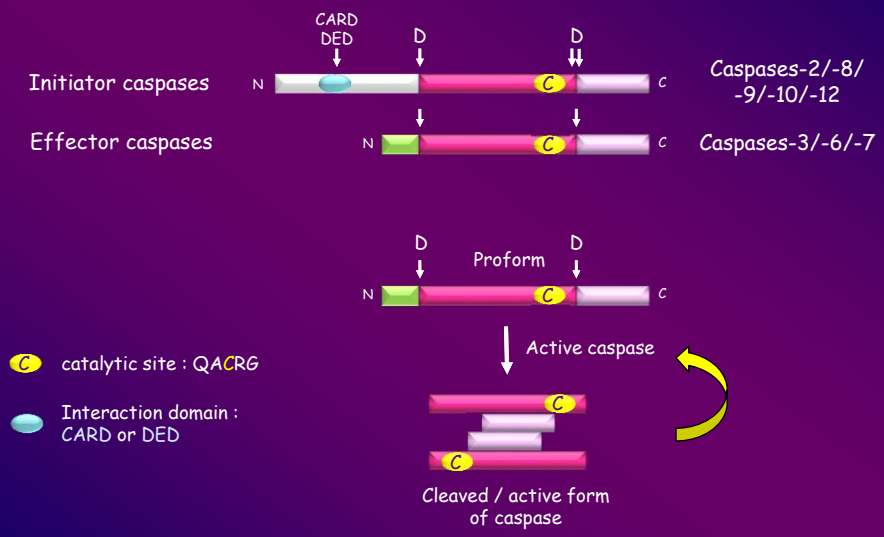
Lucken-Ardjomande and Martinou 2005 C.R. Biologies

The BCL-2 family: regulation of apoptosis

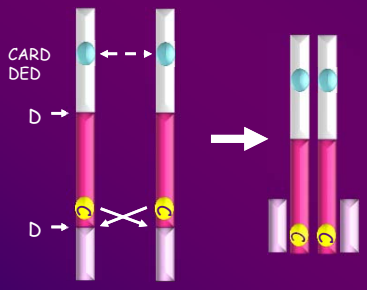


Elkhomi et al. 2011 Genes and Cancer

The caspases : effectors of cell death



Activation of initiator caspases

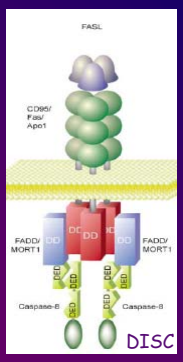


Activation of initiator caspases:

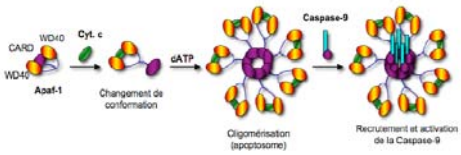
Caspase-9 (CARD) : Apoptosome

Caspases-8, -10 (DED): DISC, Complex II

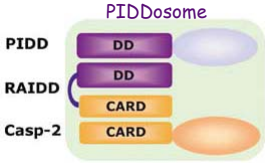
Caspase-2 (CARD): PIDDosome,



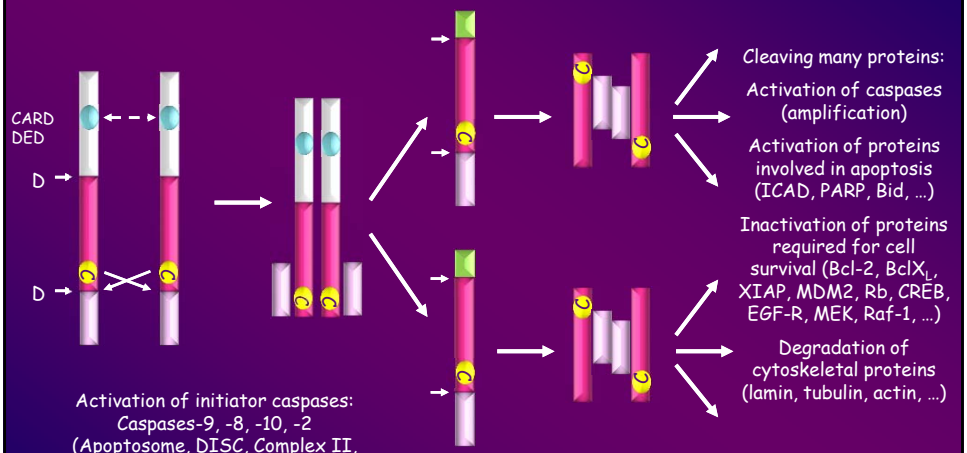
Apoptosome



PIDDosome



Activation of the caspase cascade



Activation of initiator caspases: Caspases-9, -8, -10, -2 (Apoptosome, DISC, Complex II, PIDDosome)

Activation of effector caspases: Caspases-3, -6, -7

Cleaving many proteins:

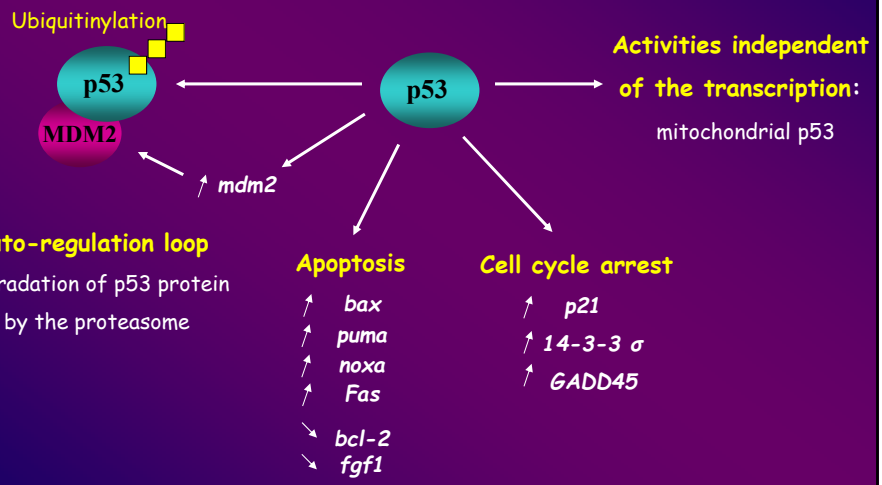
Activation of caspases (amplification)

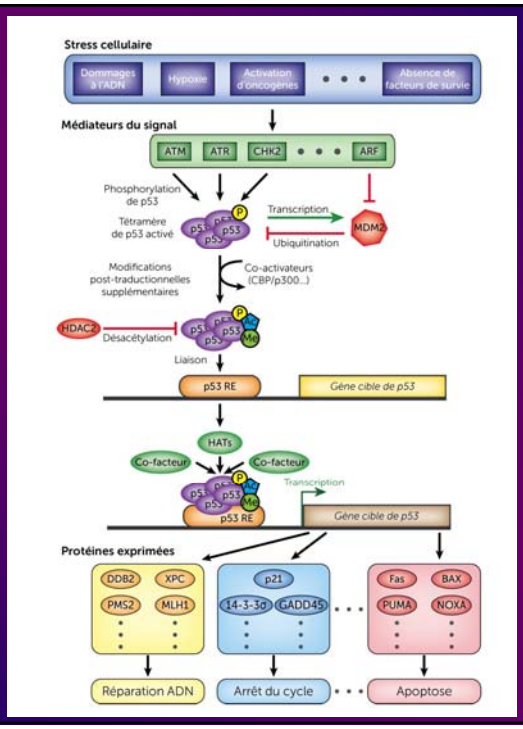
Activation of proteins involved in apoptosis (ICAD, PARP, Bid, …)

Inactivation of proteins required for cell survival (Bcl-2, $BclX_L$, XIAP, MDM2, Rb, CREB, EGF-R, MEK, Raf-1, …)

Degradation of cytoskeletal proteins (lamin, tubulin, actin, …)

The oncosuppressor p53: a key regulator of apoptosis
p53 is a transcription factor involved in apoptosis and cell cycle arrest



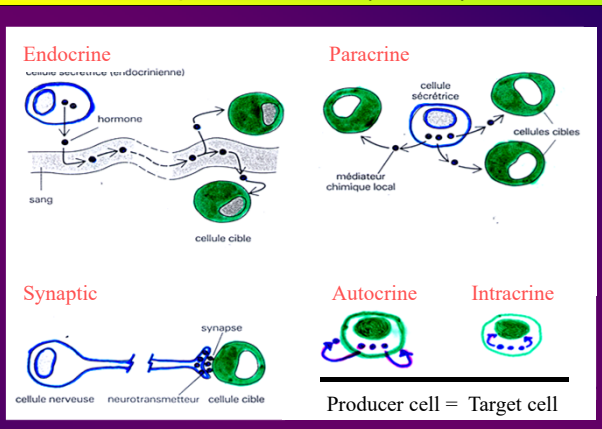


Caroline Pirou
Thèse 2016

Growth factor families

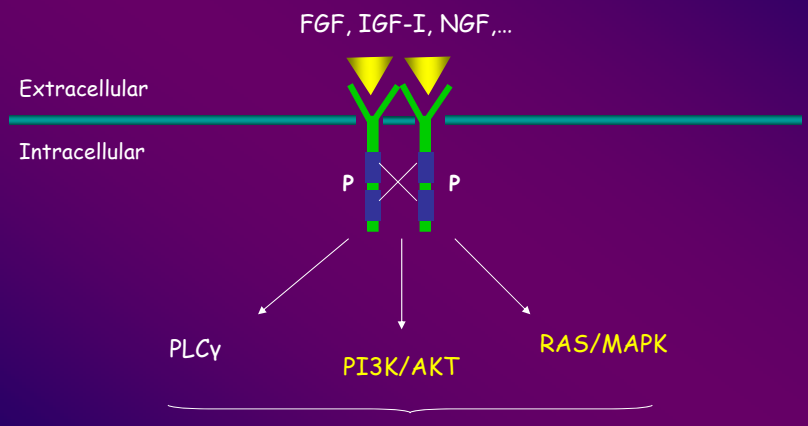
- EGF (Epidermal Growth Factor)
- PDGF (Platelet-derived growth factor)
- Growth Hormones
- VEGF (Vascular endothelial growth factor)
- FGF 1-23 (Fibroblast Growth Factor)
- Neurotrophins: NGF, NT3, NT4, BDNF
- GDNF (Glial cell line-derived neurotrophic factor), NTN (neurturin), PSP (persephin)
- Neurokines: CNTF, LIF
- Insulin, IGF-I, IGF-II

The growth factor pathways

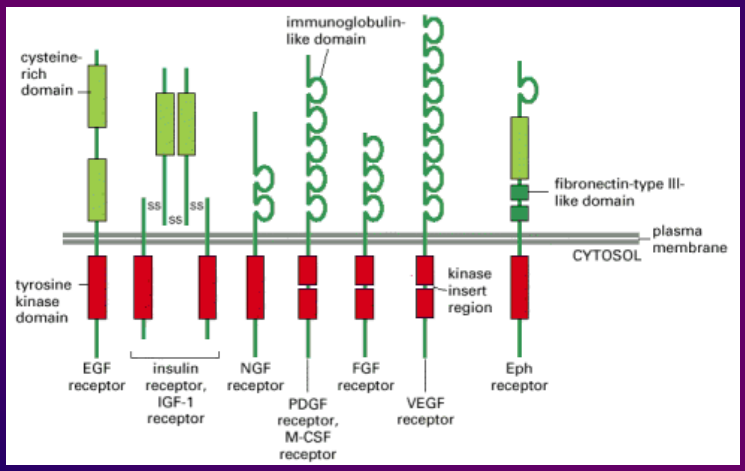


The paracrine pathway: the growth factor is produced and secreted by a cell and acts on neighboring cells.
The endocrine pathway: the growth factor is produced and secreted by a cell and then passes through the blood or lymphatic circulation to act on cells which may be very distant (Insulin, IGF-I/II)
The synaptic pathway: the growth factor is produced by a neuronal cell and then transported along the axon to synapses for acting on cells which may be very distant (neurotrophic factors)
For autocrine and intracrine pathway, the producer cell is the target cell.
The autocrine pathway: the cell produces the factor and its receptors and therefore the factor is produced and secreted to act on the producer cell.
The intracrine pathway: the cell produces the factor but it is not secreted and it acts directly into the cell by an internal pathway independent of the receptors.

