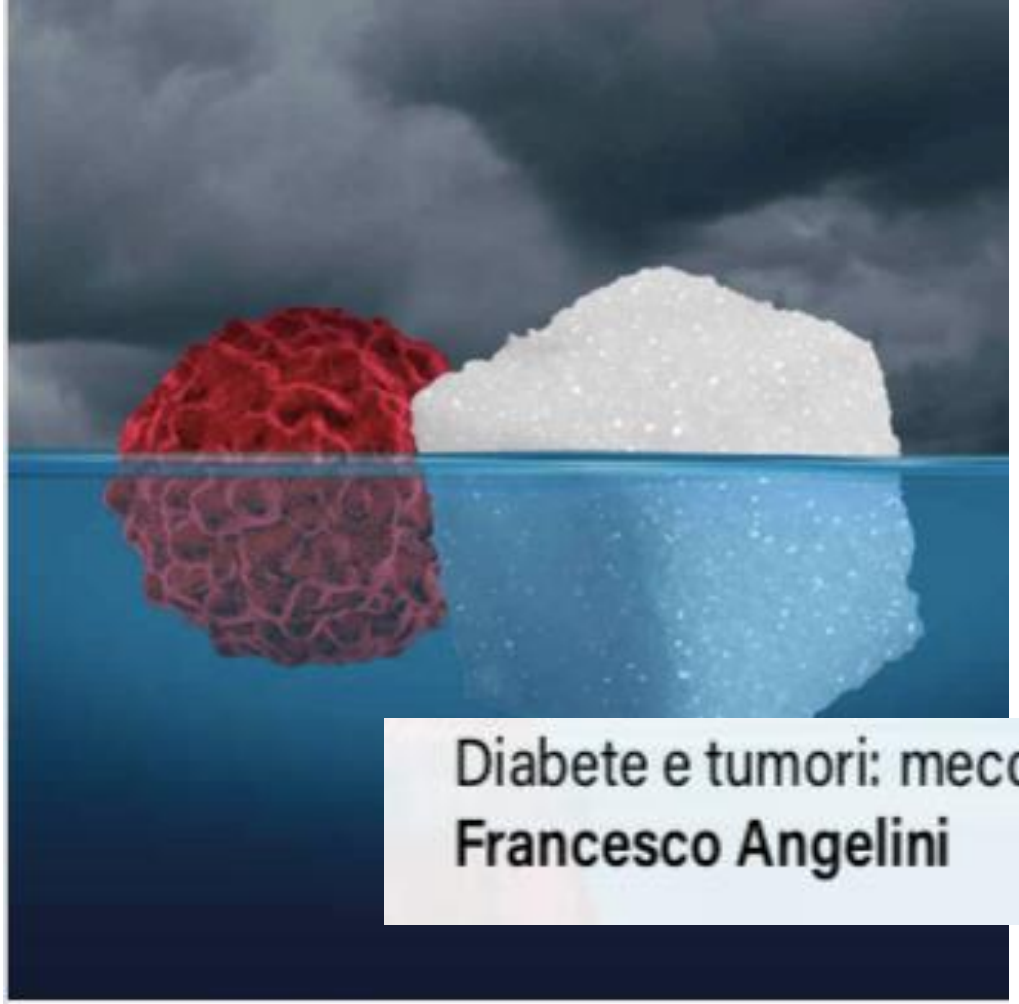


Diabete e tumori: meccanismi patogenetici e stile di vita

Francesco Angelini

Direttore Struttura Complessa di Oncologia
Ospedale “Regina Apostolorum”
Albano Laziale

