BHARATHIDASAN UNIVERSITY

Tiruchirappalli- 620024,
Tamil Nadu, India

Programme: M.Sc., Biomedical science

Course Title : Molecular medicine

Course Code : BM48C16M

Unit – III

TOPIC: NF - kB & TGF Beta & Wnt- beta

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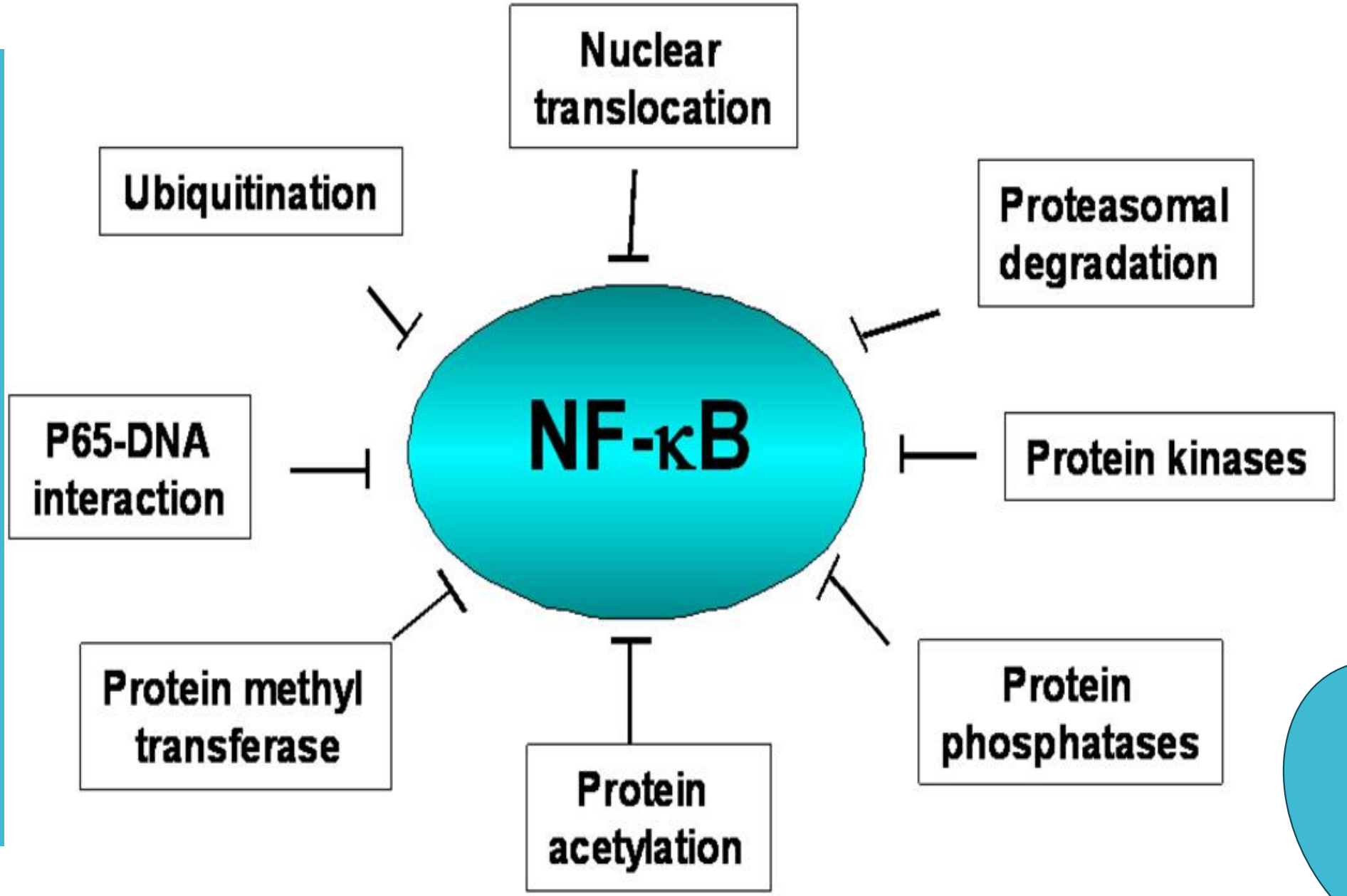
Guest lecturer
Department of Biomedical Science

NF - kB &
TGF Beta &
Wnt- beta


Nuclear translocation
Ubiquitination
Proteasomal degradation
NF-κB
P65-DNA interaction
Protein kinases
Protein methyl transferase
Protein acetylation
Protein phosphatases