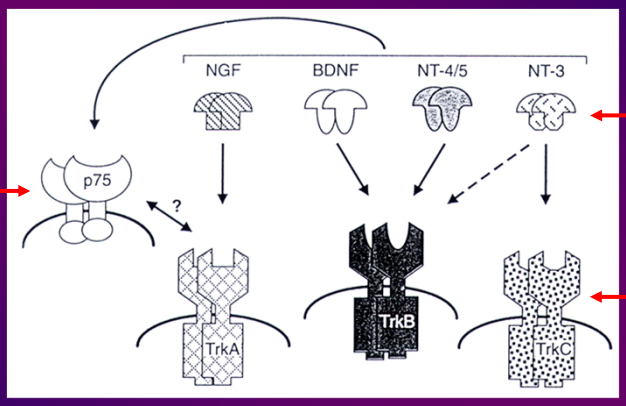
The classical pathway of action of growth/survival factors involves activation of plasma membrane receptor tyrosine kinases (paracrine, autocrine, endocrine and synaptic)



The receptor tyrosine kinases (RTK)



The High affinity receptors (RTKs) and Low affinity receptors



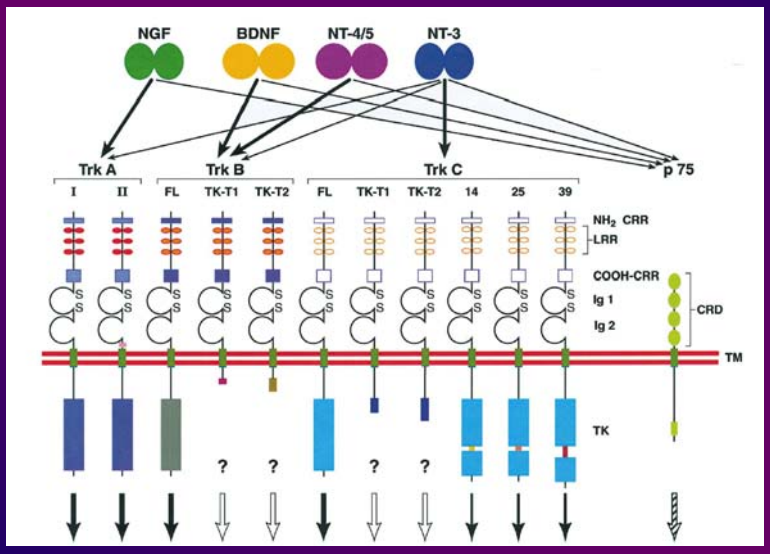
Low affinity receptors **p75**

Ligand Neurotrophins

High affinity receptors TrkA, B, C

In addition to high affinity receptors (RTK), there are low-affinity receptors, in particular for the neurotrophic factors.
The low affinity receptors either increase growth factor stability and/or increase high affinity receptor activity.
They could also induce RTK independent pathways.

The neurotrophin receptors (TrkA/B/C and p75)



The two major signaling pathways of the neurotrophic/survival factors

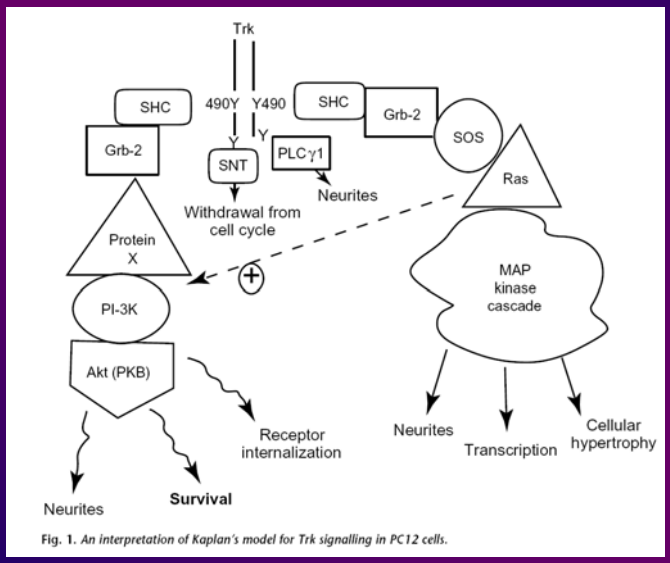
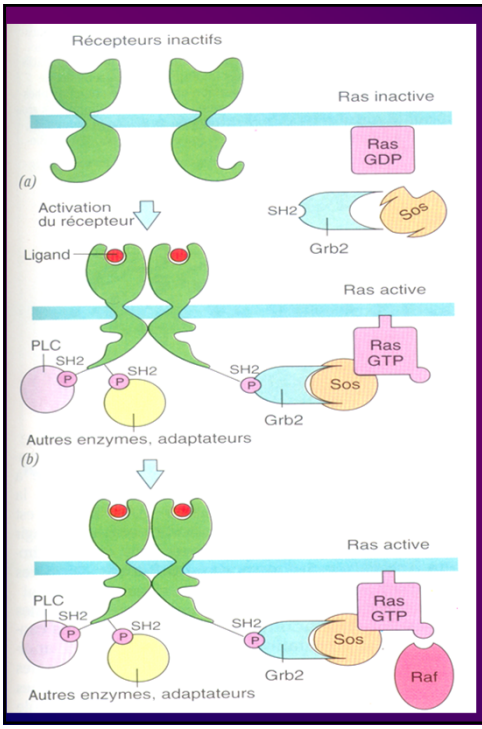


Fig. 1. *An interpretation of Kaplan's model for Trk signalling in PC12 cells.*

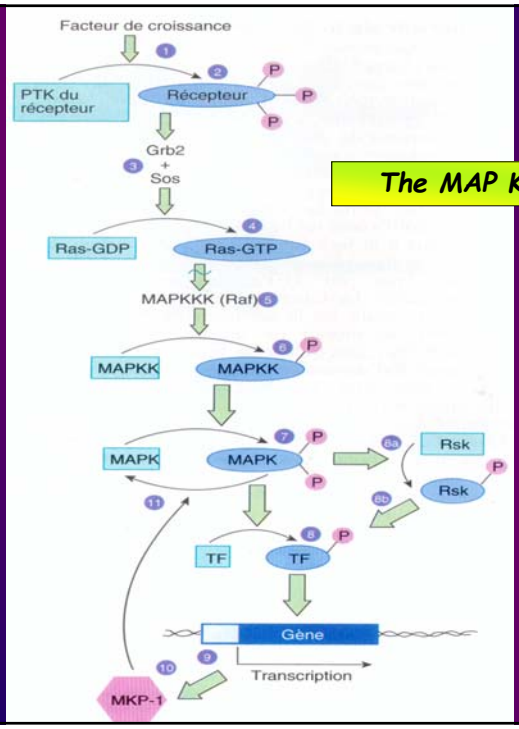
Tolkovsky 1997 TINS



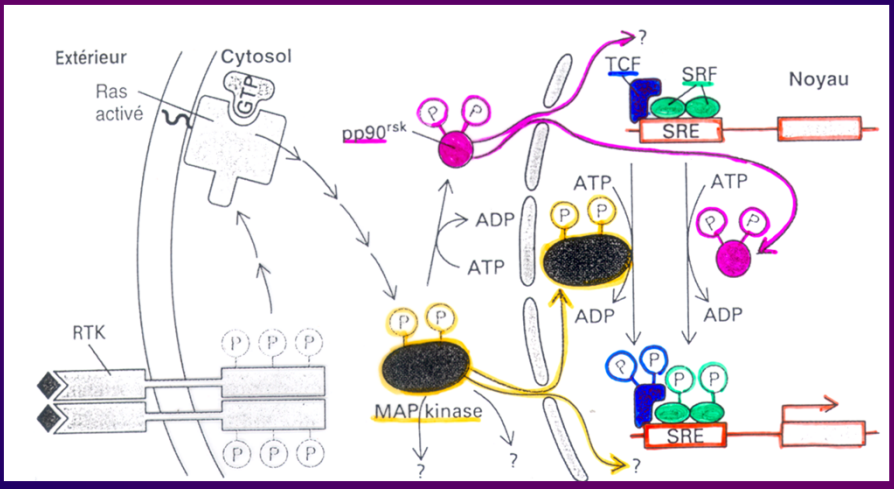
Activation of Ras by RTKs

(a) In the absence of growth factor, the receptors are inactive monomers. Ras is combined with GDP and therefore inactive.
(b) Ligand binding triggers the dimerization and autophosphorylation of the receptors. Phosphotyrosine residues newly formed function as binding sites for Grb2-Sos which induces exchange GDP and GTP on Ras.
(c) Activated Ras becomes a binding site for Raf and triggers the MAP kinase cascade.

The MAP Kinase cascade



MAP Kinases -> Transcriptional factors



The two major signaling pathways of the neurotrophic/survival factors

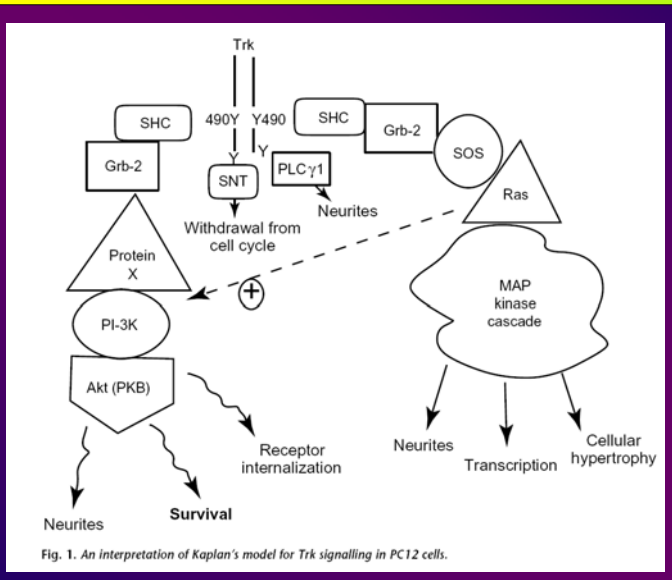
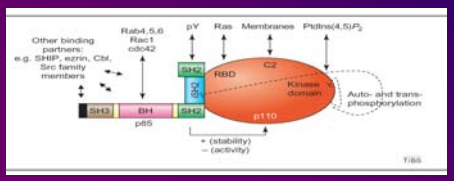


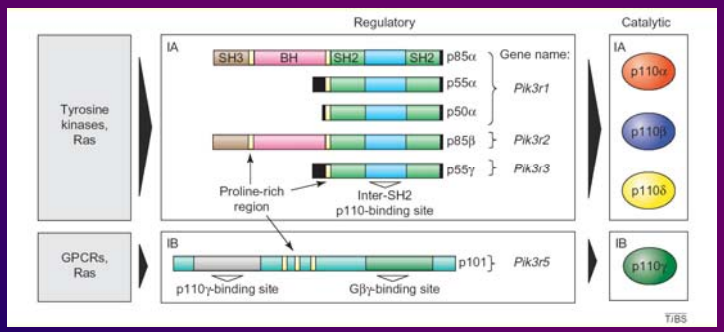
Fig. 1. *An interpretation of Kaplan's model for Trk signalling in PC12 cells.*

Tolkovsky 1997 TINS

The PI3K / AKT pathway : the main signaling pathway involved in cell survival

The PhosphoInositide 3 Kinase (PI3K)