DIABETE E TUMORI NELLA PRATICA CLINICA:
RILEVANZA, CRITICITÀ, SOLUZIONI

ROMA, 9 Novembre 2019

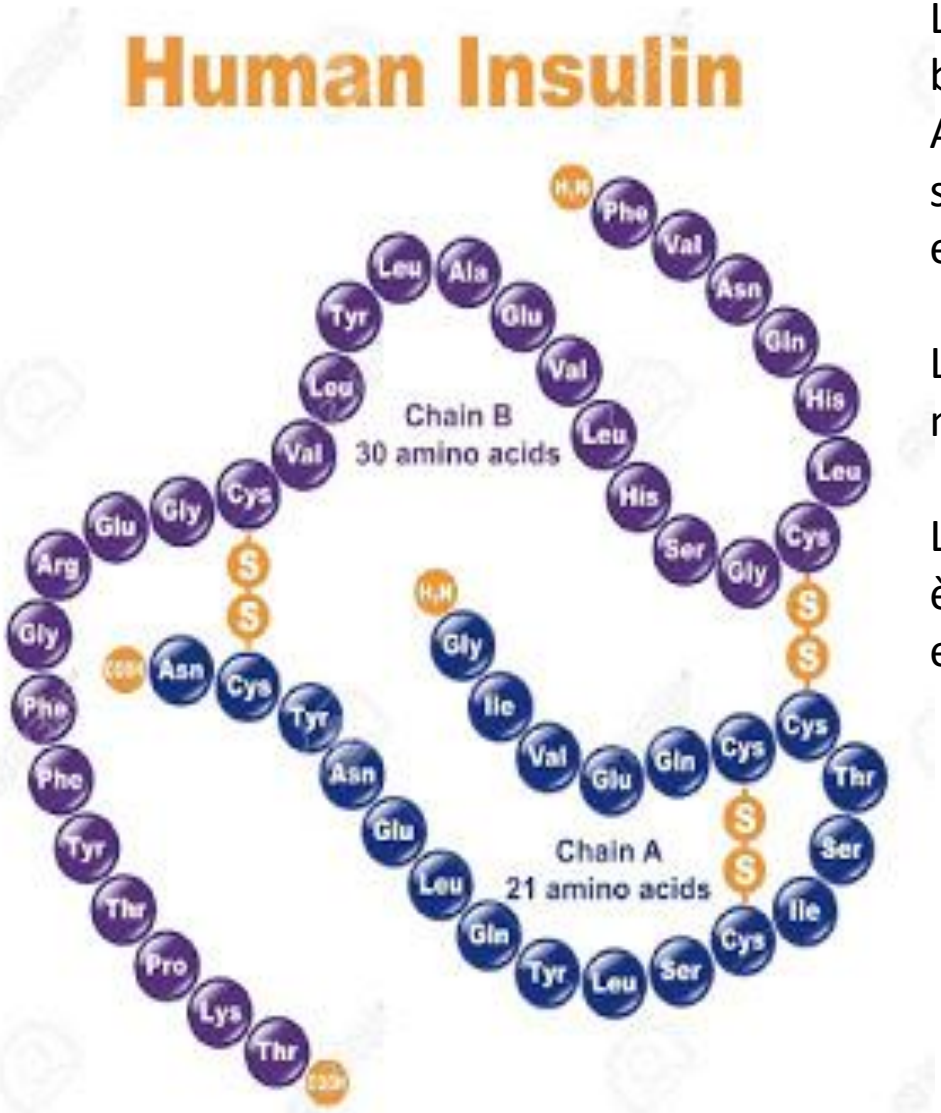
UNAHOTELS DECÒ
Via Giovanni Amendola, 57

Table 1. *Diabetes and cancer mortality in men*

Cause of Death	Diabetes Risk Relative to No Diabetes (Men)	
	Age-adjusted RR (95% CI)	Multivariable-adjusted RR (95% CI)*
Oral cavity of pharynx	1.39 (1.04–1.87)	1.44 (1.07–1.94)
Colon	1.21 (1.08–1.35)	1.15 (1.03–1.29)
Liver or intrahepatic bile duct	2.40 (2.02–2.86)	2.26 (1.89–2.70)
Pancreas	1.42 (1.25–1.61)	1.40 (1.23–1.59)
Bladder	1.23 (1.02–1.48)	1.22 (1.01–1.47)
Breast	4.37 (2.32–8.24)	4.20 (2.20–8.04)
Prostate	0.89 (0.80–0.98)	0.88 (0.79–0.97)

Cause of Death	Diabetes Risk Relative to No Diabetes (Women)	
	Age-adjusted RR (95% CI)	Multivariable-adjusted RR (95% CI)*
Stomach	1.42 (1.08–1.85)	1.24 (0.95–1.63)
Colon	1.29 (1.15–1.45)	1.18 (1.04–1.33)
Liver or intrahepatic bile duct	1.65 (1.25–2.18)	1.40 (1.05–1.86)
Pancreas	1.37 (1.19–1.58)	1.31 (1.14–1.51)
Breast	1.24 (1.11–1.39)	1.16 (1.03–1.29)
Endometrial	1.72 (1.40–2.12)	1.33 (1.08–1.65)
Cervix	1.90 (1.19–3.03)	1.47 (0.91–2.37)
Kidney and other urinary organs	1.42 (1.09–1.87)	1.15 (0.88–1.52)