p50/p105
p52/p100

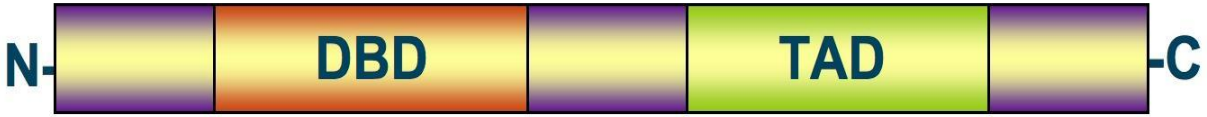
Class I

Ankyrin Repeats
Transrepression

DNA binding
IκB-binding
dimerization

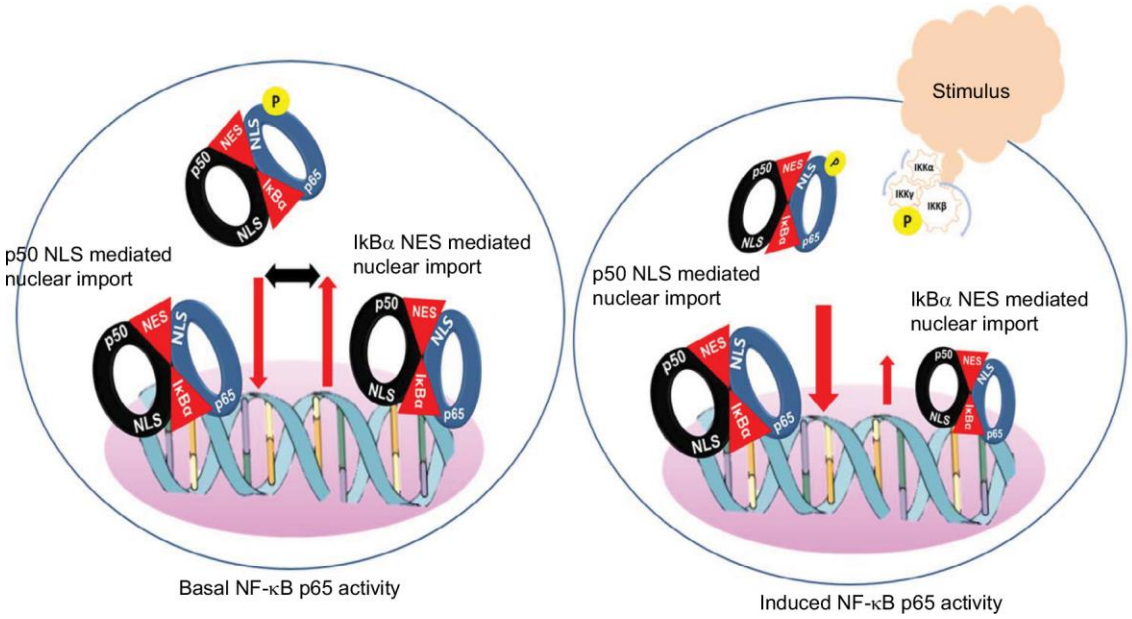
RelA
RelB

Class II

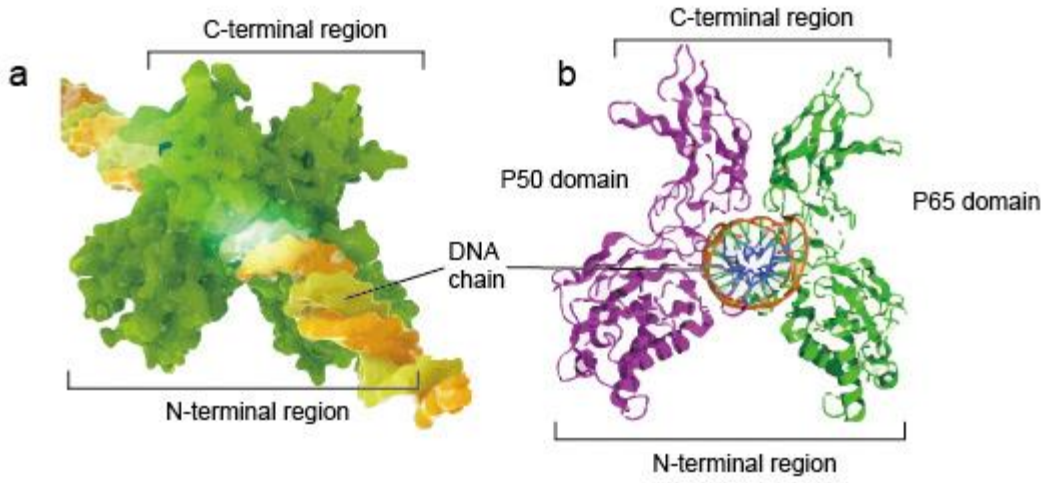


Transactivation

Model for basal & induced p65(Rel A) NF kB activity



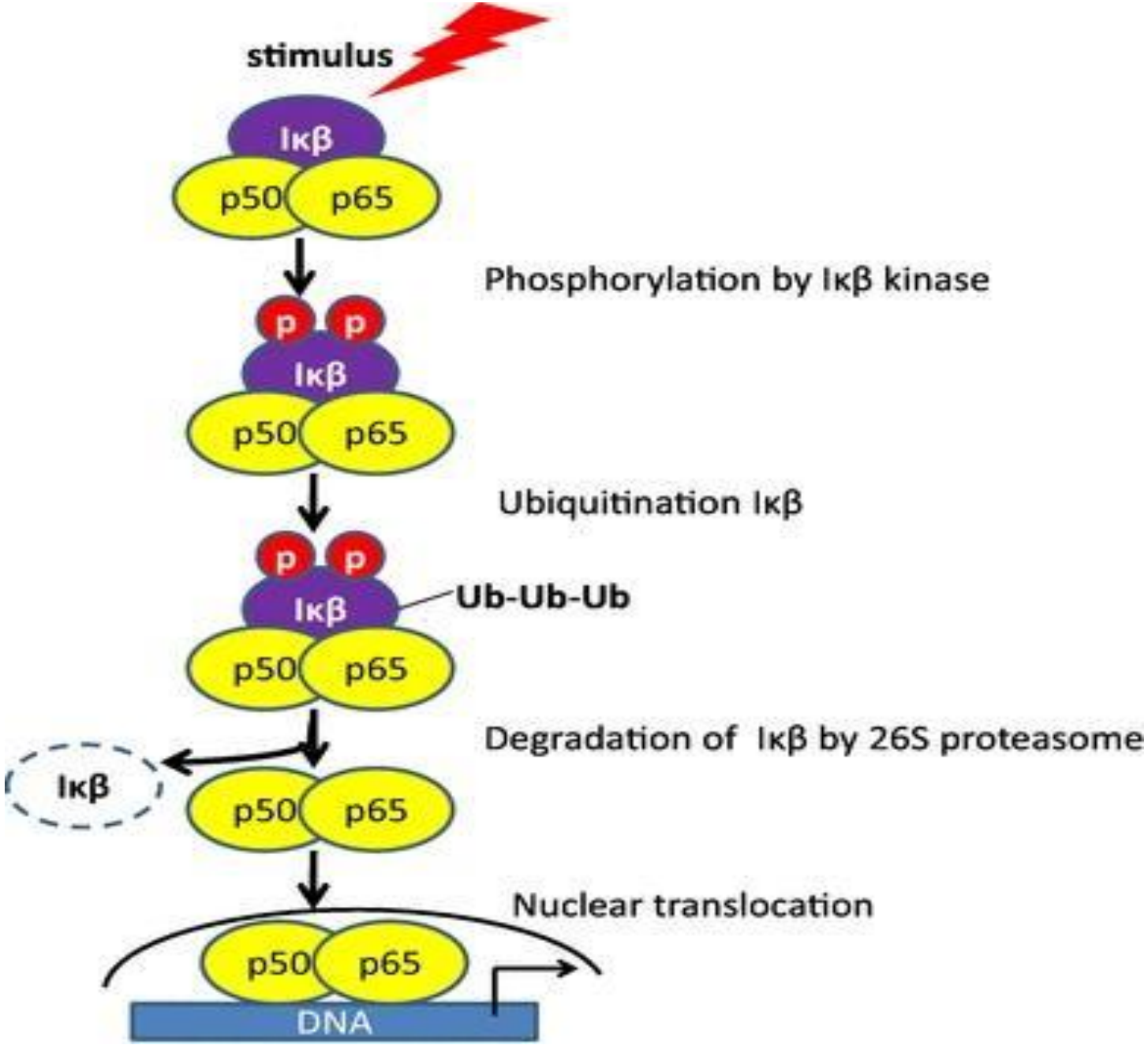
The structure of NF-kB protein dimer binding with DNA chain:



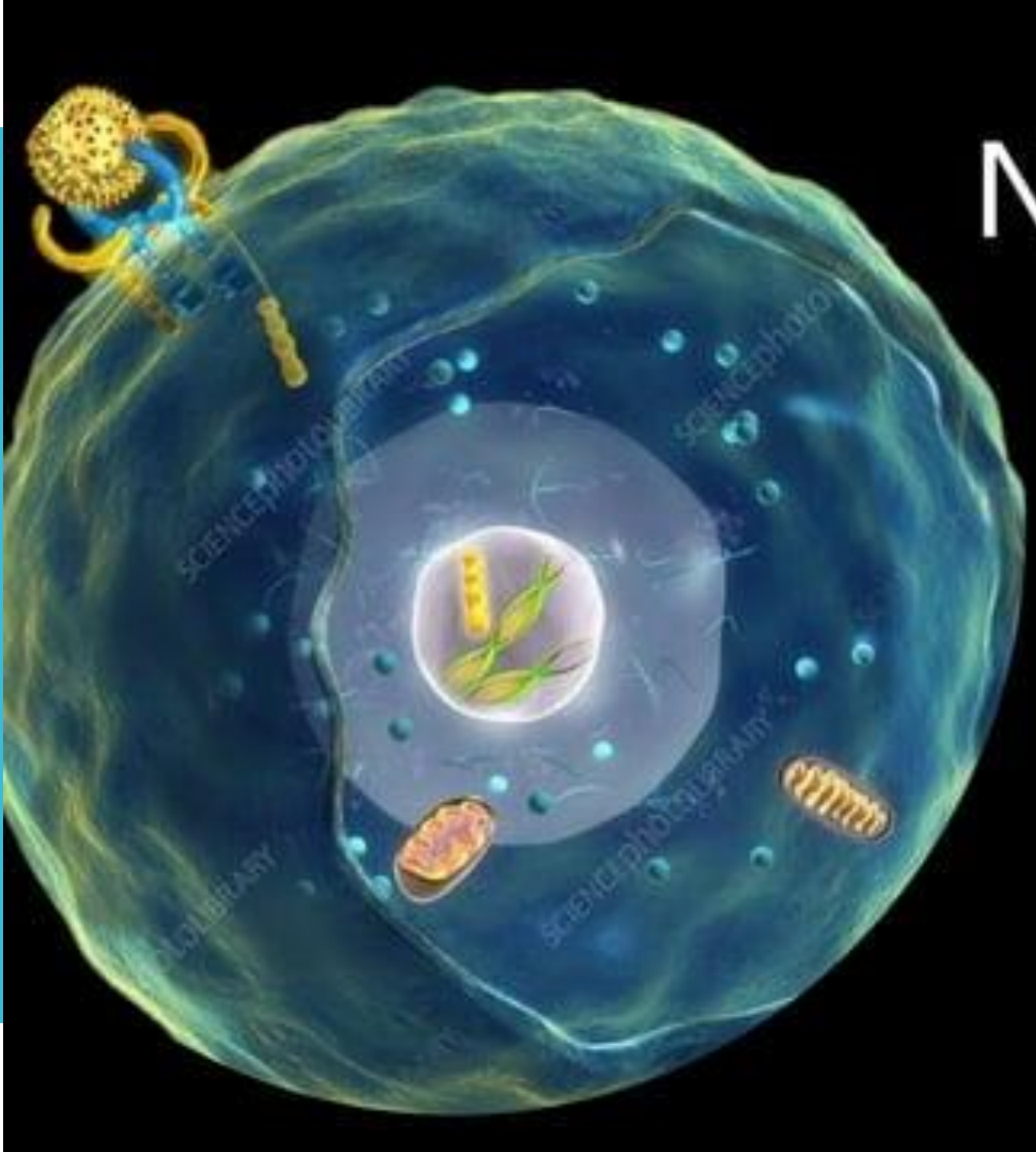
DISCOVERY:
SEN

- NF-κB was discovered in 1986 by Ranjan Sen & David Baltimore.
- The discovery occurred while Sen & Baltimore were studying the regulation of the Ig kappa light chain gene in B cells