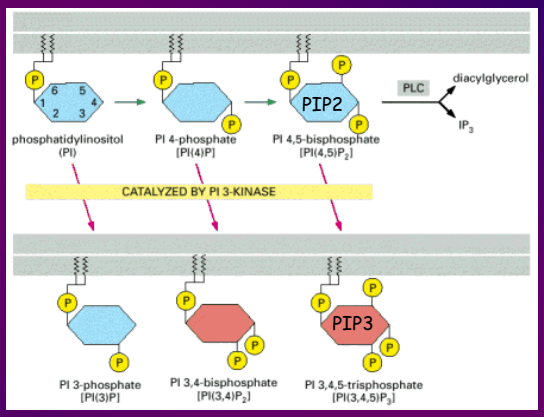
Vanhaesebroeck et al. 2005, Trends in Biochemical Sciences

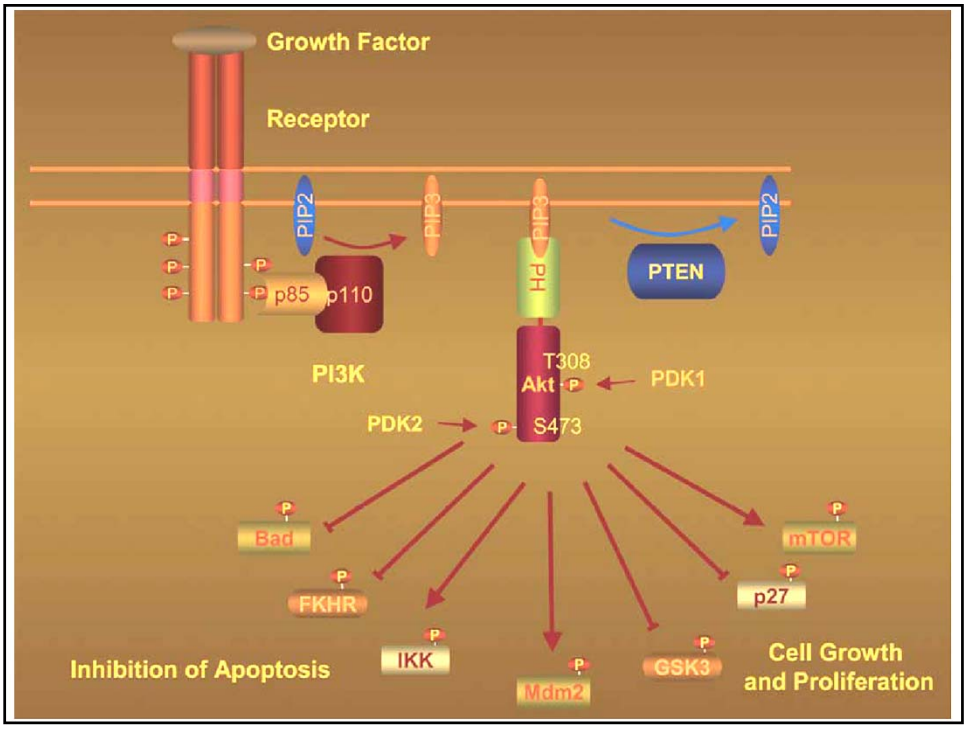
The PI3K / AKT pathway : the main signaling pathway involved in cell survival

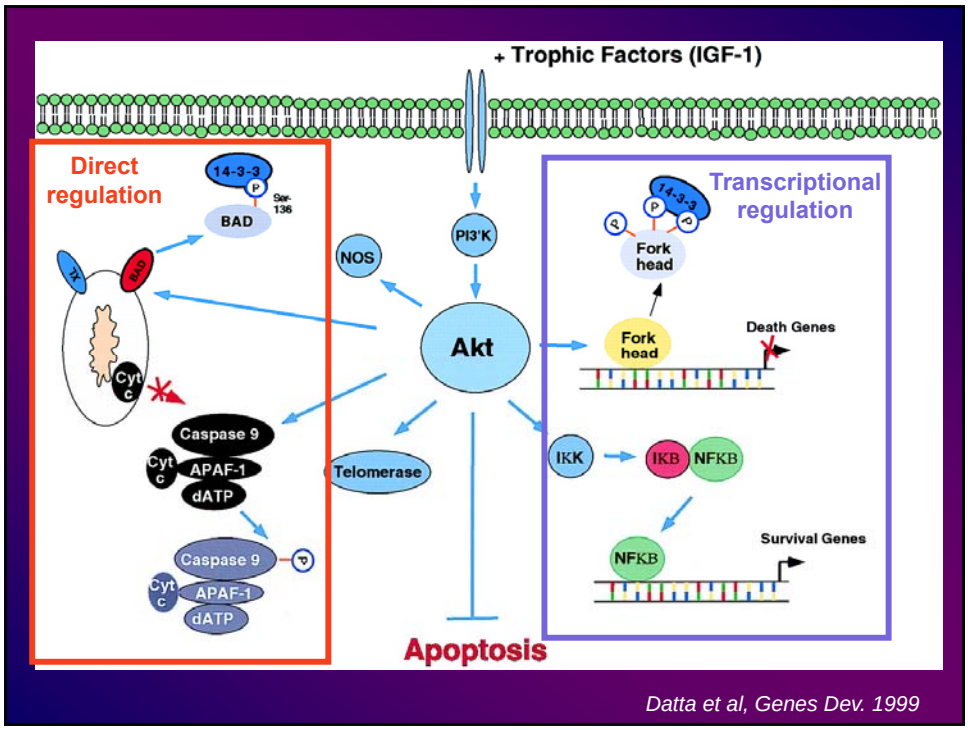
PIP2

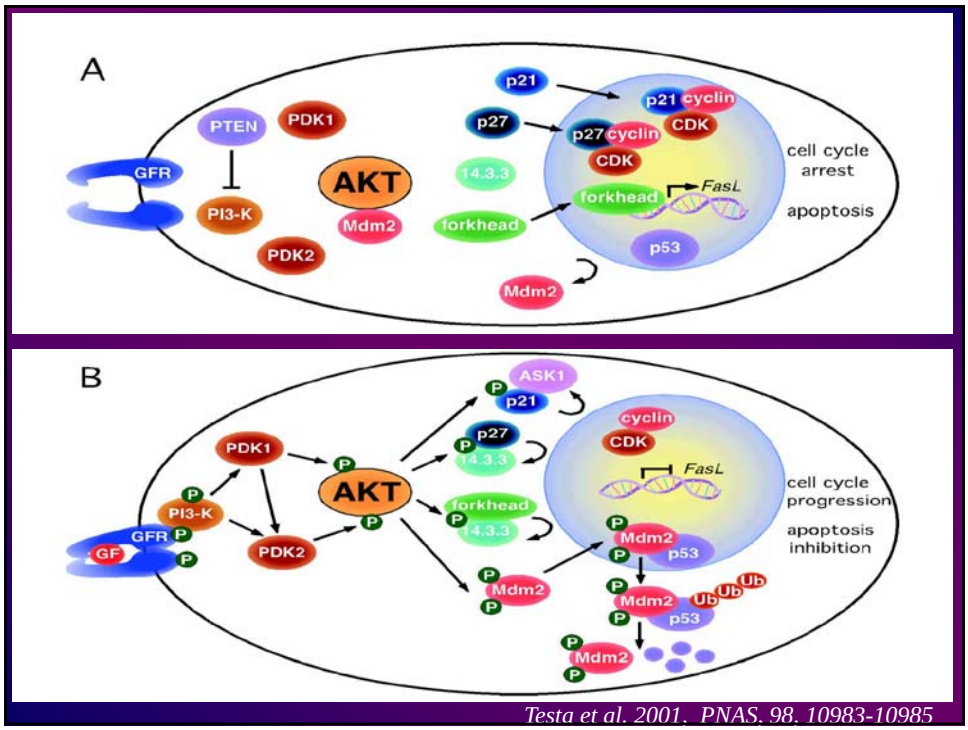
PI3K ⇅ PTEN

PIP3





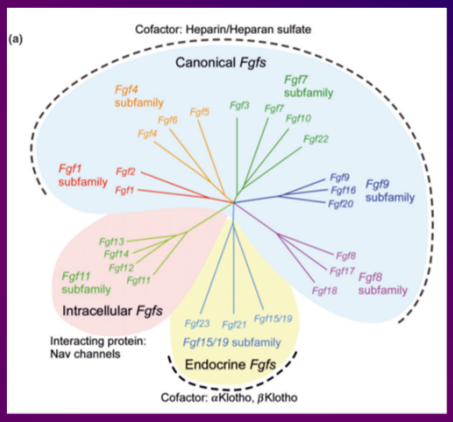

+ Trophic Factors (IGF-1)
Direct regulation
14-3-3
P
Ser-136
BAD
BAD
PI3'K
NOS
Akt
Transcriptional regulation
14-3-3
Fork head
Fork head
Death Genes
Cyt c
Caspase 9
Cyt c
APAF-1
dATP
Telomerase
IKK
IKB
NFKB
Caspase 9
Cyt c
APAF-1
dATP
NFKB
Survival Genes
Apoptosis
Datta et al, Genes Dev. 1999


A
PTEN
PDK1
GFR
PI3-K
AKT
Mdm2
PDK2
p21
p27
14.3.3
forkhead
p21 cyclin
p27 cyclin
CDK
CDK
FasL
forkhead
p53
Mdm2
cell cycle arrest
apoptosis
B
ASK1
PDK1
PI3-K
GFR
GF
AKT
PDK2
p21
p27
14.3.3
forkhead
14.3.3
cyclin
CDK
FasL
Mdm2
p53
Mdm2
Mdm2
Ub
Ub
Ub
p53
Mdm2
cell cycle progression
apoptosis inhibition
Testa et al. 2001. PNAS. 98. 10983-10985

The fibroblast growth factor signaling pathway

TABLE 1 | Nomenclature of the Mammalian *Fgf* and *Fgfr* family

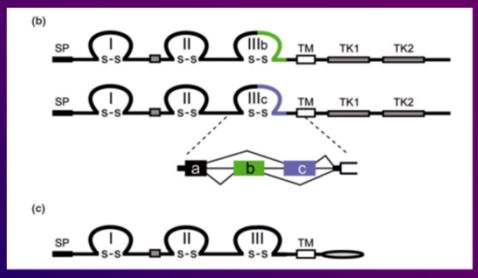
HUGO/MGI Symbol	Name	Alternative Symbol	Name, Comments
(a) *Fgf*			
FGF1/Fgf1	Fibroblast Growth Factor 1	*aFgf*	Acidic Fgf
		Hbgf1	Heparin-binding growth factor 1
		Ecgr	Endothelial cell growth factor
FGF2/Fgf2	Fibroblast Growth Factor 2	*bFgf*	Basic Fgf
		Hbgf2	Heparin-binding growth factor 2
FGF3/Fgf3	Fibroblast Growth Factor 3	*Int-2*	Int-2 oncogene
		V-Int-2	MMTV integration site 2
FGF4/Fgf4	Fibroblast Growth Factor 4	*Hst1*	Human stomach tumor oncogene
		Hstf1	Heparin secretory transforming protein 1
		K-fgf, Kfgf	Kaposi sarcoma Fgf
FGF5/Fgf5	Fibroblast Growth Factor 5		
FGF6/Fgf6	Fibroblast Growth Factor 6	*Hst2*	Hst2 oncogene
FGF7/Fgf7	Fibroblast Growth Factor 7	*Kgf*	Keratinocyte growth factor
FGF8/Fgf8	Fibroblast Growth Factor 8	*Aigf*	Androgen induced growth factor
		Kal6	
FGF9/Fgf9	Fibroblast Growth Factor 9	*Gaf*	Glia activating factor
		Eks	Elbow knee synostosis
FGF10/Fgf10	Fibroblast Growth Factor 10	*Kgf-2*	Keratinocyte growth factor 2
FGF11/Fgf11	Fibroblast Growth Factor 11	*Fhf3*	Fibroblast Growth Factor homologous factor 3
FGF12/Fgf12	Fibroblast Growth Factor 12	*Fhf1*	Fibroblast Growth Factor homologous factor 1
FGF13/Fgf13	Fibroblast Growth Factor 13	*Fhf2*	Fibroblast Growth Factor homologous factor 2
FGF14/Fgf14	Fibroblast Growth Factor 14	*Fhf4*	Fibroblast Growth Factor homologous factor 4
		Sca27	spinocerebellar ataxia 27
Fgf15	Fibroblast Growth Factor 15		Rodent ortholog of vertebrate *Fgf19*
FGF16/Fgf16	Fibroblast Growth Factor 16		
FGF17/Fgf17	Fibroblast Growth Factor 17		Called FGF-13 in some older literature
FGF18/Fgf18	Fibroblast Growth Factor 18		
FGF19	Fibroblast Growth Factor 19		Human ortholog of rodent *Fgf15*
FGF20/Fgf20	Fibroblast Growth Factor 20		
FGF21/Fgf21	Fibroblast Growth Factor 21		
FGF22/Fgf22	Fibroblast Growth Factor 22		
FGF23/Fgf23	Fibroblast Growth Factor 23		