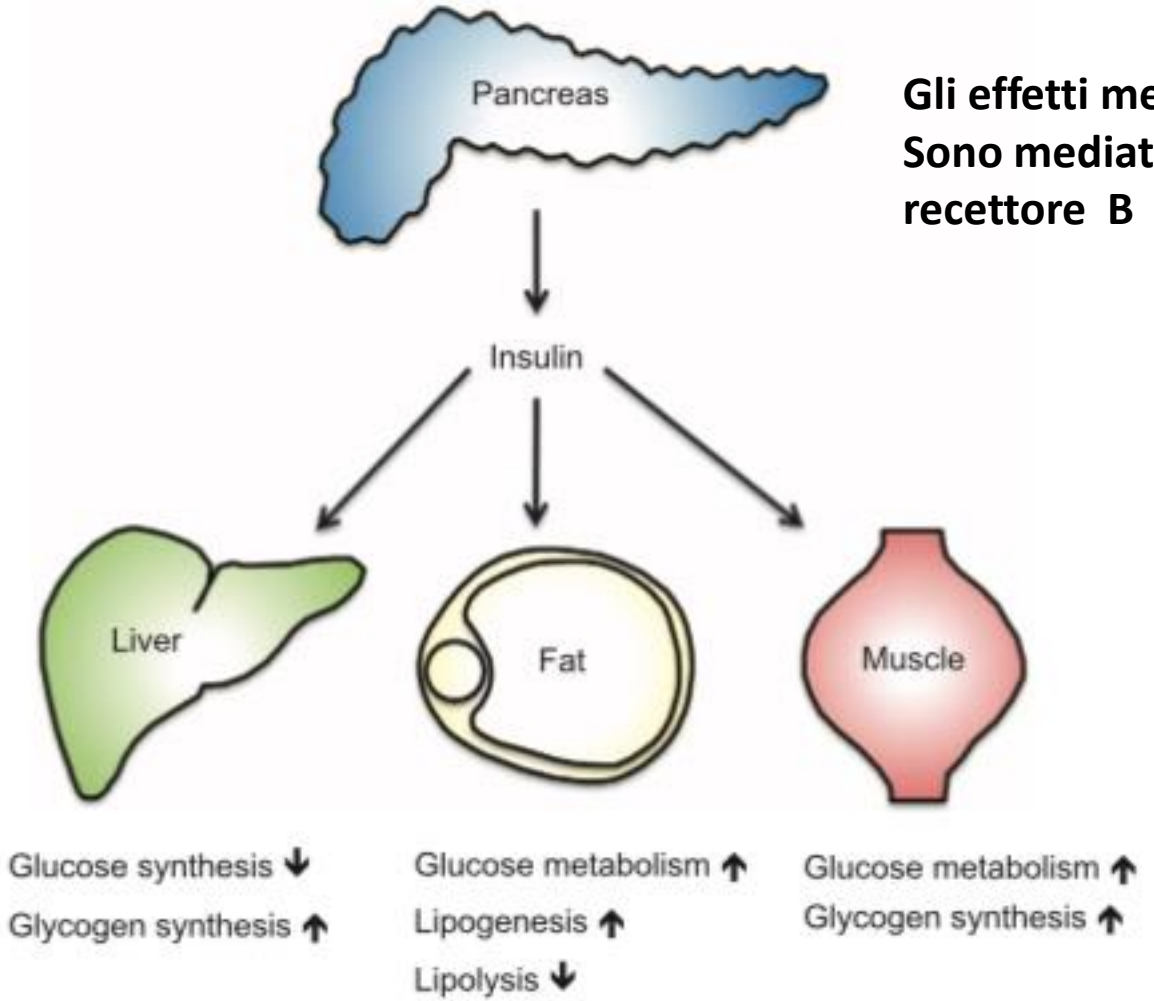
Gallagher , Phisiol Rev , 2015



L’insulina è un ormone prodotto dalle cellule beta del pancreas e formato da due sub-unità , A di 21 aminoacidi e B di 30 aminoacidi . La secrezione pancreatica avviene in risposta alla elevazione dei tassi di glucosio plasmatico .

L’attività dell’insulina si esplica sia in senso metabolico che mitogenico.

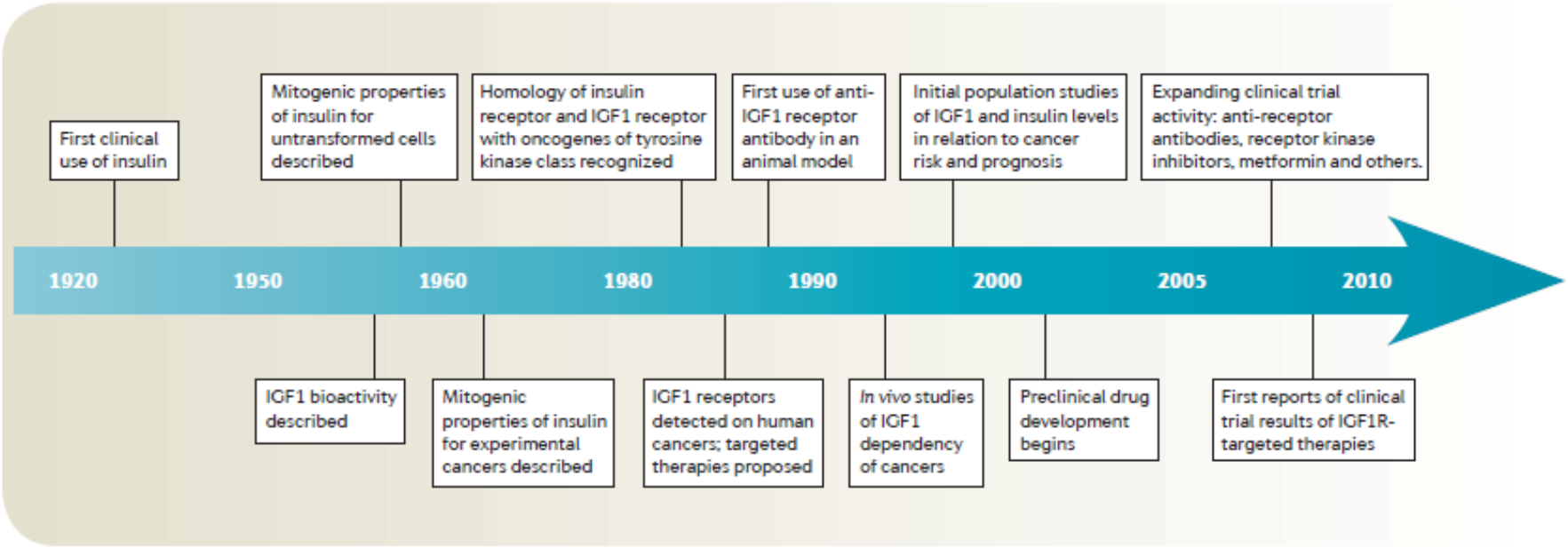
L’azione dell’insulina nei tessuti bersaglio è mediata da due isoforme recettoriali (A e B) , eterodimeri con attivita TK