Activation of NF-kB



5 fingers to Remember NF-kB cell signalling

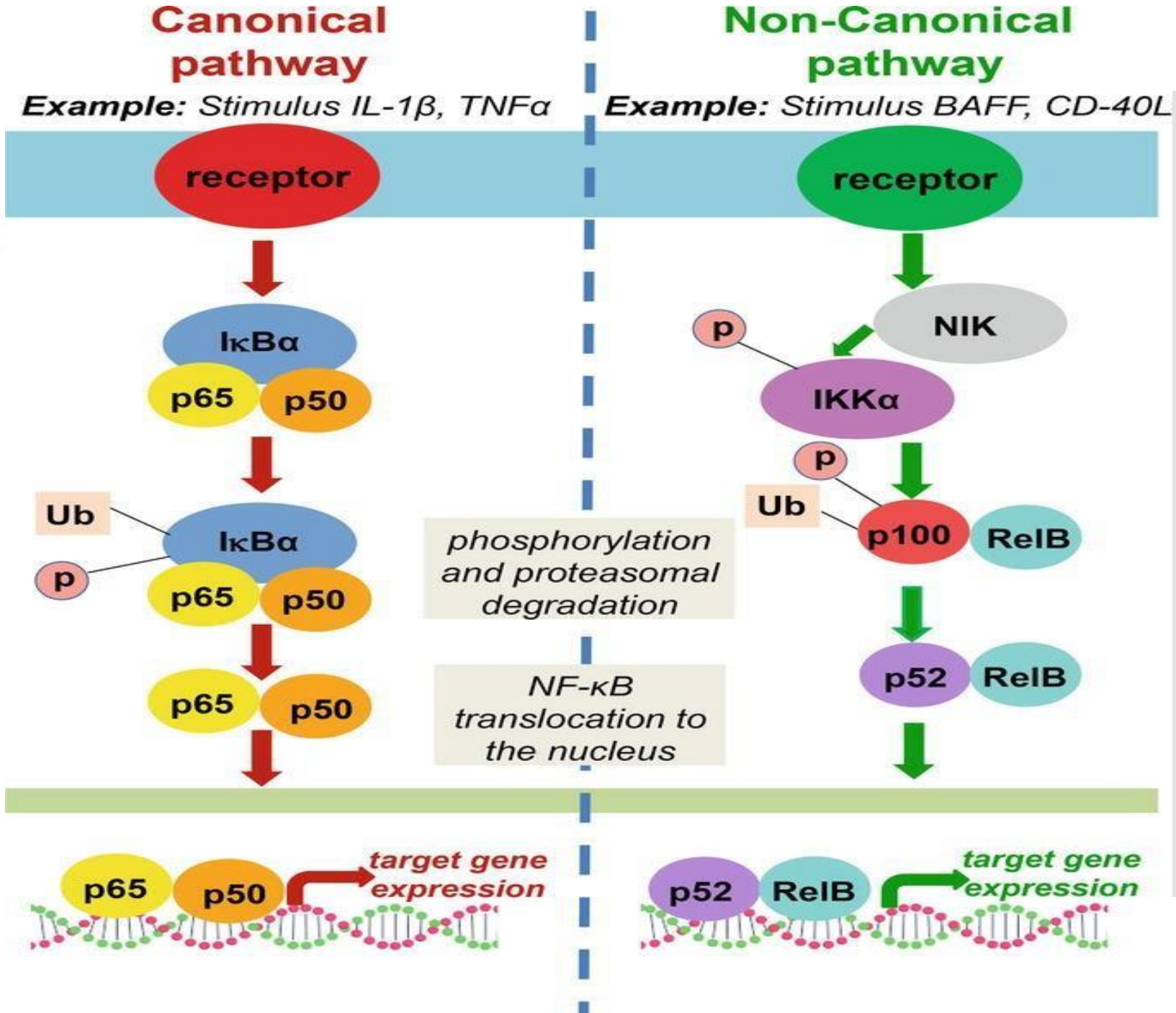


Nf-kB signaling

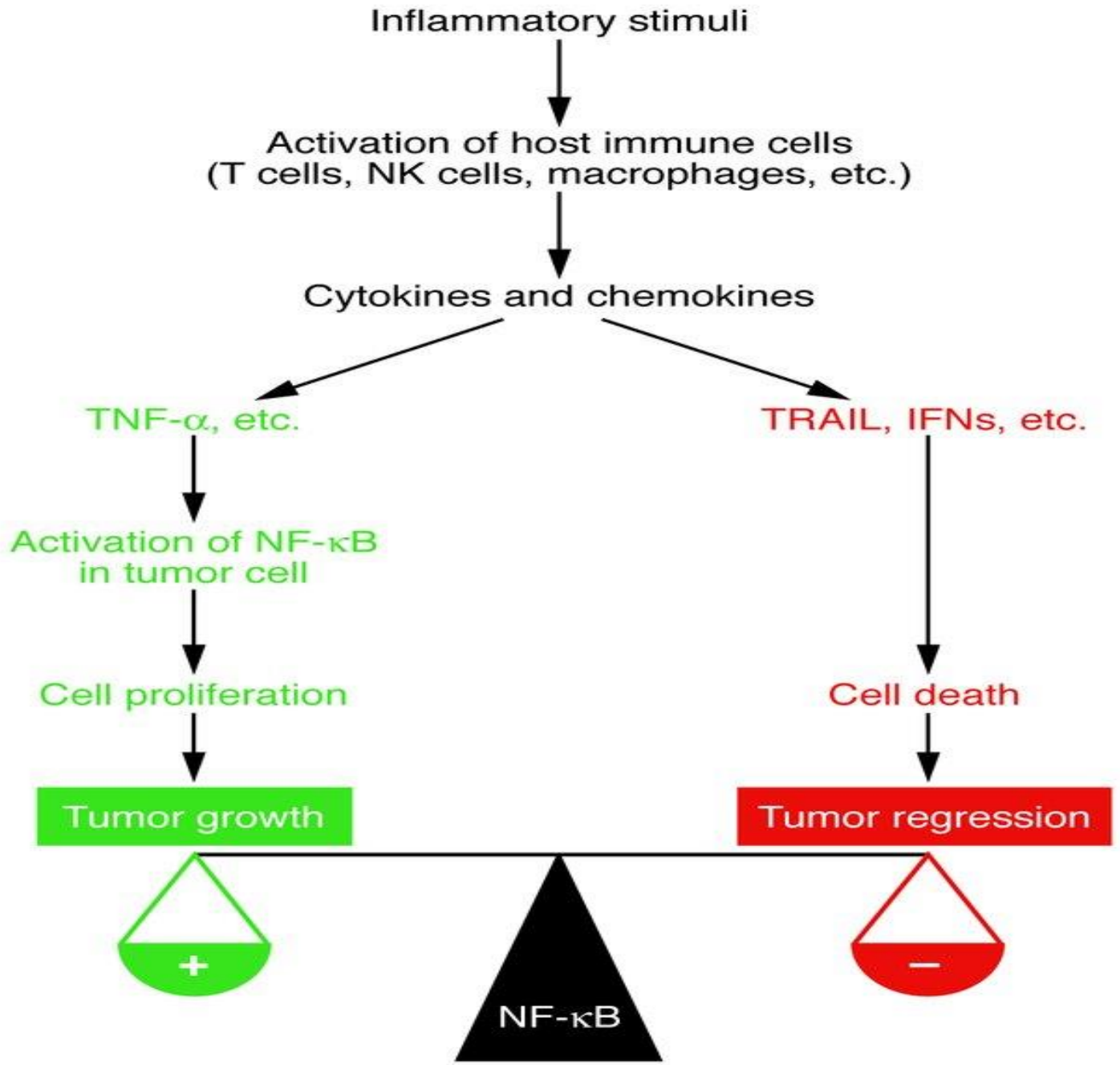
Pathway

Pathways of

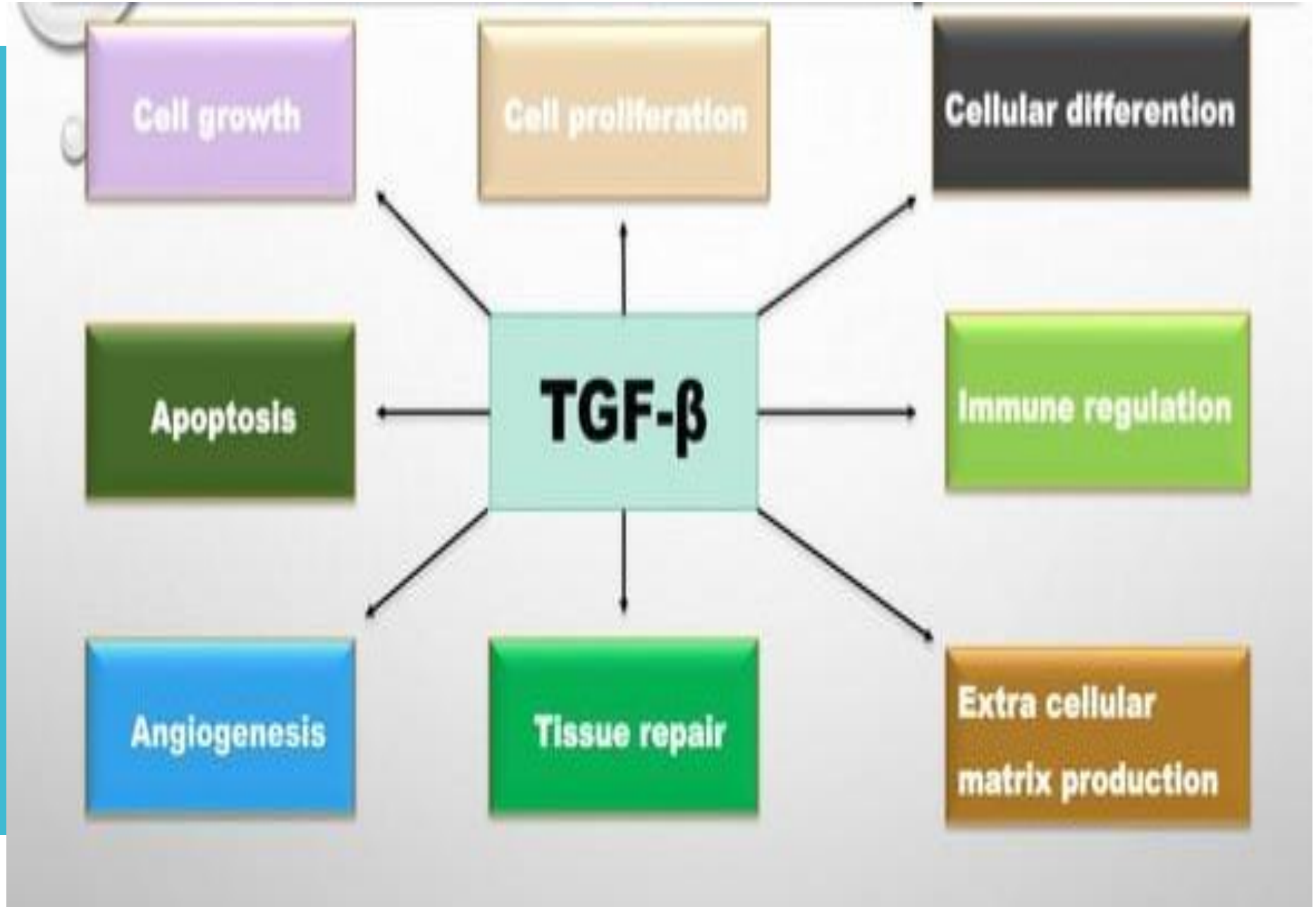

NF-κB


Canonical pathway
Example: Stimulus IL-1β, TNFα
Non-Canonical pathway
Example: Stimulus BAFF, CD-40L
receptor
receptor
IκBα
p65
p50
NIK
p
IKKα
p
Ub
Ub
IκBα
p
p65
p50
p100
RelB
phosphorylation and proteasomal degradation
p65
p50
p52
RelB
NF-κB translocation to the nucleus
p65
p50
target gene expression
p52
RelB
target gene expression

Inhibition of NF-kB in cancer cells



CHARACTERISTICS	CANONICAL	NON-CANONICAL
1. Basic characteristics	Rapid & transient	Slow & persistent