Ornitz and Itoh, Dev. Biol. 2015

The fibroblast growth factor signaling pathway

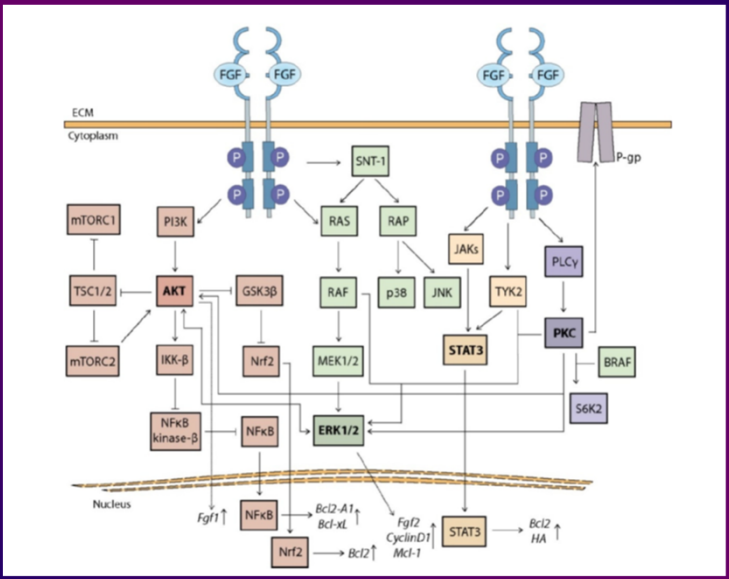
(b) *Fgfr*			
FGFR1/Fgfr1	Fgf receptor 1	*Flg*	Fms-like gene
		Flt2	Fms-like tyrosine kinase 2
		Cek	Chicken embryo kinase 1
		KAL2	Kallman syndrome 2
		K-sam	KATO-III cell-derived stomach cancer amplified gene
FGFR2/Fgfr2	Fgf Receptor 2	*Bek*	Bacterial expressed kinase
		Cek3	Chicken embryo kinase 3
		Kgfr	KGF receptor
FGFR3/Fgfr3	Fgf Receptor 3	*Cek2*	Chicken embryo kinases 2
		Ach	Achondroplasia
FGFR4/Fgfr4	Fgf Receptor 4	*Tkf*	Tyrosine kinase related to Fibroblast Growth Factor receptor
FGFRL1/Fgfrl1	Fgf receptor like 1	*Fgfr5*	Fgf receptor 5



FGF subfamily	FGF	Cofactor	Receptor specificity
FGF1 subfamily	FGF1 FGF2		All FGFRs FGFR 1c, 3c > 2c, 1b, 4Δ
FGF4 subfamily	FGF4 FGF5 FGF6		FGFR 1c, 2c > 3c, 4Δ
FGF7 subfamily	FGF3 FGF7 FGF10 FGF22	+ Heparin or Heparan sulfate	FGFR 2b > 1b
FGF8 subfamily	FGF8 FGF17 FGF18		FGFR 3c > 4Δ > 2c > 1c >> 3b
FGF9 subfamily	FGF9 FGF16 FGF20		FGFR 3c > 2c > 1c, 3b >> 4Δ
FGF15/19 subfamily	FGF15/19 FGF21 FGF23	+βKlotho +αKlotho	FGFR 1c, 2c, 3c, 4Δ FGFR 1c, 3c FGFR 1c, 3c, 4

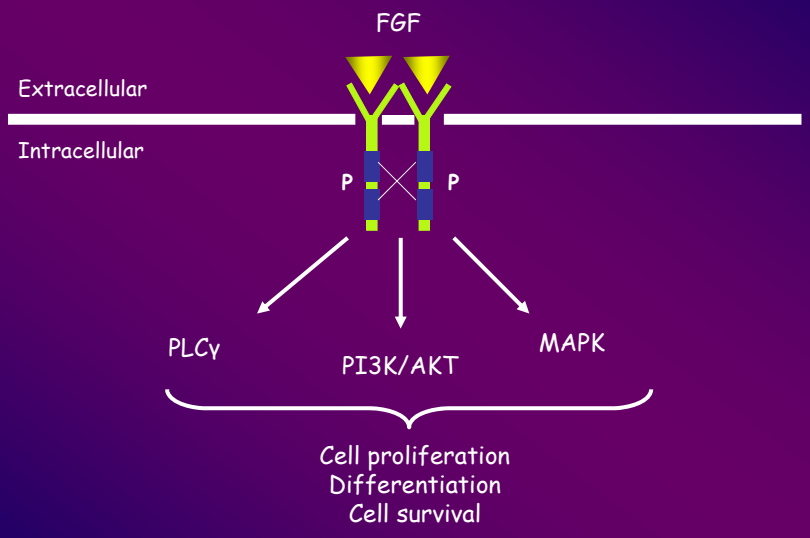
Ornitz and Itoh, Dev. Biol. 2015

The fibroblast growth factor signaling pathway



Szymczyk et al. 2021 Cancers, 13, 5796

In addition to the classical receptor tyrosine kinase pathways of FGF…



…there are other FGF pathways: the intracrine pathway.

The fibroblast growth factors

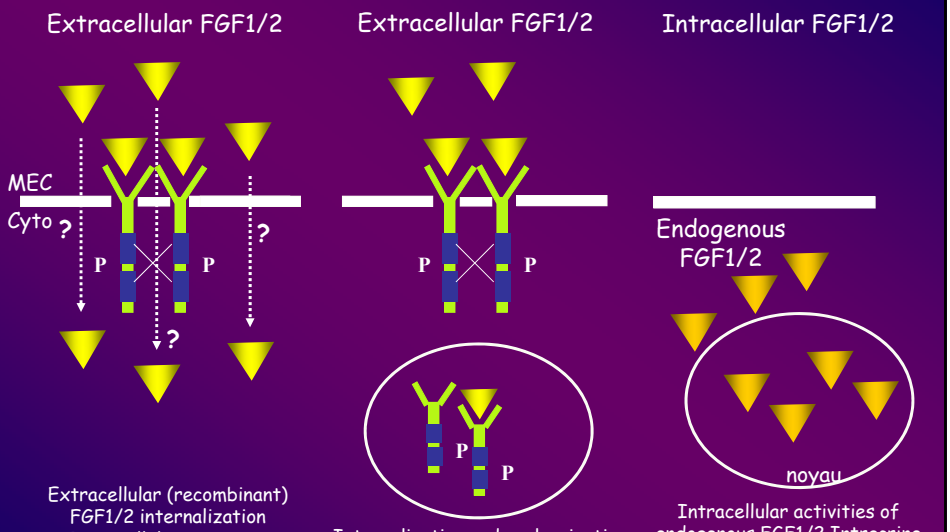
FGFs	Taille (aa) (MM 18-38 kda)	séquence signal glycolysation	Expression	Nuclear localization sequence
FGF1/FGFa	155	non	ubiquitaire	
FGF2/FGFb	155, 196, 201, 210	non	ubiquitaire	NLS
FGF3/int-2	271, 245	oui	embryon, carcinome mammaire	NLS
FGF4/hst-1	206	oui	embryon	
FGF5	267	oui	embryon, muscle adulte, sarcome de kaposi	
FGF6/hst-2	198	oui	muscle squelettique	
FGF7/KGF	194	oui	fibroblaste, UVSMC, mésenchyme embryonnaire	
FGF8/AIGF	181	oui	ectoderme embryonnaire	
FGF9/GAF	174	oui	gliome	
FGF10	215	oui	embryon, poumon adulte	
FGF11-14/FHF1-4	244,245, 225, 247	non	CNS (embryon, adulte)	NLS
FGF15	218	oui	CNS embryonnaire	

Abréviations: KGF: Keratinocyte growth factor, AIGF: androgen-induced growth factor, GAF: glia activating factor, UVSMC: uterine vascular smooth muscle cells, FHF: fibroblast growth factor homologous factor

Activités des FGFs (exogènes)

- facteurs **mitogènes** *in vitro*
- facteurs de **différenciation** et de **transdifférenciation** *in vitro* et *in vivo*
- facteurs de **survie** *in vitro* et *in vivo*
- facteurs **transformant** *in vitro* et **tumorigènes** *in vivo*
- facteurs **angiogéniques**
- facteurs de **réparation** tissulaire

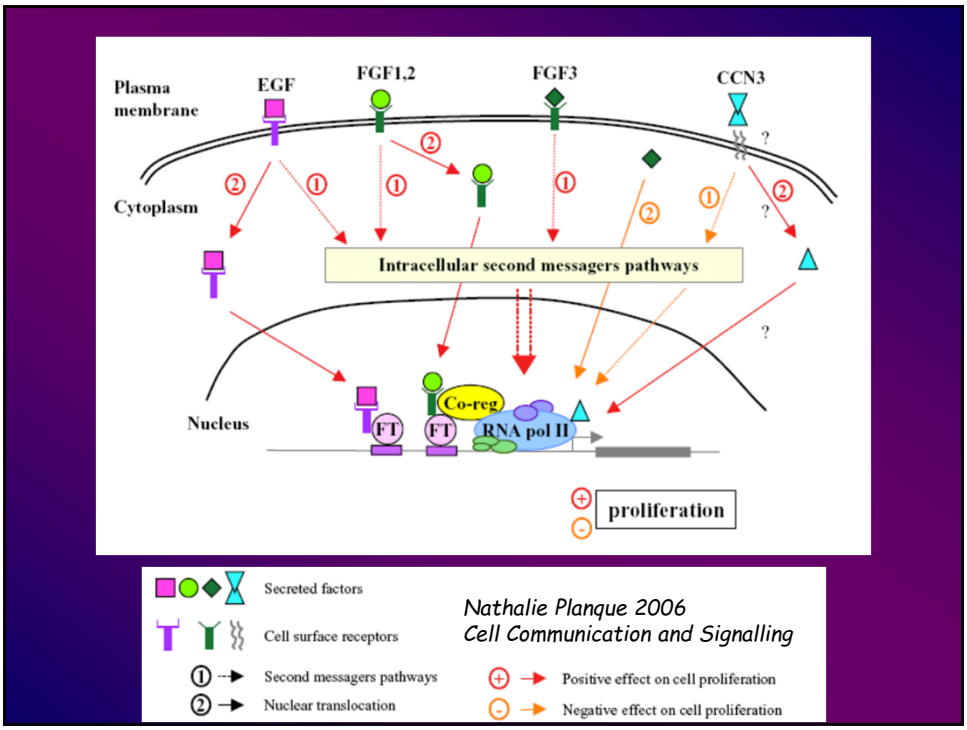
The Fibroblast Growth Factors 1/2 (FGF1/2)



Extracellular (recombinant) FGF1/2 internalization
Intracellular activities (cytoplasm/nucleus)
Wiedlocha 2004