Gli effetti metabolici dell'insulina Sono mediati prevalentemente dal recettore B

Effetti metabolici dell'insulina

Attività mitogenica dell'insulina

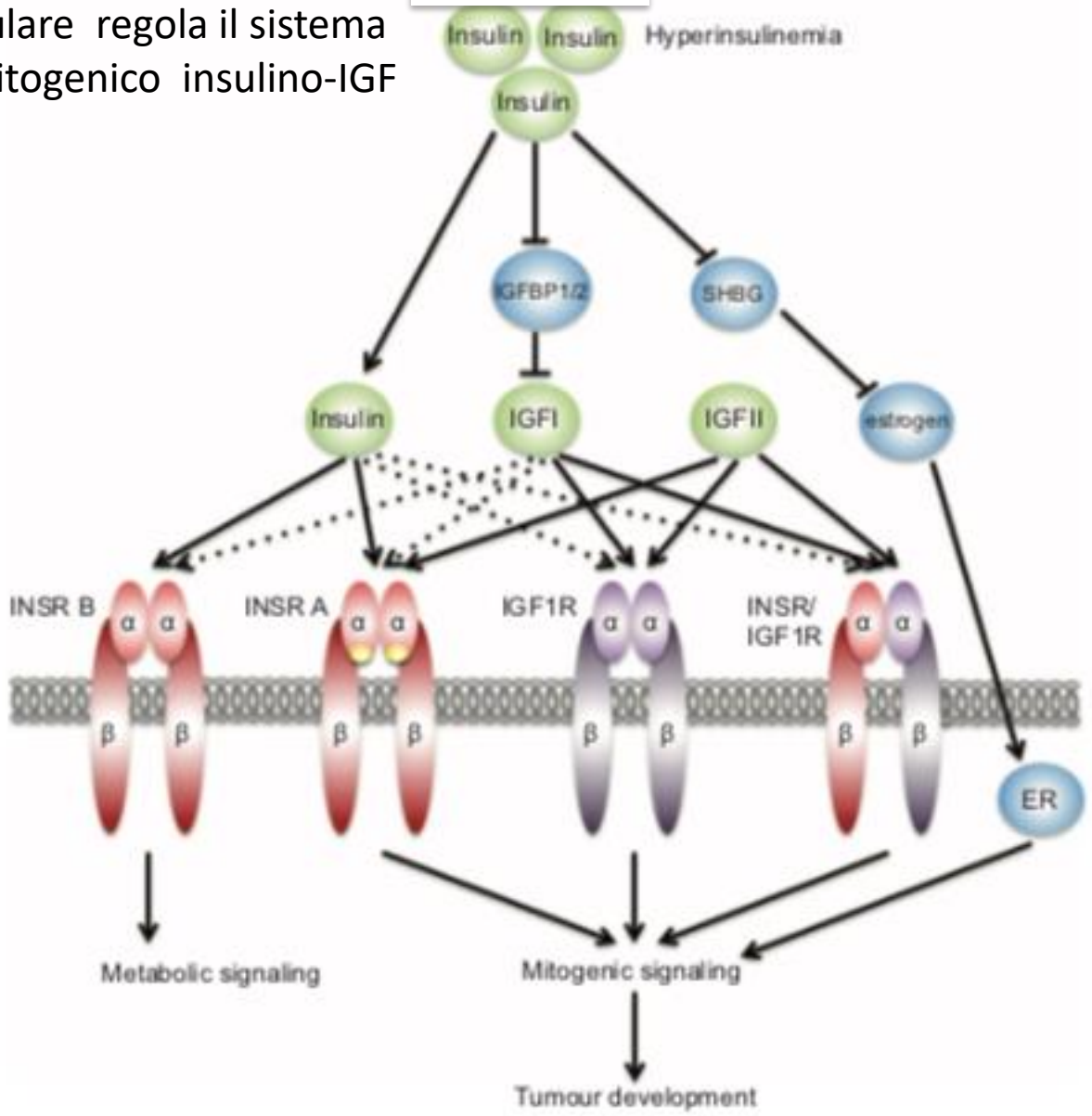


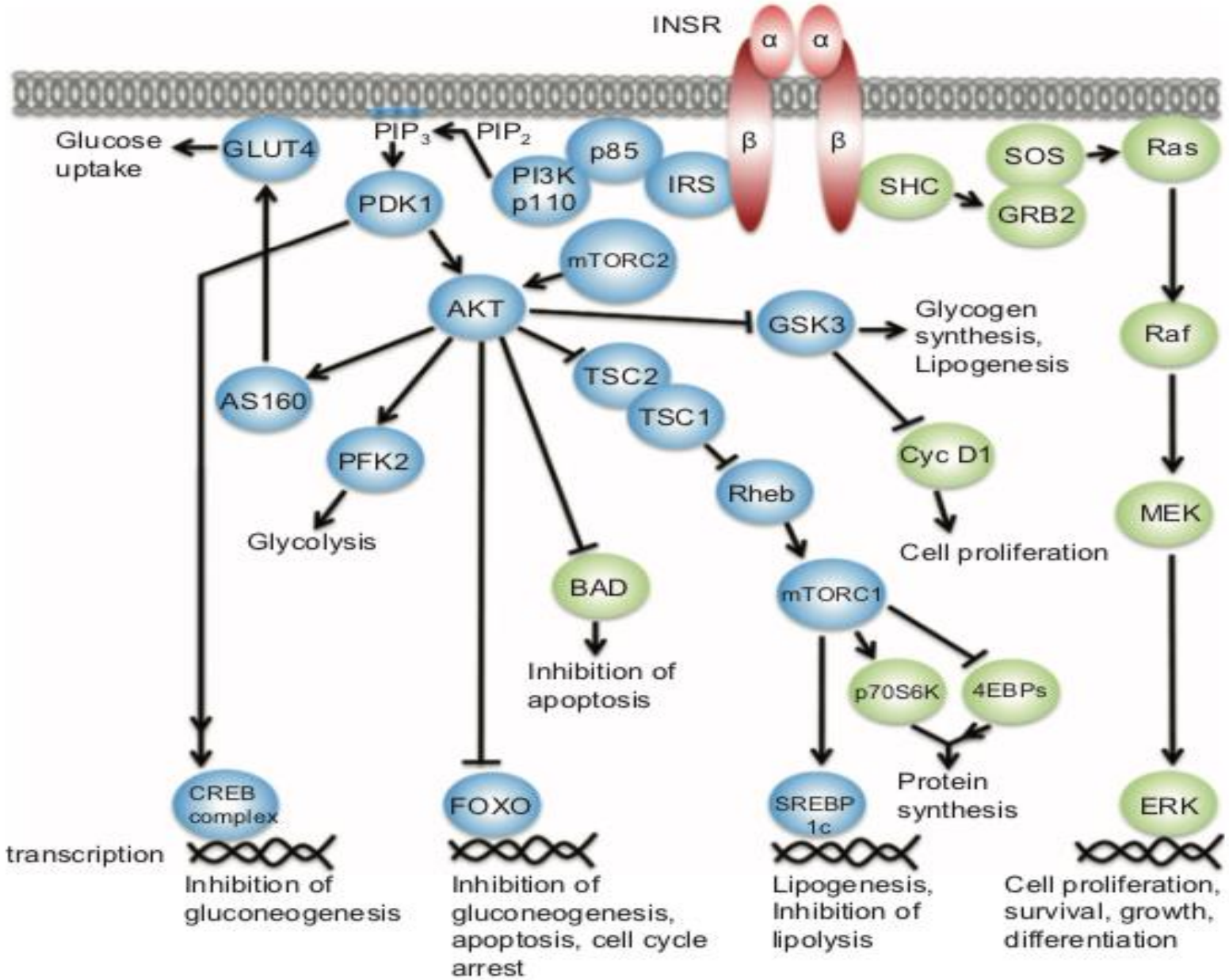
Iperinsulinismo