2. Protein synthesis	Independent of protein synthesis	Dependent on protein synthesis
3. Response to stimuli	Respond to numerous stimuli	Respond to a subset of TNFR signals
4. Functions	Diverse functions	Specific functions


Cell growth
Cell proliferation
Cellular differention
Apoptosis
TGF-β
Immune regulation
Angiogenesis
Tissue repair
Extra cellular matrix production

History of TGF – beta

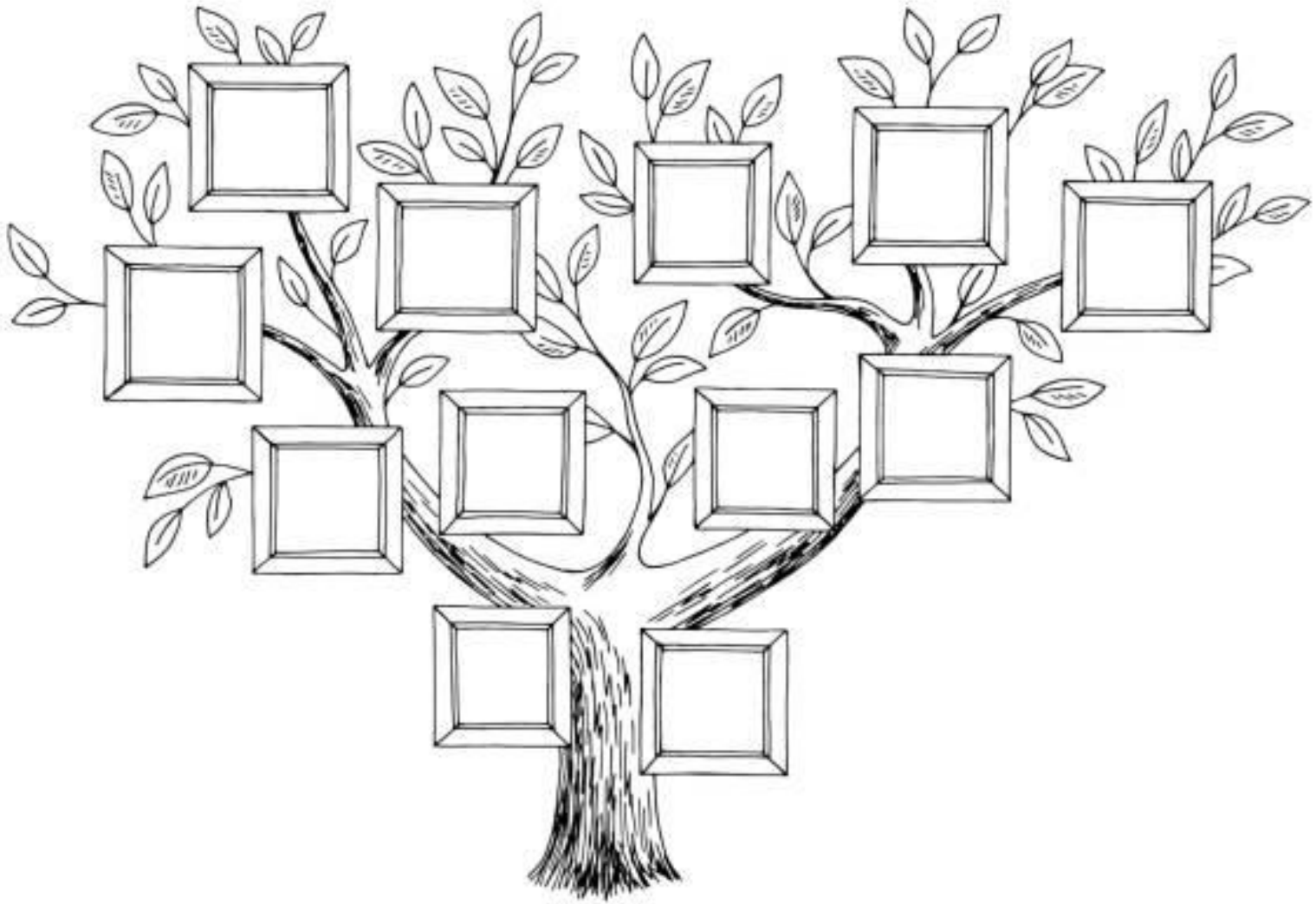
In the early 19 polypeptides & hormones.

A new polype SGF (Sarcoma Growth Factor)
discovered in c transformed rat kidney fibroblasts.

They were call Transforming Growth Factor-α (TGF-α) &
Transforming Growth Factor-β (TGF-β).