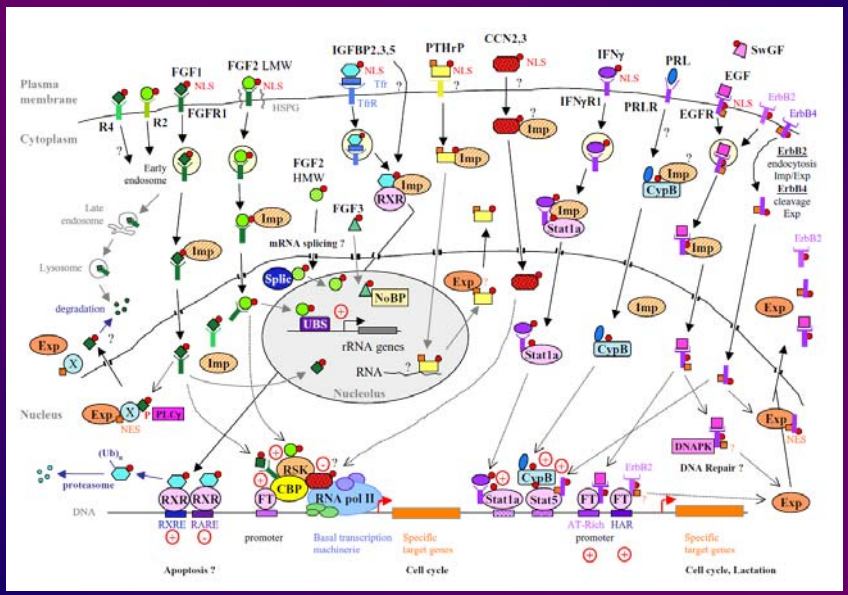
Internalization and nuclearization of FGF receptors
Stachowiak 2007

Intracellular activities of endogenous FGF1/2 Intracrine pathway (cytoplasm/nucleus)
Renaud 1996, Bouleau 2005, Rodriguez-Enfedaque 2009, Delmas 2016, Pirou 2017, Manousakidi 2018

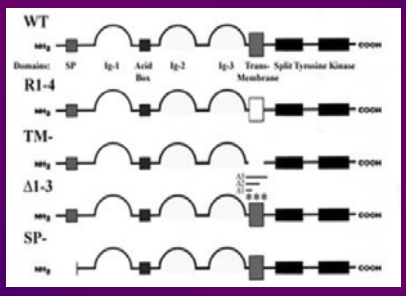


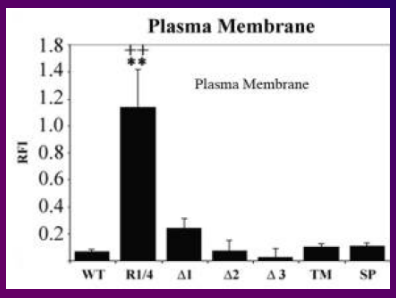
Nathalie Planque 2006
Cell Communication and Signalling

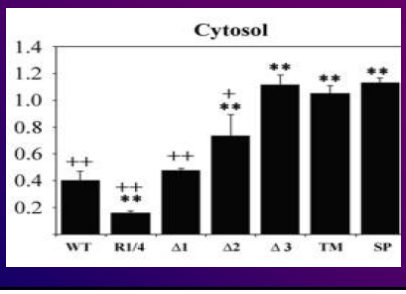
Nathalie Planque 2006 Cell Communication and Signalling
« Nuclear trafficking of secreted factors and cell-surface receptors: new pathways to regulate cell proliferation and differentiation, and involvement in cancers. »

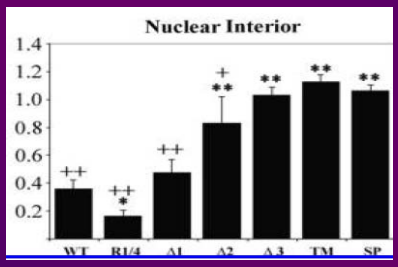


Stachowiak et al. 2007 DNA and Cell Biology
« Integrative nuclear signaling in cell development- A role for FGF receptor-1. »









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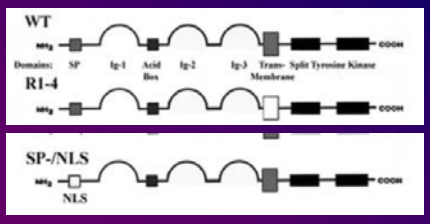
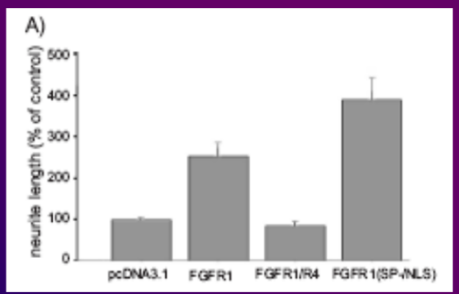
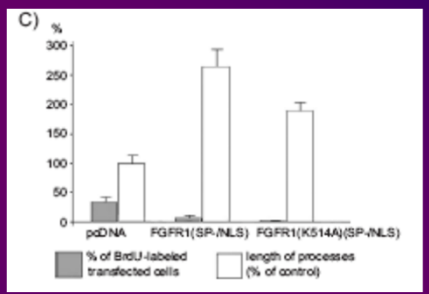
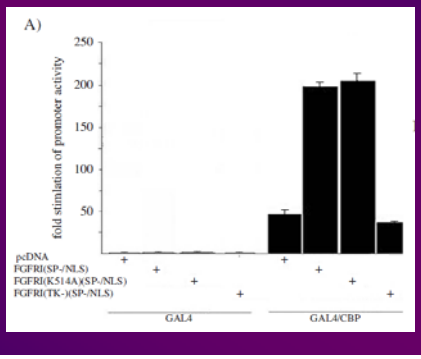
« Integrative nuclear signaling in cell development- A role for FGF receptor-1. »







Nuclear FGFR1 stimulates neuronal differentiation of human neuronal primary cells (A) and meduloblastomaTE671 cells (B).
The kinase activity of FGFR1 is not required for this activity (K514A mutant TK- of FGFR1 receptor)



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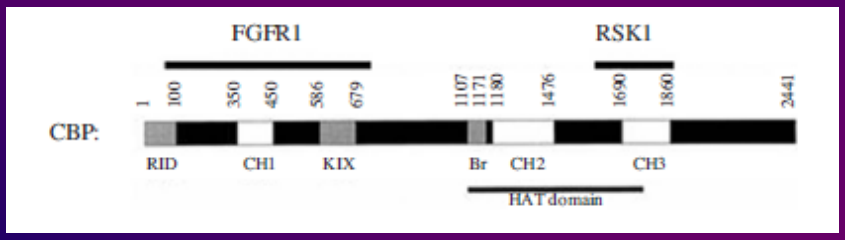
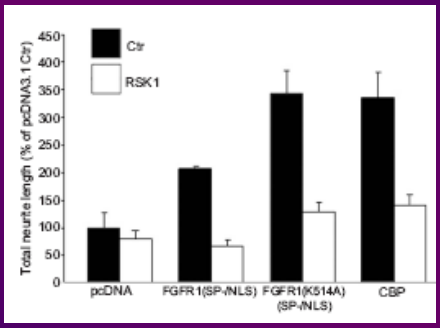


CBP=CREB binding protein: acetyltransferase that activates the transcription of genes which contain AMPc response elements and/or regulates transcription factor activity.
RSK1=p90^{RSK}: serine threonine kinase that regulates several transcription factors.



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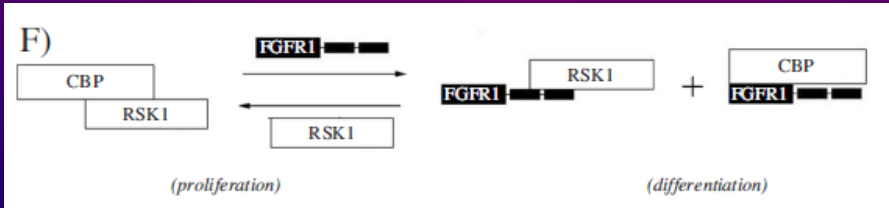
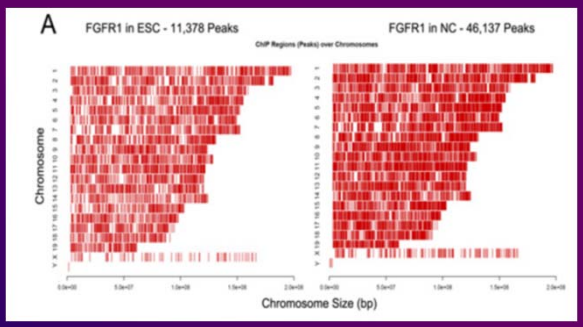


RESEARCH ARTICLE

Global Developmental Gene Programing Involves a Nuclear Form of Fibroblast Growth Factor Receptor-1 (FGFR1)

Christopher Terranova[1], Sridhar T. Narla[1], Yu-Wei Lee[1], Jonathan Bard[2], Abhirath Parikh[3], Ewa K. Stachowiak[1], Emmanuel S. Tzanakakis[3], Michael J. Buck[4], Barbara Birkaya[1], Michal K. Stachowiak[1]*

ESC: pluripotent embryonic stem cell (maintained in presence of LIF)
NCs: neuronal cells induced by Retinoic Acid (RA)



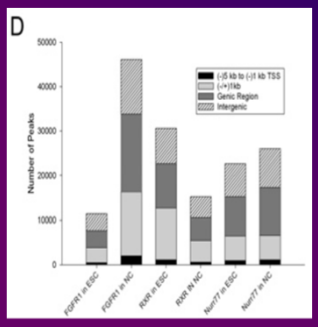


Fig 1. Genome-wide analyses of nFGFR1, RXR and Nur77 binding in pluripotent ESCs and RA-induced NCs. (A) nFGFR1, **(B)** RXR and **(C)** Nur77 peaks are present on all chromosomes, in both ESCs and NCs. **(D)** Genomic distribution of nFGFR1, RXR and Nur77 peaks within proximal promoters (-1kb to +1 kb relative to TSS), distal promoters (-5 kb to -1 kb relative to TSS), genic and intergenic regions in ESCs and NCs. **(E-G)** Enrichment of FGFR1, RXR and Nur77 peaks within promoter and genic regions.

Terranova et al. 2015 PLOSone

RESEARCH ARTICLE

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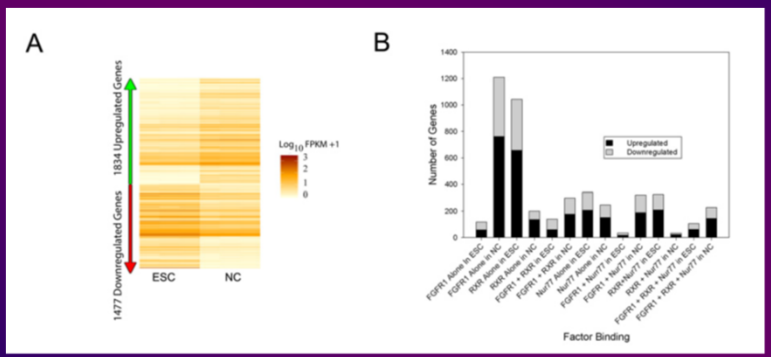
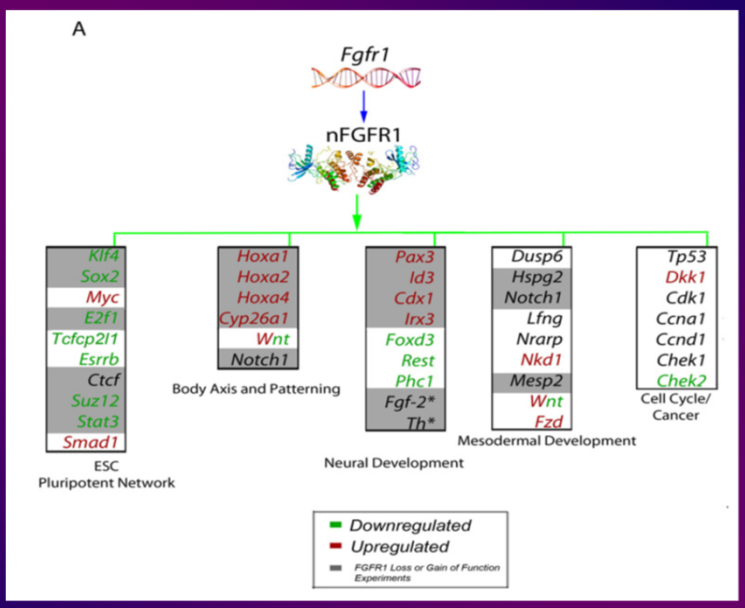


Fig 3. Binding of nFGFR1, RXR and Nur77 to expressed genes. (A) Heatmap representation of genes that were differentially expressed in pluripotent ESCs and RA-induced NCs from three independent biological replicates. Out of 14,443 expressed genes, 1,834 were up-regulated and 1,477 were down-regulated in NCs [Fold Change (FC) ≥-/+2.0 and p-value <0.035 were considered significant]. Values are displayed as fragments per kb of transcript per million fragments mapped (FPKM). **(B)** Binding of nFGFR1, RXR and Nur77 within the proximal promoter of differentially regulated genes. In NCs, the population of regulated genes that are targeted by nFGFR1 (2,058 genes) was markedly higher than the population of regulated genes that are not (480 genes).