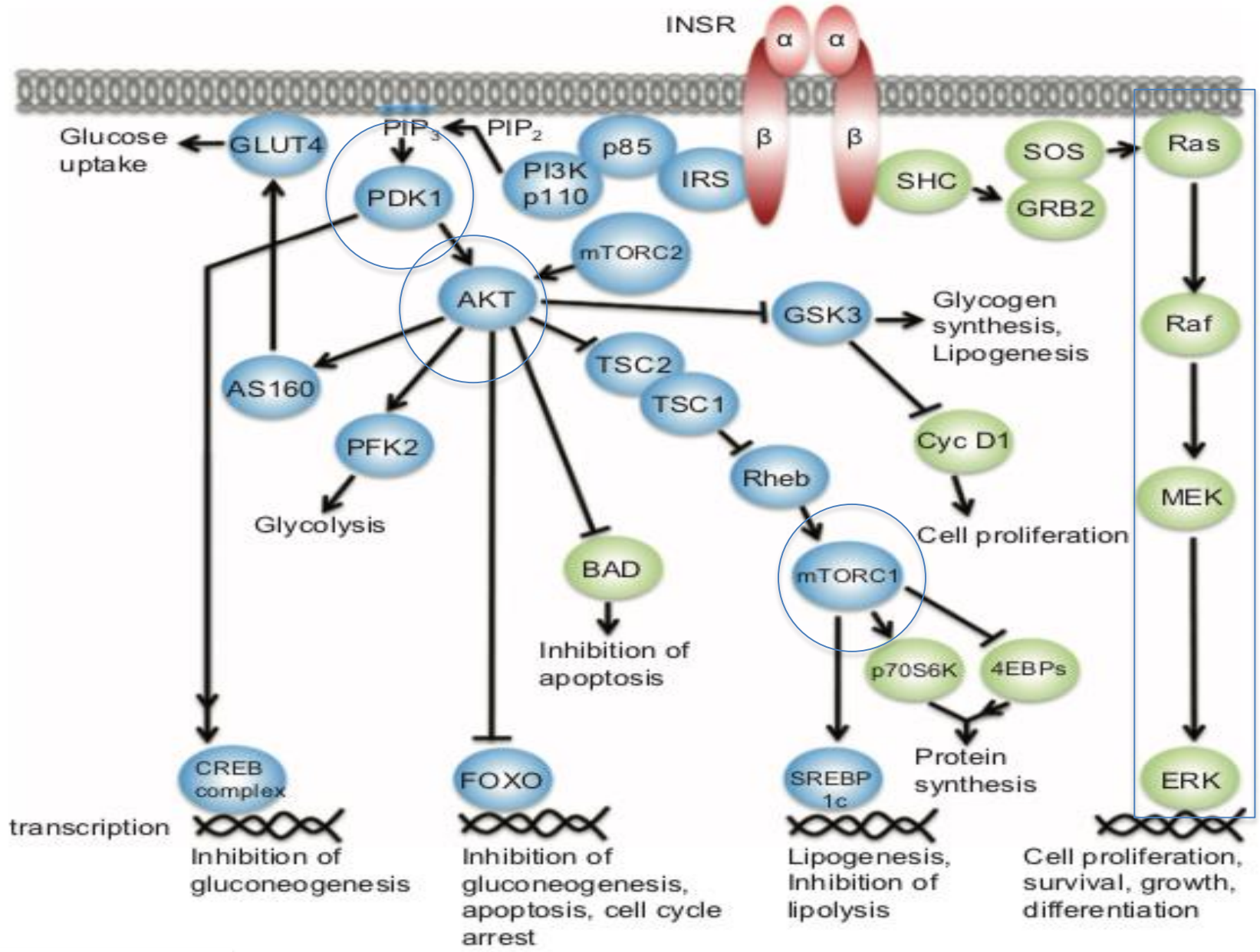
- Maggior produzione epatica di Insulin Like Growth Factor I (IGF-I) in risposta al GH ipofisario
- Minore produzione epatica di IGF I e II Binding Proteins con maggiore disponibilità plasmatica di IGF