TGF-β was furt Roberts & Sporn
polypeptide ca fibroblast growth & collagen
production

TGF – beta fa



There are 3 known isoforms expressed in mammalian tissues;

TGF-β1 ------ the most abundant & ubiquitously expressed isoform, was cloned from human term placental mRNA

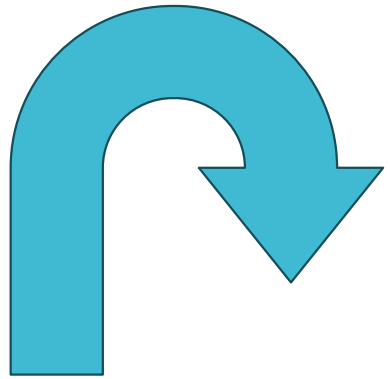
TGF-β2 ------ 1st described in human glioblastoma cells.

TGF-β2 is capable of suppressing interleukin-2-dependent growth of T cells (G-TsF).

------- expressed by neurons & astroglial cells in embryonic NS.

TGF-β3 ------ isolated from a cDNA library of human rhabdomyosarcoma cell line; it shares 80% of AA sequence with TGF-β1 & TGF-β2.

3 types of cell surface proteins mediate TGF-β signaling:



TβRI & TβRII mediate signal transduction.

TβRI ------ highly conserved 30 AAs long GS domain in the cytoplasmic part, which needs to be phosphorylated to activate TβRI.

TβRII ------ contains 10 bp polyadenine repeat in the coding region of the extracellular domain.

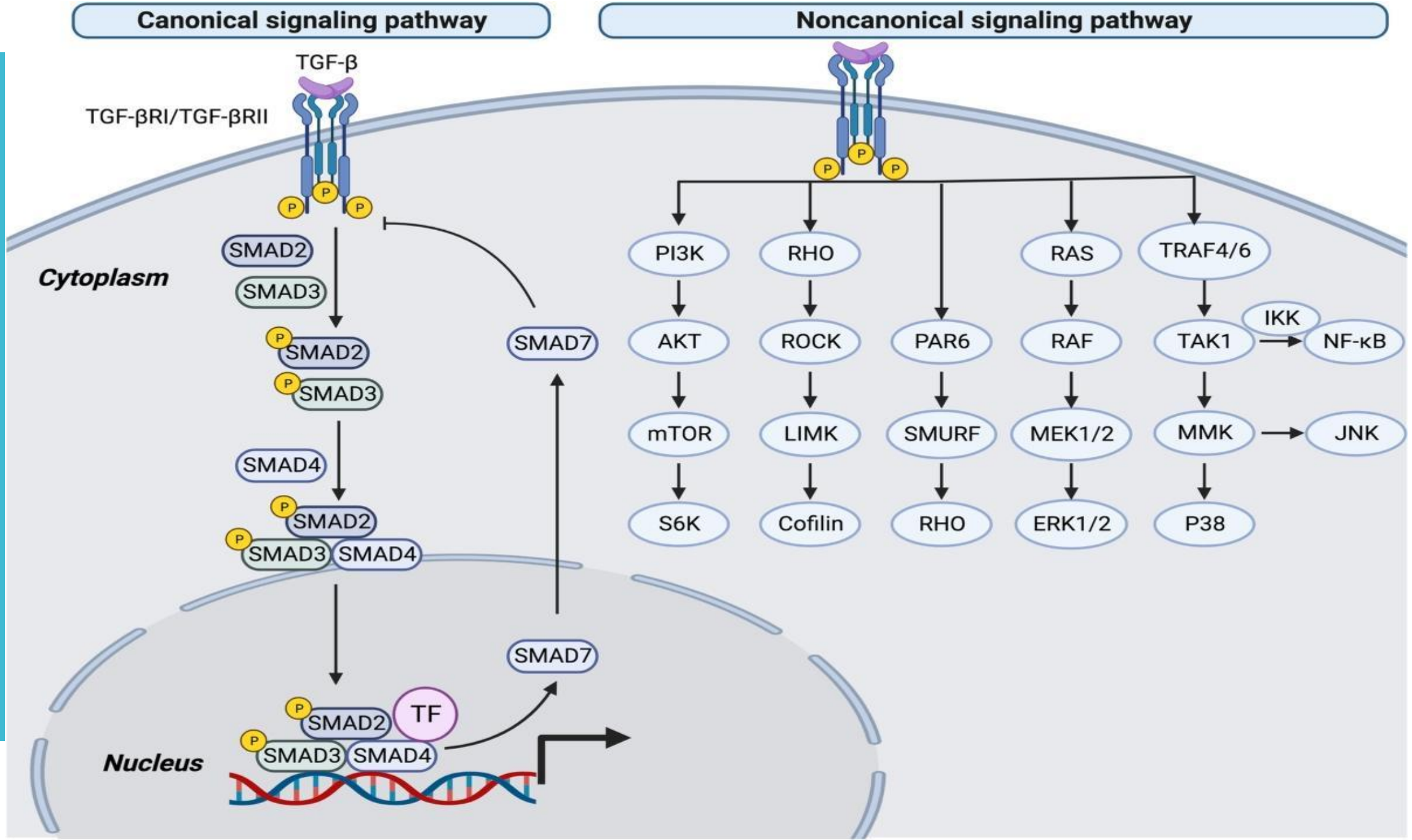
TβRIII ----- also called betaglycan, is the largest (250–350 kDa) & most abundant binding molecule.

SMAD PROTEINS:

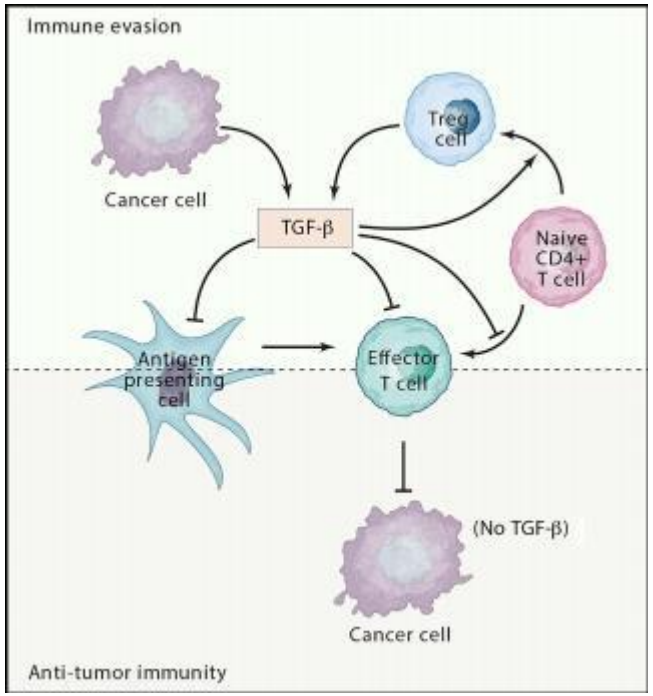
On binding with its surface receptors, TGF –beta proteins transmit their signals to an intracellular protein called SMAD.