Terranova et al. 2015 PLOSone



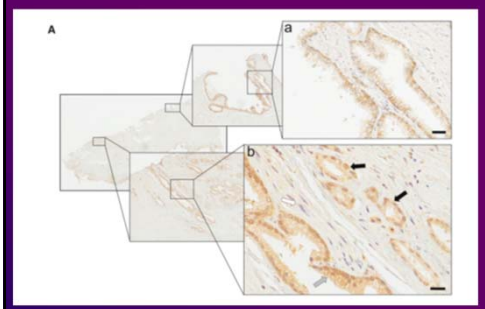
Terranova et al. 2015 PLOSone

Cancer de la prostate
Aleksic et al. 2018

Molecular Cell Biology — Cancer Research

Nuclear IGF1R Interacts with Regulatory Regions of Chromatin to Promote RNA Polymerase II Recruitment and Gene Expression Associated with Advanced Tumor Stage

Tamara Aleksic[1], Nicki Gray[2], Xiaoning Wu[1], Guillaume Rieunier[2], Eliot Osher[2], Jack Mills[3], Clare Verrill[4], Richard J. Bryant[5,6], Cheng Han[1,7], Kathryn Hutchinson[1], Adam G. Lambert[8], Rajeev Kumar[8], Freddie C. Hamdy[9], Ulrike Weyer-Czernilofsky[10], Michael P. Sanderson[10], Thomas Bogenrieder[10], Stephen Taylor[2], and Valentine M. Macaulay[1,8]



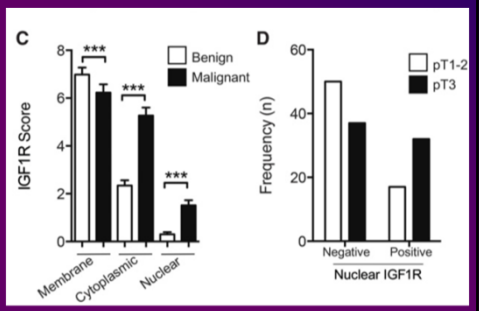
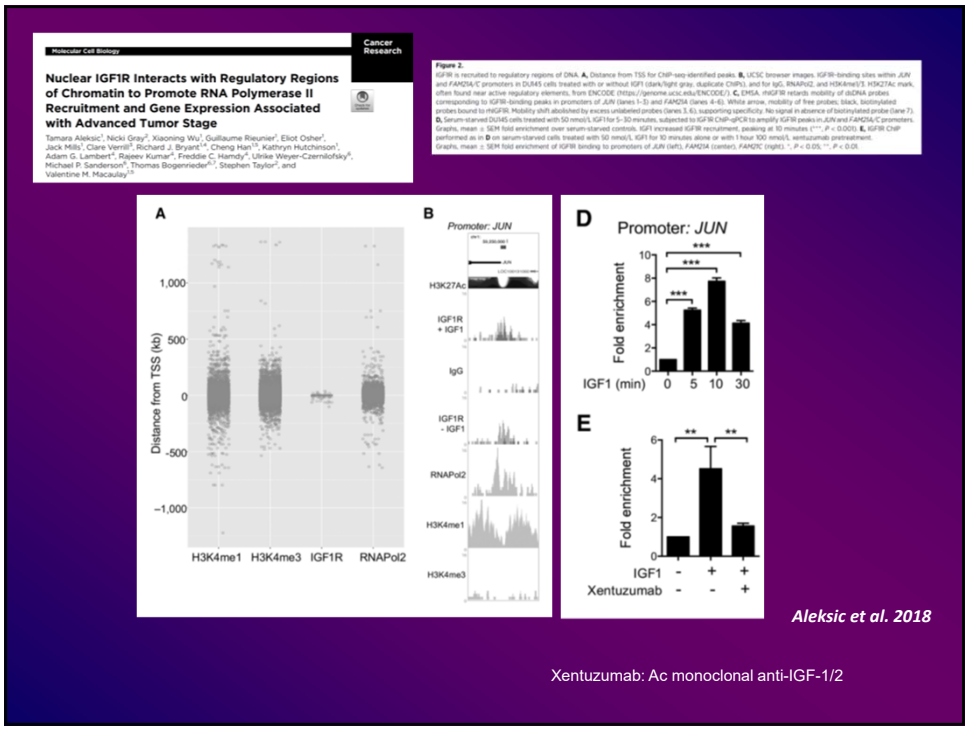
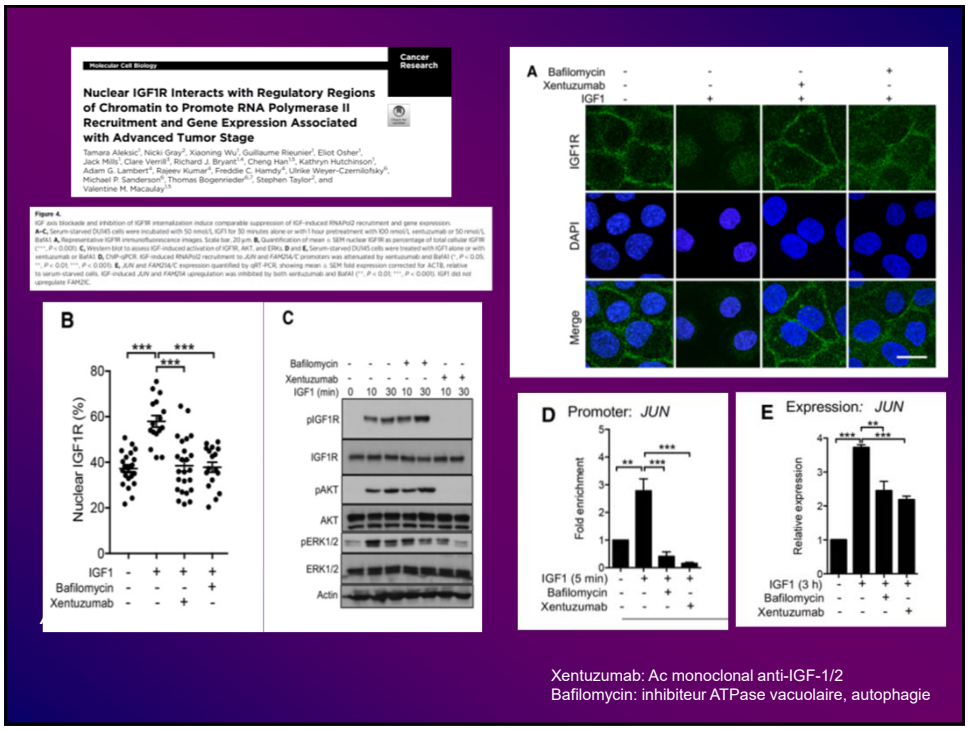


Figure 1.
Nuclear IGF1R is associated with advanced tumor stage. **A,** IGF1R IHC in radical prostatectomy. **a,** Benign epithelium showing membrane IGF1R, with cytoplasmic IGF1R in basal cells; **b,** Mixed Gleason 3 (gray arrow) and 4 (black arrow) cancer containing more IGF1R than benign epithelium, prominent cytoplasmic and nuclear IGF1R, and perineural invasion (white arrow). Scale bar, 20 μm. **B,** IGF1R IHC scored for total IGF1R ($n = 137$ RPs). Graph, total IGF1R score (bars, mean ± SEM, red) in benign and malignant epithelia. The cancers contained significantly more IGF1R than benign prostatic epithelium from the same RP (***, $P < 0.001$, Wilcoxon matched pairs signed rank test). **C,** IGF1R quantification in plasma membrane, cytoplasm, nucleus ($n = 137$ RPs; ***, $P < 0.001$, Wilcoxon test). **D,** Stage pT3 prostate cancers contain more nuclear IGF1R than stage pT1-2 cancers ($P = 0.01$).



Aleksic et al. 2018

Xentuzumab: Ac monoclonal anti-IGF-1/2

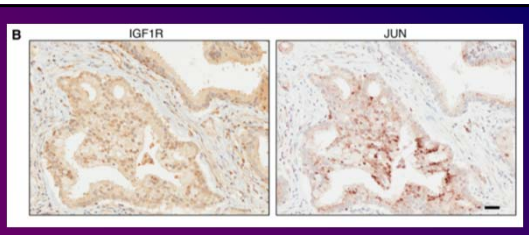


Xentuzumab: Ac monoclonal anti-IGF-1/2
Bafilomycin: inhibiteur ATPase vacuolaire, autophagie

Molecular Cell Biology
Cancer Research

Nuclear IGF1R Interacts with Regulatory Regions of Chromatin to Promote RNA Polymerase II Recruitment and Gene Expression Associated with Advanced Tumor Stage

Tamara Aleksic[1], Nicki Gray[2], Xiaoning Wu[1], Guillaume Rieunier[1], Eliot Osher[1], Jack Mills[1], Clare Verrill[3], Richard J. Bryant[1,4], Cheng Han[1,5], Kathryn Hutchinson[1], Adam G. Lambert[6], Rajeev Kumar[6], Freddie C. Hamdy[6], Ulrike Weyer-Czernilofsky[6], Michael P. Sanderson[6], Thomas Bogenrieder[6,7], Stephen Taylor[2], and Valentine M. Macaulay[1,5]