- IGF I e II , mediatori del GH , hanno azione di stimolo della protidosintesi , della sintesi di acidi nucleici , del numero e dimensione delle cellule .
- I recettori per IGF-I e II sono simili ai recettori per l'insulina e con essi possono formare ibridi INSR /IGFR-I/IGFR-II

L’interazione insulina – IGF -< INSR-IGFR –INSR/IGFR a livello della membrana cellulare regola il sistema metabolico e mitogenico insulino-IGF dipendente.




INSR
α
α
β
β
Glucose uptake
GLUT4
PIP3
PIP2
PI3K p110
p85
IRS
PDK1
SHC
SOS
GRB2
Ras
mTORC2
AKT
GSK3
Glycogen synthesis, Lipogenesis
Raf
AS160
TSC2
TSC1
PFK2
Glycolysis
Cyc D1
Rheb
MEK
Cell proliferation
BAD
mTORC1
Inhibition of apoptosis
p70S6K
4EBPs
Protein synthesis
CREB complex
FOXO
SREBP 1c
ERK
transcription
Inhibition of gluconeogenesis
Inhibition of gluconeogenesis, apoptosis, cell cycle arrest
Lipogenesis, Inhibition of lipolysis
Cell proliferation, survival, growth, differentiation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Ras
Raf
MEK
ERK
mTORC2
AKT
GSK3
Glycogen synthesis, Lipogenesis
AS160
TSC2
TSC1
Rheb
Cyc D1
Cell proliferation
PFK2
Glycolysis
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Inhibition of apoptosis
mTORC1
p70S6K
4EBPs
Protein synthesis
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FOXO
Inhibition of gluconeogenesis, apoptosis, cell cycle arrest
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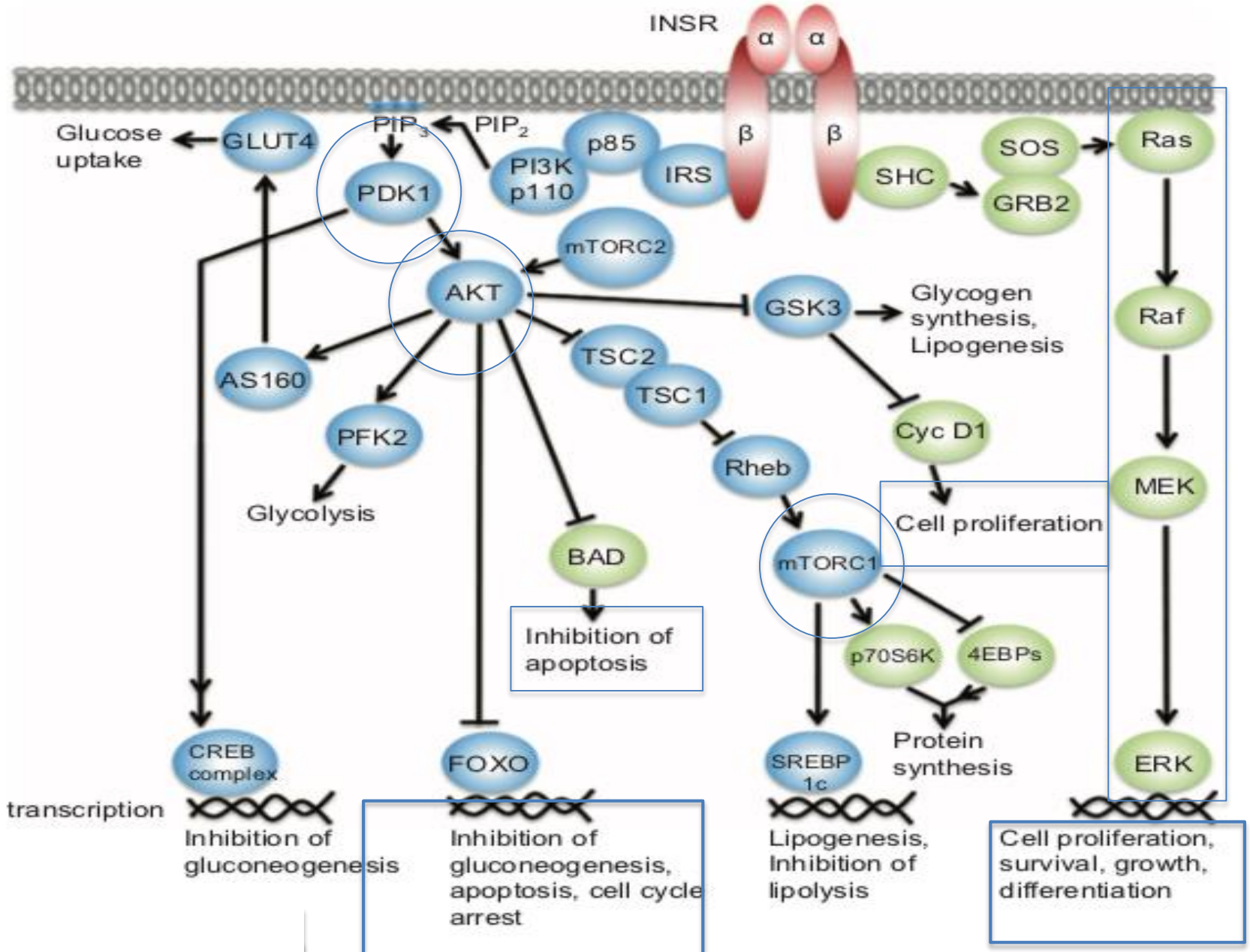
Lipogenesis, Inhibition of lipolysis
Cell proliferation, survival, growth, differentiation