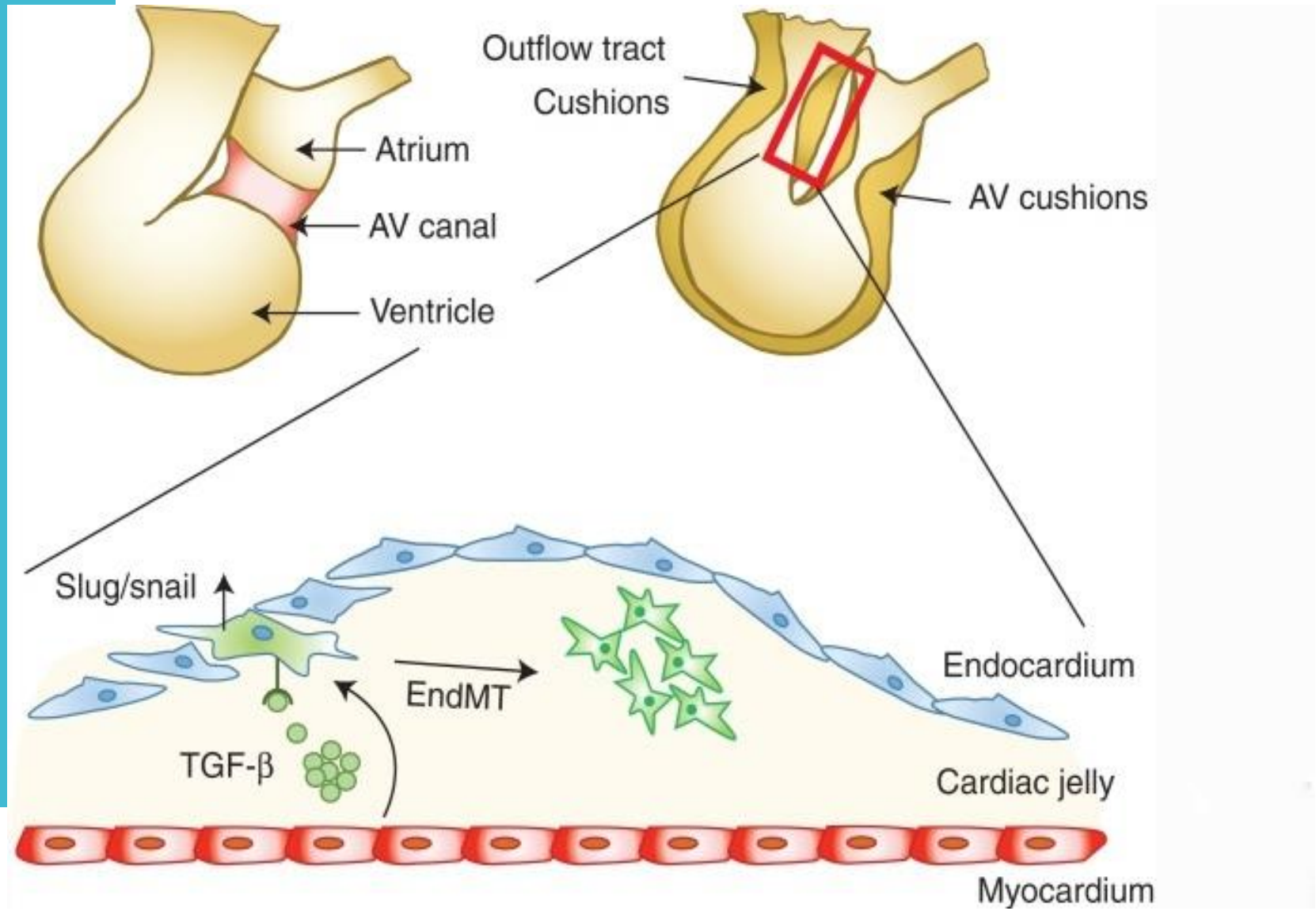
SMADs can be classified into 3 groups based on their function:

- ✓ the receptor-regulated SMADs (R-SMADs) --- SMAD1, SMAD2, SMAD3, SMAD5 & SMAD8
- ✓ the common SMAD (Co-SMAD) ---- SMAD4
- ✓ the inhibitory SMADs (I-SMADs) ---- SMAD6 & SMAD7


Canonical signaling pathway
Noncanonical signaling pathway
TGF-β
TGF-βRI/TGF-βRII
Cytoplasm
SMAD2
SMAD3
SMAD4
SMAD7
PI3K
RHO
RAS
TRAF4/6
AKT
ROCK
PAR6
RAF
TAK1
IKK
NF-κB
mTOR
LIMK
SMURF
MEK1/2
MMK
JNK
S6K
Cofilin
RHO
ERK1/2
P38
TF
Nucleus

Adaptive imm



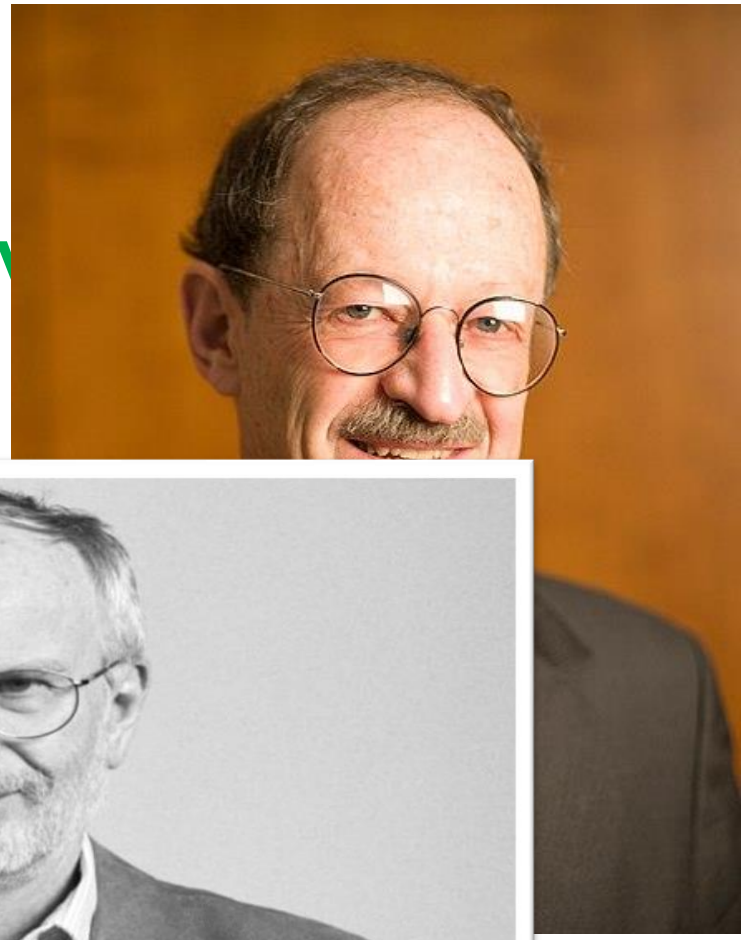

Outflow tract
Cushions
Atrium
AV canal
Ventricle
AV cushions
Slug/snail
EndMT
TGF-β
Endocardium
Cardiac jelly
Myocardium