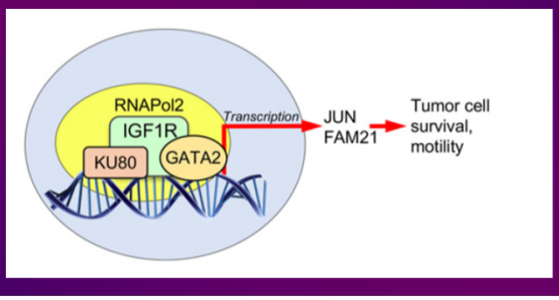
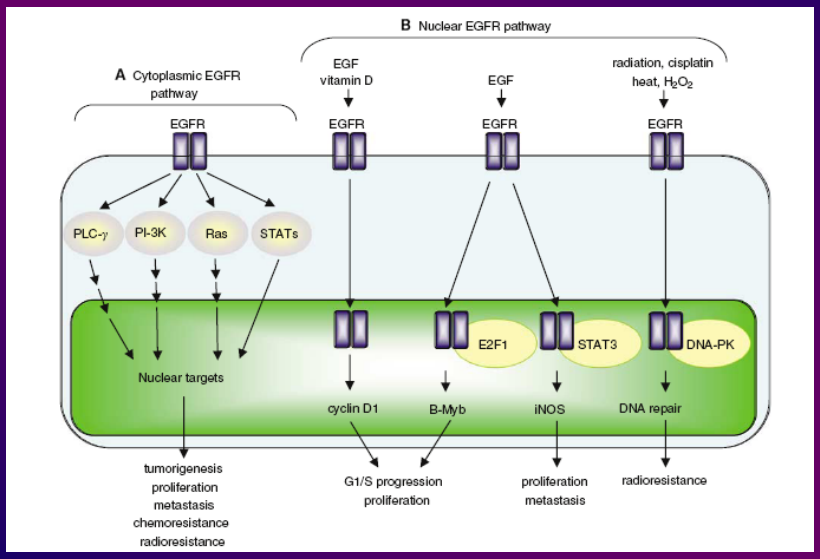
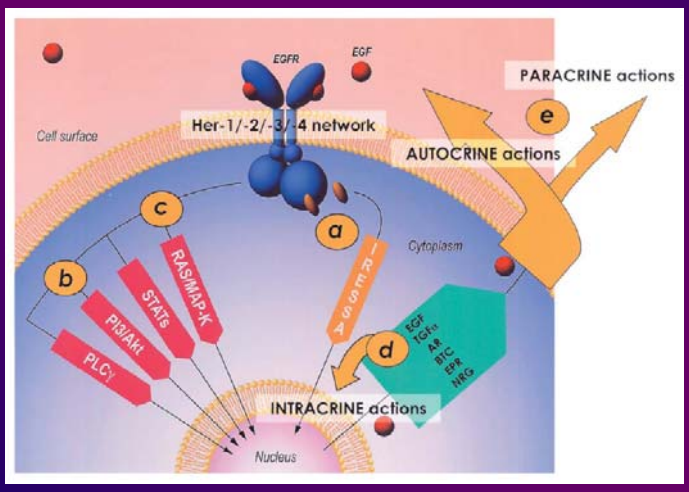


Figure 6.
Nuclear IGF1R is present on promoters of clinical prostate cancers and correlates with JUN expression. **A,** Fresh-frozen prostate cancers underwent IGF1R or control (IgG) ChIP-qPCR for IGF1R–binding regions of *JUN* and *FAM21A* promoters. Top, relative IGF1R enrichment; center, representative IGF1R IHC from adjacent FFPE tumor (scale bar, 20 μm); bottom, Gleason grades and IGF1R scores in membrane (M), cytoplasm (C), nucleus (N). **B,** IGF1R and JUN IHC on adjacent RP sections, showing Gleason 4 pattern gland (scale bar, 30 μm). **C,** Graph, total JUN immunoreactive scores in $n = 80$ RPs correlated with nuclear IGF1R (Spearman coefficient). **D,** Nuclear IGF1R binds to DNA and interacts with transcriptional regulators, inducing expression of genes that promote tumor cell survival and migration.

Lo HW and Hung MC 2006 British Journal of Cancer
« Nuclear EGFR signalling network in cancer: linking EGFR pathway to Cell cycle progression, nitric oxide pathway and patient survival. »



Ferrer-Soler et al. 2007 Int. J. Mol. Med.
« An update of the mechanisms of resistance to EGFR-tyrosine kinase inhibitors in breast cancer: Gefitinib (Iressa™)-induced changes in the expression and nucleo-cytoplasmic trafficking of HER-ligands. »



PSL RESEARCH UNIVERSITY PARIS

École Pratique des Hautes Études

LGBC Laboratoire de génétique et biologie cellulaire

UNIVERSITÉ DE VERSAILLES ST-QUENTIN-EN-YVELINES

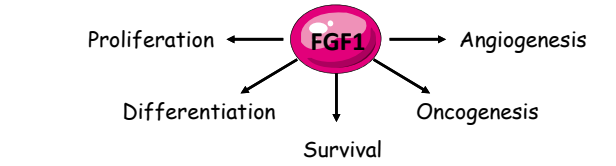
Study of the FGF1 intracrine pathway

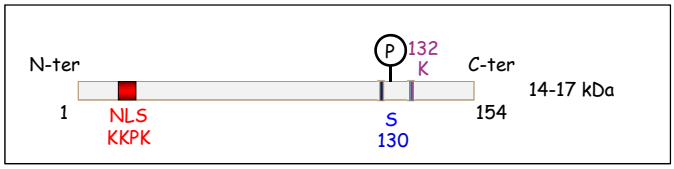
Flore Renaud

Laboratoire de Génétique et Biologie Cellulaire

LGBC EA4589 UVSQ/EPHE
Versailles / Montigny le Bretonneux

Fibroblast Growth Factor 1

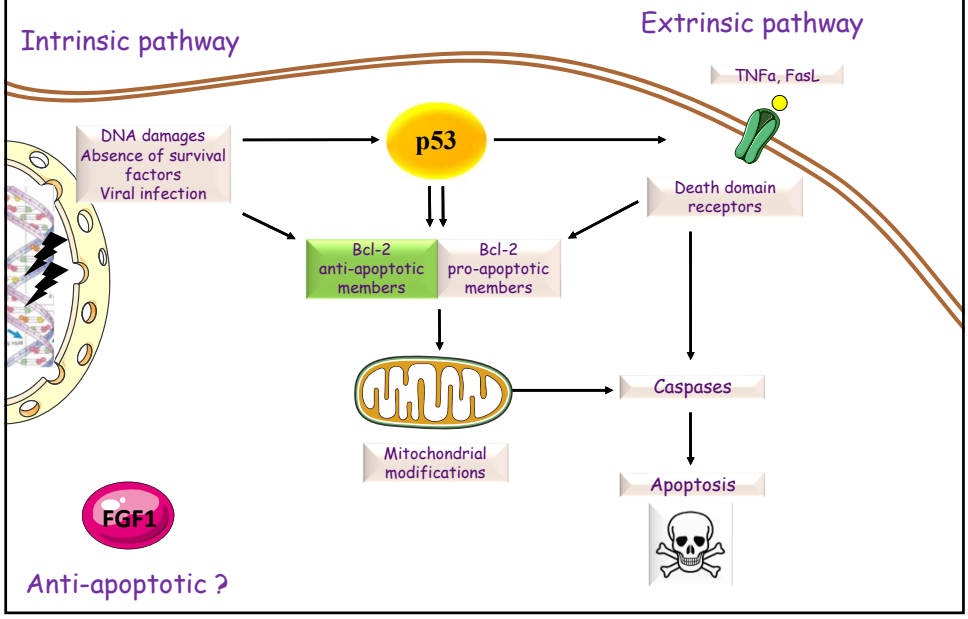




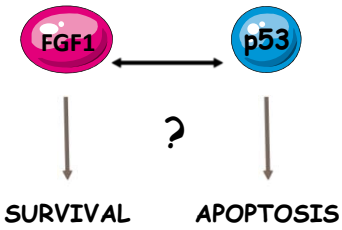
- No secretion peptide signal -> Intracellular localization
- A nuclear localization sequence -> Nuclear localization
- Phosphorylation by PKCδ in the nucleus

→ *Intracrine/nuclear pathway*

Could FGF1 inhibit apoptosis through the intracrine pathway? How? What is the mechanism?



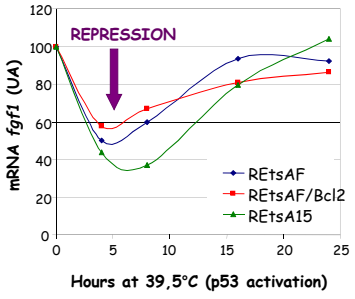
Study of the interactions between FGF1 and p53 pathways



Different cell models:

- *Embryonic fibroblasts*
- *Neuronal cell lines :*
  - *PC12 (pheochromocytoma),*
  - *SH-SY5Y (neuroblastoma)*
- *Ovarian cancer cell lines:*
  - *COV434 (granulosa),*
  - *A2780 (serous epithelial)*

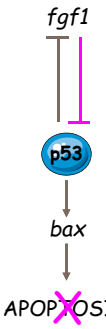
p53 represses fgf1 expression in rat embryonic fibroblasts

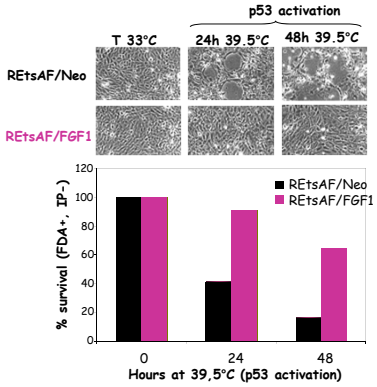


1/ *fgf1* is a p53 target gene.

Bouleau et al. Oncogene 2005

FGF1 inhibits p53 pro-apoptotic and anti-proliferative activities by an intracrine pathway in rat embryonic fibroblasts



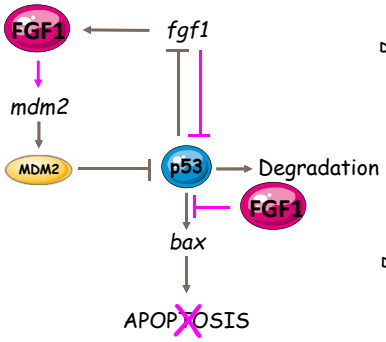


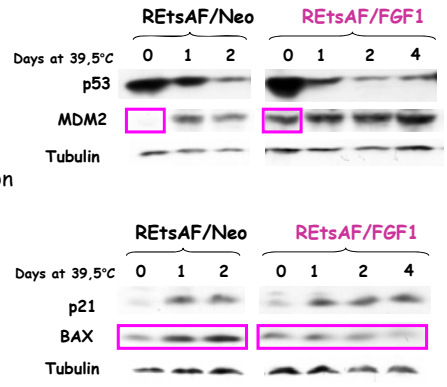
1/ *fgf1* is a p53 target gene.

2/ FGF1 inhibits p53 pro-apoptotic and anti-proliferative activities by an intracrine pathway.

Bouleau et al. Oncogene 2005

FGF1 inhibits p53 pro-apoptotic and anti-proliferative activities by an intracrine pathway in rat embryonic fibroblasts





1/ *fgf1* is a p53 target gene.

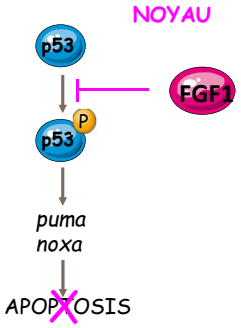
2/ FGF1 inhibits p53 pro-apoptotic and anti-proliferative activities by an intracrine pathway.

- ✓ FGF1 increases *mdm2* expression and p53 degradation
- ✓ FGF1 inhibits some p53 transcriptional activities (*bax*)

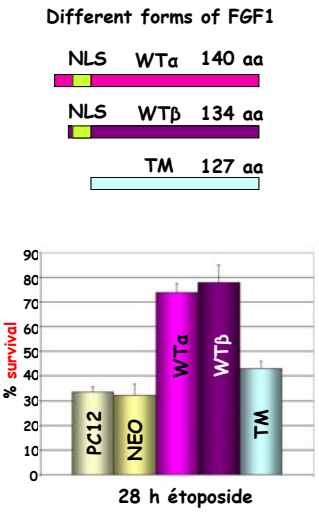
Bouleau et al. Oncogene 2005

Intracellular FGF1 inhibits p53-dependent apoptosis in PC12 cells by an intracrine/nuclear pathway

1/ Extracellular and intracellular FGF1 inhibits p53-dependent apoptosis.



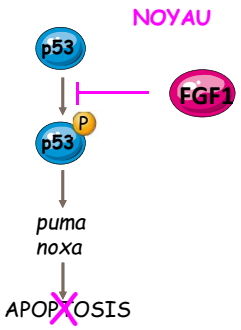
2/ FGF1 nucleairization is required for its neurotrophic and anti-apoptotic activities.