INSR
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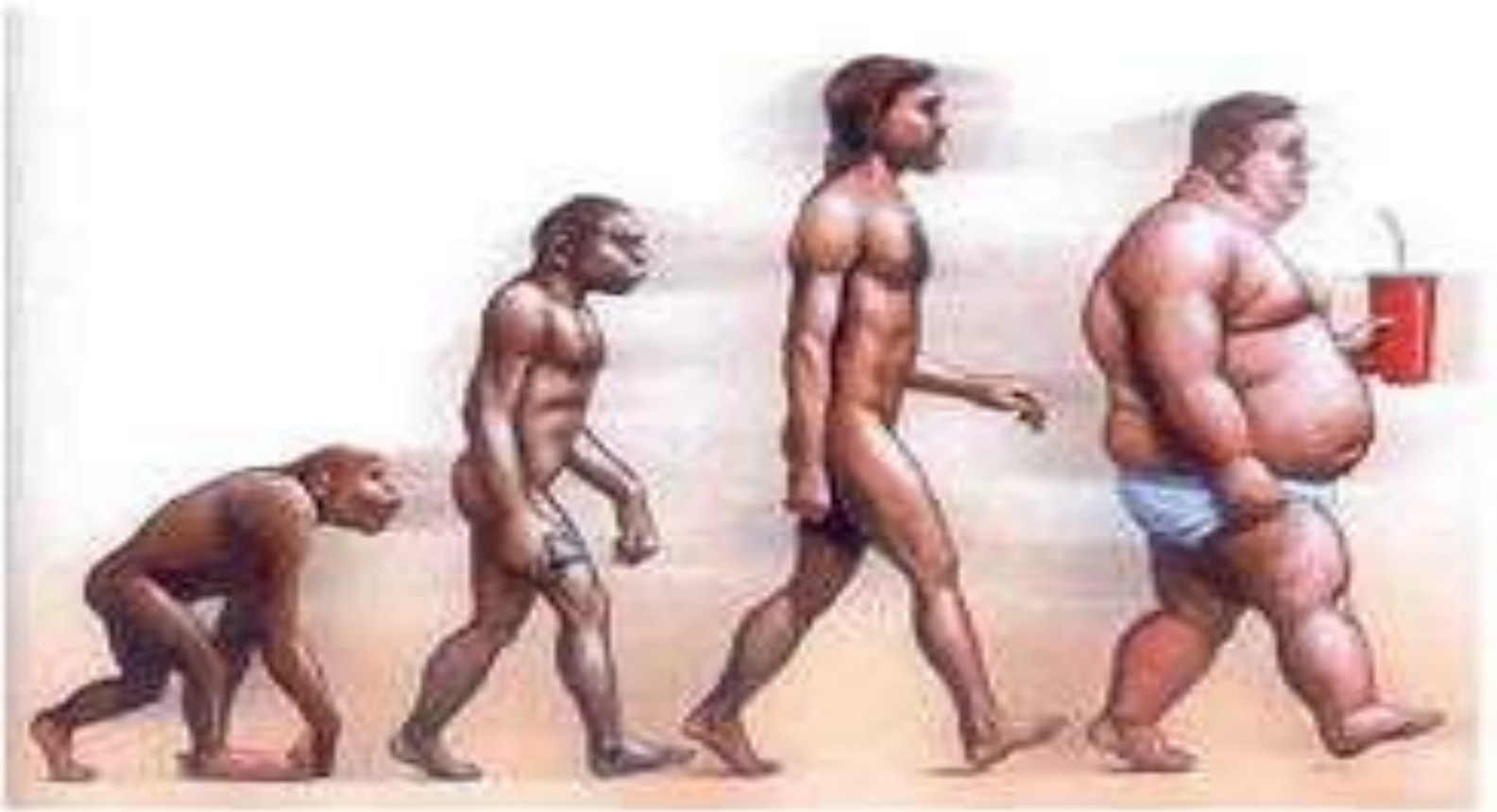
transcription
Inhibition of gluconeogenesis
Inhibition of gluconeogenesis, apoptosis, cell cycle arrest
Lipogenesis, Inhibition of lipolysis
Cell proliferation, survival, growth, differentiation