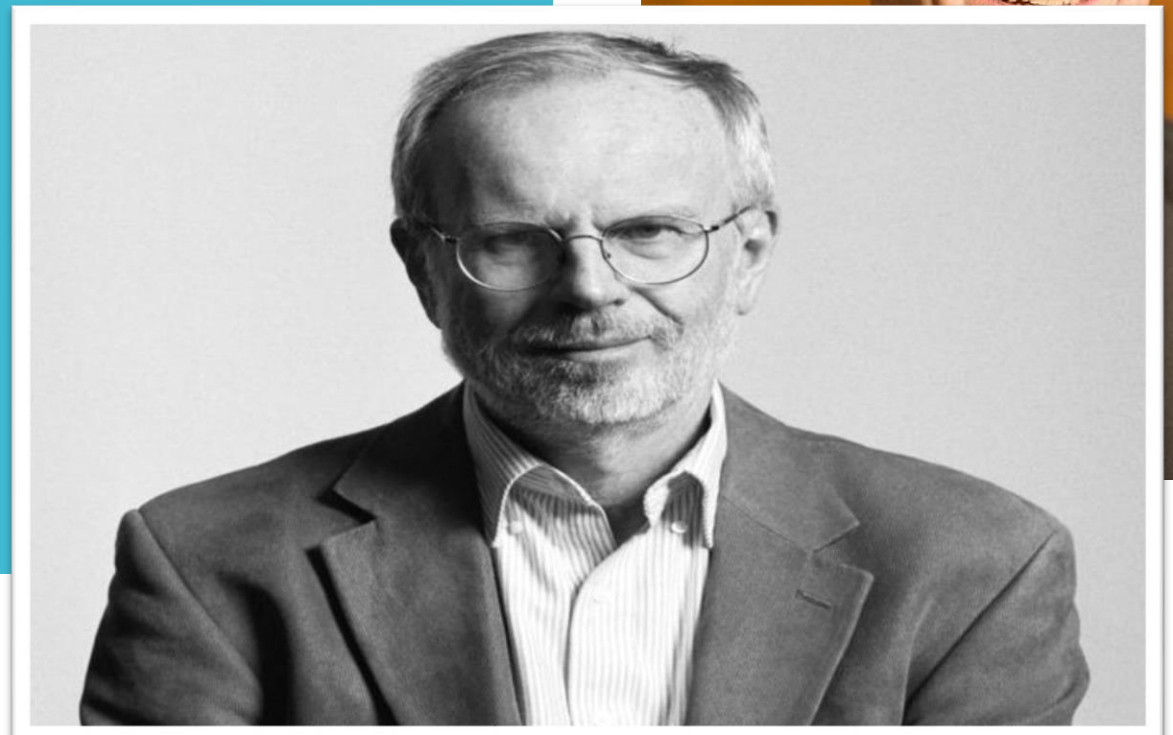
Discovery of W

Nusse & Varmus

pathway in 1982

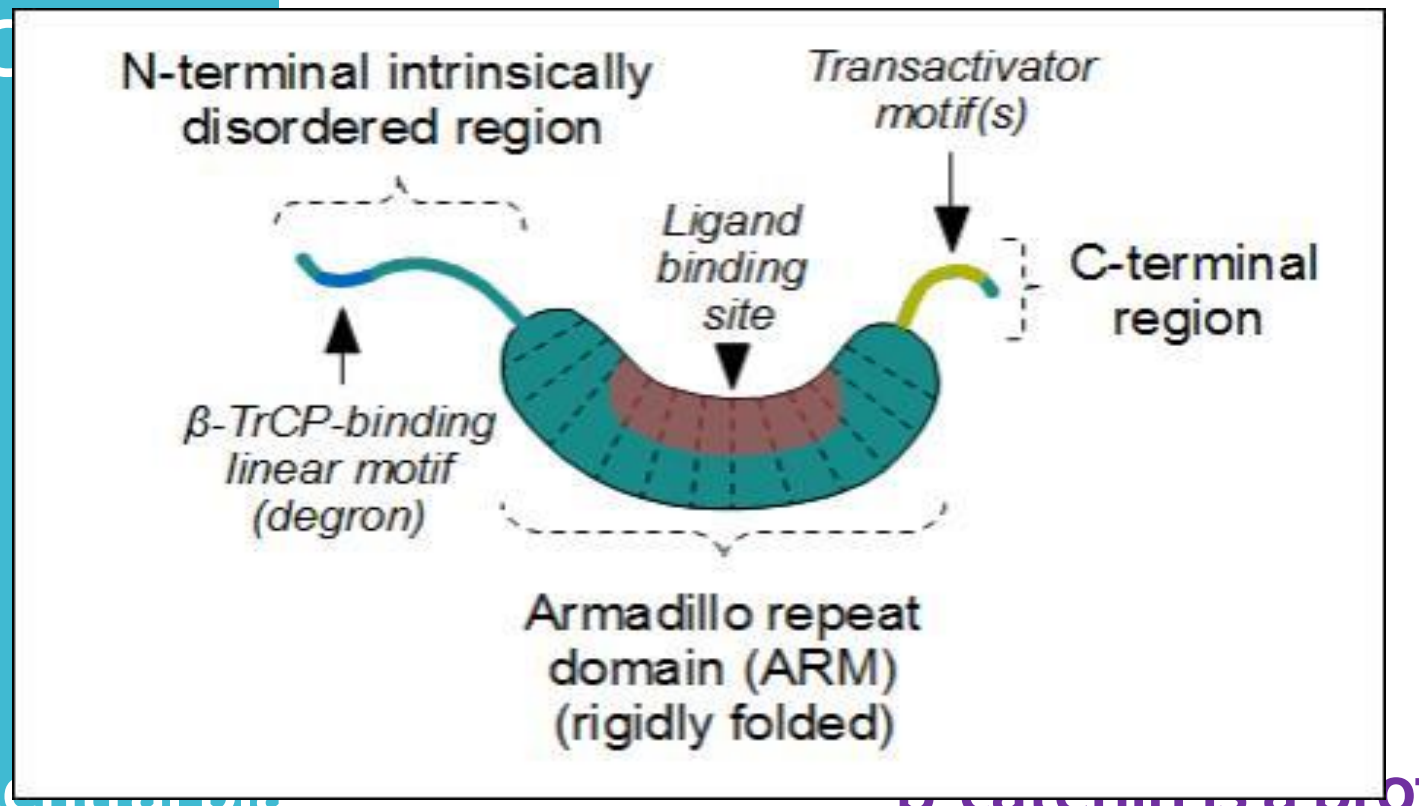
Mammary Tumor V

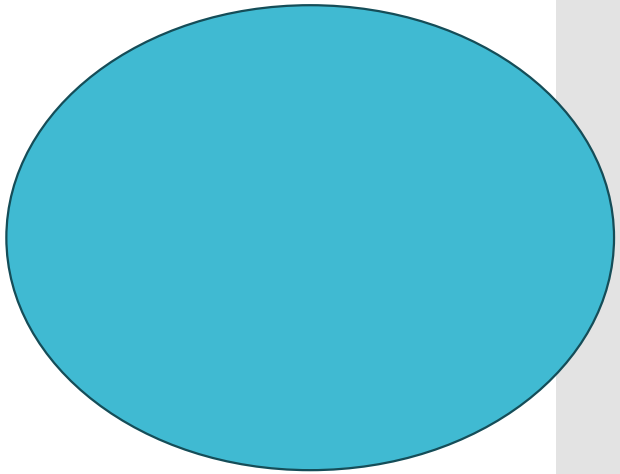




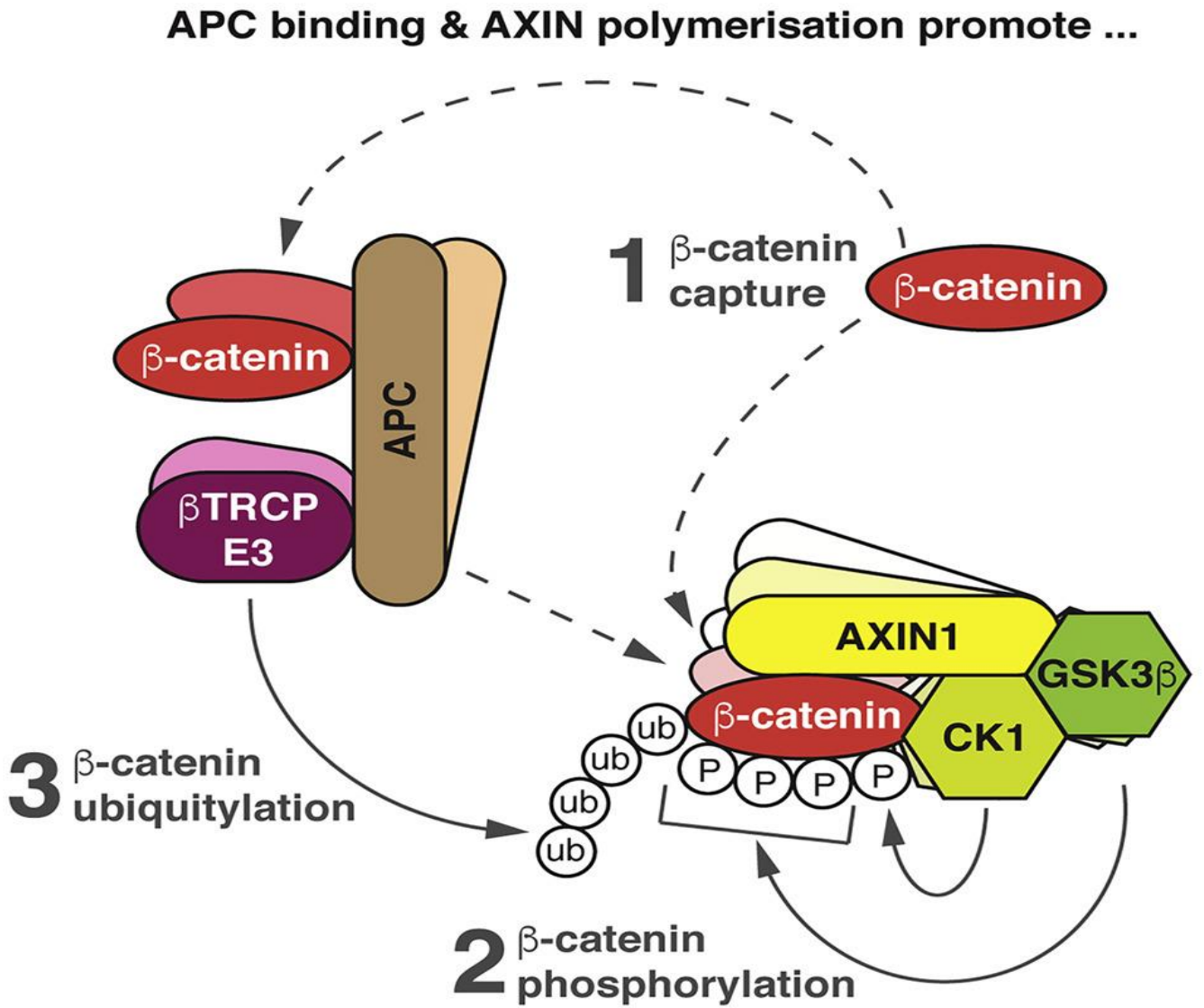
Mouse

Beta-C

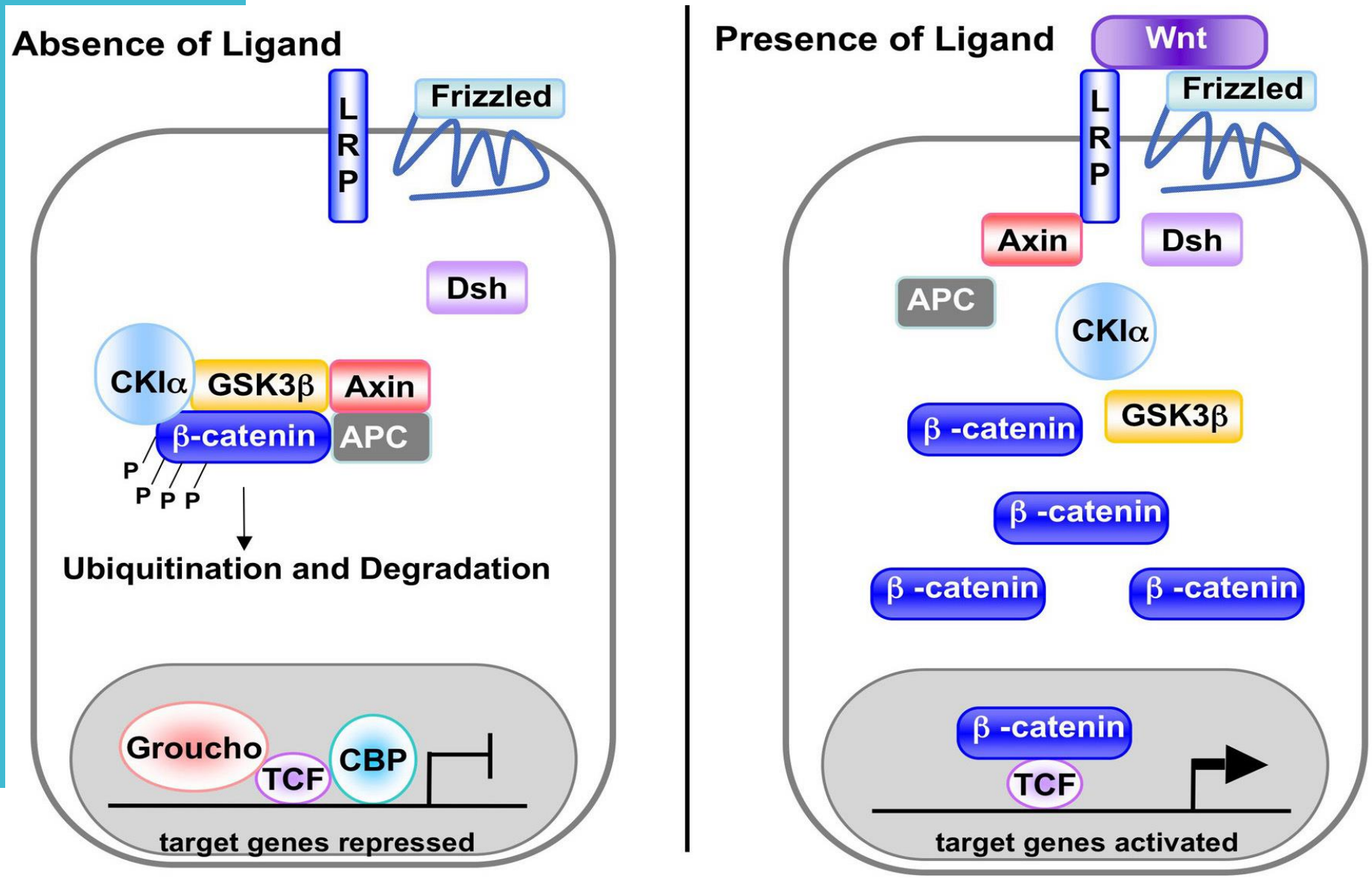




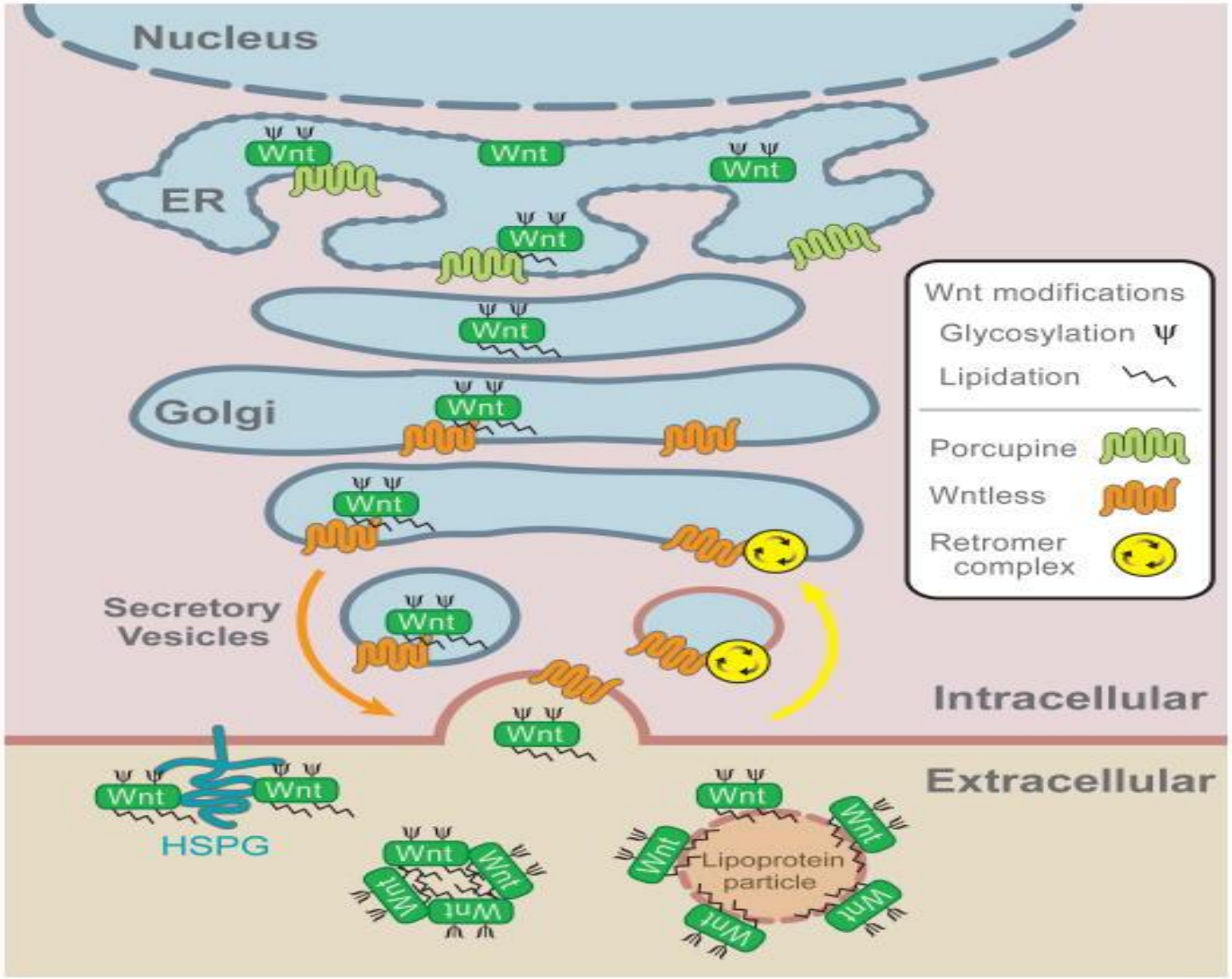
A c p-catenin is a protein stabilized, translocates to the nucleus genes.


APC binding & AXIN polymerisation promote ...
1 β-catenin capture
β-catenin
β-catenin
APC
βTRCP E3
AXIN1
GSK3β
β-catenin
CK1
ub
ub
ub
ub
P
P
P
P
3 β-catenin ubiquitylation
2 β-catenin phosphorylation

Mechanism:


Absence of Ligand
LRP
Frizzled
Dsh
CKIα
GSK3β
Axin
β-catenin
APC
P
P P P
Ubiquitination and Degradation
Groucho
TCF
CBP
target genes repressed
Presence of Ligand
Wnt
LRP
Frizzled
Axin
Dsh
APC
CKIα
β -catenin
GSK3β
β -catenin
β -catenin
β -catenin
β -catenin
TCF
target genes activated

Wnt biogenesis & secretion :



Reference :

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- **Lenka kubiczkova *et al.*, (2012). TGF-β an eecellent servant but a bad master.**

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- **Peiqi Liu, Yue Li, Weilin Wang, Yuzuo Bai, Huimin Jia, Zhengwei Yuan, Zhonghua Yang. (2022). Role and mechanisms of the NF-κB signalling pathway in various developmental processes. 153. https://doi.org/10.1016/j.biopha.2022.113513.**

THANK YOU