Bouleau et al. 2007
Rodriguez-Enfedaque et al. 2009

Intracellular FGF1 inhibits p53-dependent apoptosis in PC12 cells by an intracrine/nuclear pathway

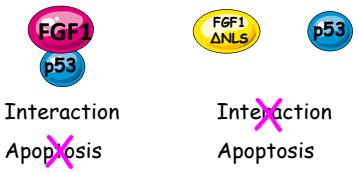
1/ Extracellular and intracellular FGF1 inhibits p53-dependent apoptosis.



2/ FGF1 nucleairization is required for its neurotrophic and anti-apoptotic activities.

3/ FGF1 interacts with p53 (directly or indirectly?).

The nuclear localization sequence is required for this interaction.



Bouleau et al. 2007
Rodriguez-Enfedaque et al. 2009

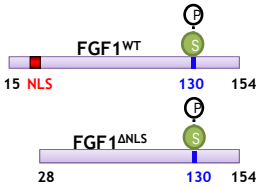
Both nuclearization and phosphorylation regulate FGF1 activities in neuronal cell lines (PC12, SH-SY5Y)

	Nuclear localization	Phospho-rylation	Survival	Differentiation (PC12)
FGF1WT	✓	+/-	✓	✓

In both neuronal cell lines (PC12 and SH-SY5Y cell lines):
1/ Intracellular FGF1 inhibits p53-dependent apoptosis

Delmas et al. 2016, Pirou et al. 2017

Both nuclearization and phosphorylation regulate FGF1 activities in neuronal cell lines (PC12, SH-SY5Y)

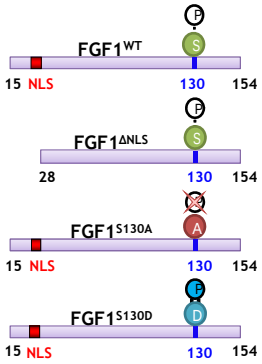


	Nuclear localization	Phospho-rylation	Survival	Differentiation (PC12)
FGF1WT	✓	+/-	✓	✓
FGF1ΔNLS	✗	+/-	✗	✗

In both neuronal cell lines (PC12 and SH-SY5Y cell lines):
1/ Intracellular FGF1 inhibits p53-dependent apoptosis
2/ FGF1 nuclearization is required for its anti-apoptotic activity.

Delmas et al. 2016, Pirou et al. 2017

Both nuclearization and phosphorylation regulate FGF1 activities in neuronal cell lines (PC12, SH-SY5Y)

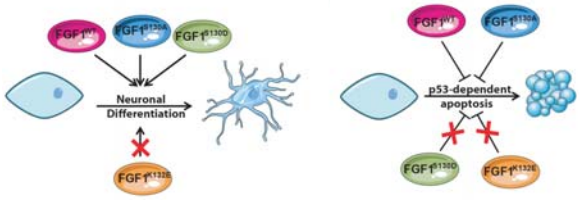


	Nuclear localization	Phospho-rylation	Survival	Differentiation (PC12)
$FGF1^{WT}$	✓	+/-	✓	✓
$FGF1^{\Delta NLS}$	✗	+/-	✗	✗
$FGF1^{S130A}$	✓	Inhibits	✓	✓
$FGF1^{S130D}$	✓	Mimics	✗	✓

In both neuronal cell lines (PC12 and SH-SY5Y cell lines):
1/ Intracellular FGF1 inhibits p53-dependent apoptosis
2/ FGF1 nuclearization is required for its anti-apoptotic activity.
3/FGF1 phosphorylation inhibits its anti-apoptotic activity

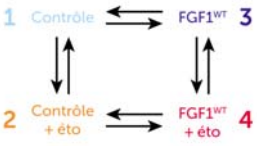
Delmas et al. 2016, Pirou et al. 2017

Study of the nuclear FGF1 pathway: Transcriptome analysis of PC12 cells +/- FGF1 +/- p53



RNA-seq analysis in PC12 cells

P < 0,01	$FGF1^{WT}$ VS Ctrl	Ctrl + éto VS Ctrl	$FGF1^{WT}$ + éto VS $FGF1^{WT}$	$FGF1^{WT}$ + éto VS Ctrl + éto
Up-regulated genes number	1709	1891	1065	284
Down-regulated genes number	1780	2591	1381	340



Genes and/or signaling pathway regulated:

- *fgf1* (amplification loop)
- Transcription factors (*Etv1, Egr1, c-jun, …*)
- Wnt/β-catenin pathway (*APC, DKK3, Wnt7a*)
- Jak/Stat pathway.

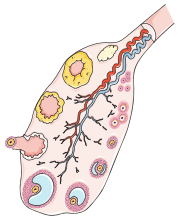
Caroline Pirou, PhD 2016

Study of FGF1 activity in chemoresistance of ovarian cancers

In ovarian cancer:

- *fgf1* overexpression correlated with high grade and chemoresistance of ovarian tumor cells (Smith et al. 2012).

- FGF1 increases tumor growth *in vivo* (*King et al. 2014*).



Study of FGF1 activity (and mechanism) in the resistance of ovarian tumor cells to etoposide or cisplatin treatment

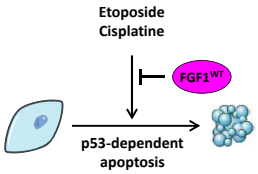
2 ovarian tumor cell lines:

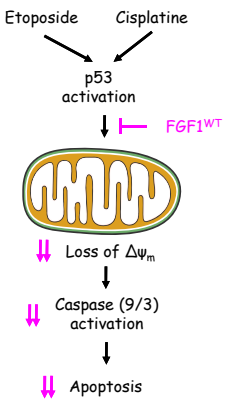
- COV434: cell line issued from a granulosa tumor
- A2780: cell line issued from a serous epithelial tumor (used by Smith and King teams)

Study of FGF1 activity in chemoresistance of ovarian cancers

In COV434 cells:

- Extracellular and intracellular FGF1 protects COV434 cells from etoposide- and cisplatin-induced apoptosis.



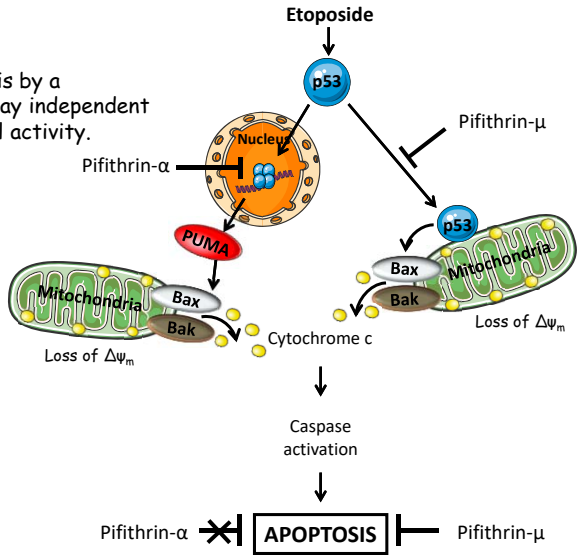


Manousakidi et al. 2018

Study of FGF1 activity in chemoresistance of ovarian cancers

In COV434 cells:

- p53 induces apoptosis by a mitochondrial pathway independent of its transcriptional activity.



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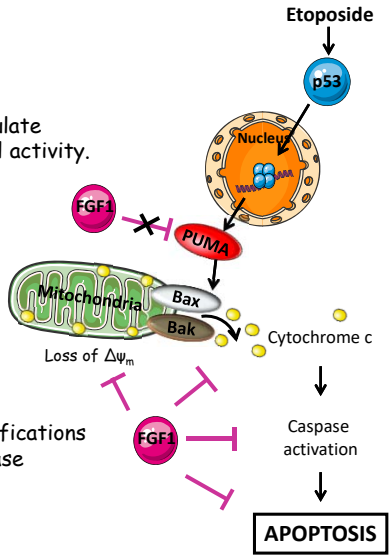
Study of FGF1 activity in chemoresistance of ovarian cancers

In COV434 cells:

- FGF1 does not regulate p53 transcriptional activity.



- FGF1 inhibits:
  - ➢ mitochondrial modifications
  - ➢ cytochrome c release
  - ➢ caspase activation

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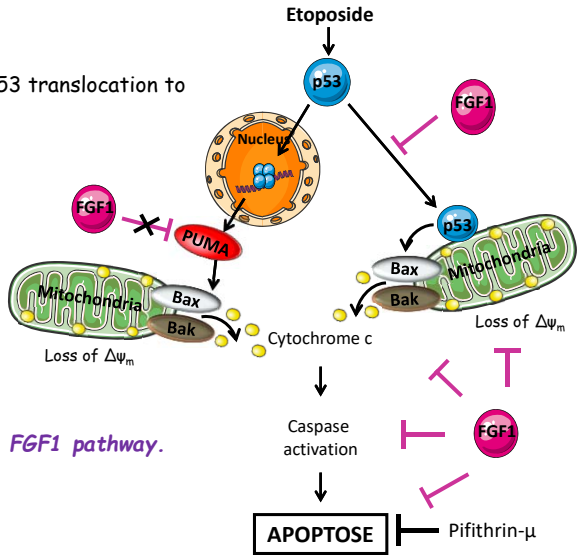
Study of FGF1 activity in chemoresistance of ovarian cancers

In COV434 cells:

- FGF1 inhibits p53 translocation to mitochondria.



→ *New intracrine FGF1 pathway.*

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UNIVERSITÉ DE VERSAILLES ST-QUENTIN-EN-YVELINES

« Etude des régulations de la voie mitochondriale de l'apoptose par la voie d'action intracrine du FGF1 »

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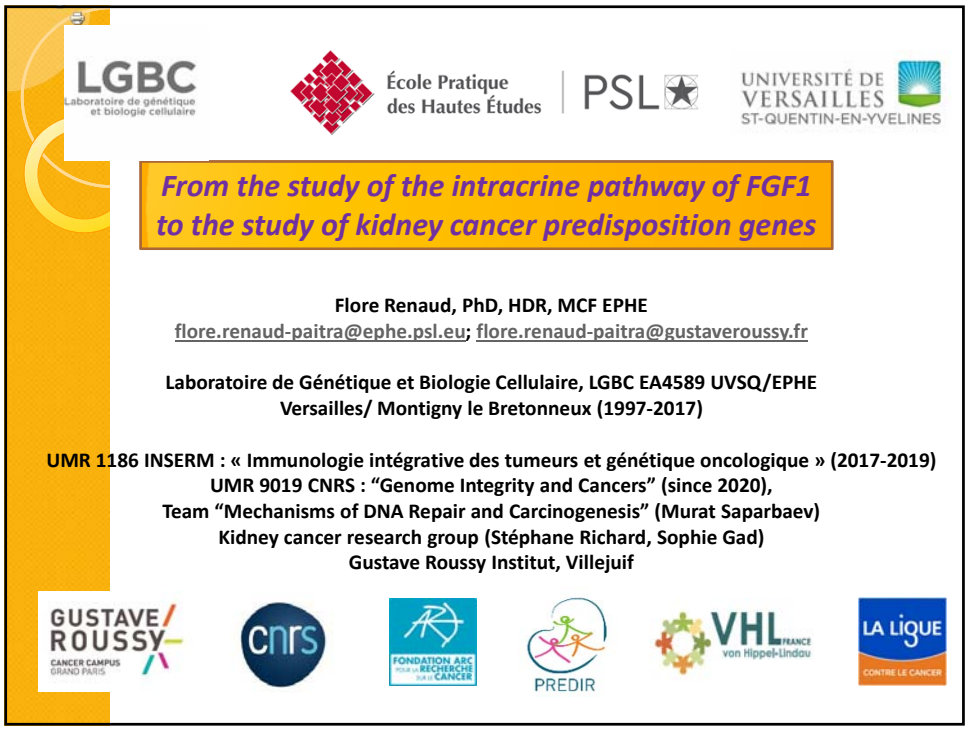
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From the study of the intracrine pathway of FGF1 to the study of kidney cancer predisposition genes
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UMR 9019 CNRS : "Genome Integrity and Cancers" (since 2020),
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Kidney cancer research group (Stéphane Richard, Sophie Gad)
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