L’evoluzione della specie



SPECIAL REPORT

Table 2. Strength of the Evidence for a Cancer-Preventive Effect of the Absence of Excess Body Fatness, According to Cancer Site or Type.*

Cancer Site or Type	Strength of the Evidence in Humans†	Relative Risk of the Highest BMI Category Evaluated versus Normal BMI (95% CI)‡
Esophagus: adenocarcinoma	Sufficient	4.8 (3.0–7.7)
Gastric cardia	Sufficient	1.8 (1.3–2.5)
Colon and rectum	Sufficient	1.3 (1.3–1.4)
Liver	Sufficient	1.8 (1.6–2.1)
Gallbladder	Sufficient	1.3 (1.2–1.4)
Pancreas	Sufficient	1.5 (1.2–1.8)
Breast: postmenopausal	Sufficient	1.1 (1.1–1.2)§
Corpus uteri	Sufficient	7.1 (6.3–8.1)
Ovary	Sufficient	1.1 (1.1–1.2)
Kidney: renal-cell	Sufficient	1.8 (1.7–1.9)
Meningioma	Sufficient	1.5 (1.3–1.8)
Thyroid	Sufficient	1.1 (1.0–1.1)§
Multiple myeloma	Sufficient	1.5 (1.2–2.0)

Diabete-obesità-neoplasie

OPEN

Citation: Cell Death and Disease (2015) 6, e2037; doi:10.1038/cddis.2015.381

www.nature.com/cddis

Review

Obesity and cancer, a case for insulin signaling

Y Poloz[1] and V Stambolic*,[1,2]

Physiol Rev 95: 727–748, 2015
Published June 17, 2015; doi:10.1152/physrev.00030.2014

OBESITY AND DIABETES: THE INCREASED RISK OF CANCER AND CANCER-RELATED MORTALITY

Emily Jane Gallagher and Derek LeRoith

Icahn School of Medicine at Mount Sinai, New York, New York

Insulin Sensitivity, Insulin Secretion, and Abdominal Fat

The Insulin Resistance Atherosclerosis Study (IRAS) Family Study

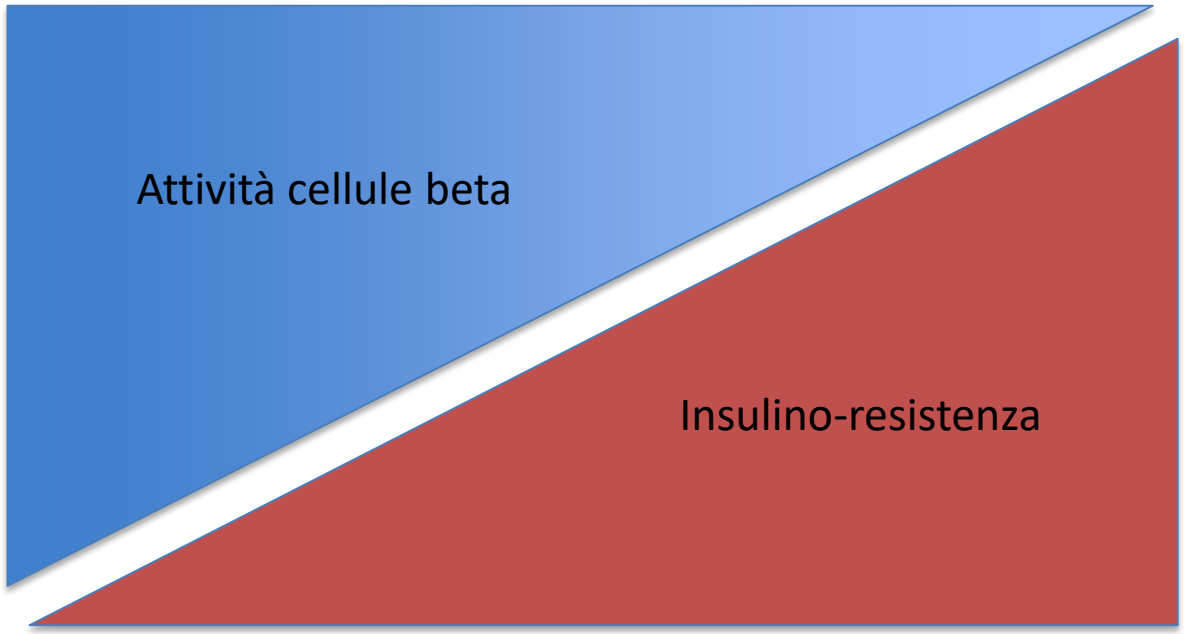
Lynne E. Wagenknecht,[1] Carl D. Langefeld,[1] Ann L. Scherzinger,[2] Jill M. Norris,[2] Steven M. Haffner,[3] Mohammed F. Saad,[4] and Richard N. Bergman[5]

DIABETES, VOL. 52, OCTOBER 2003

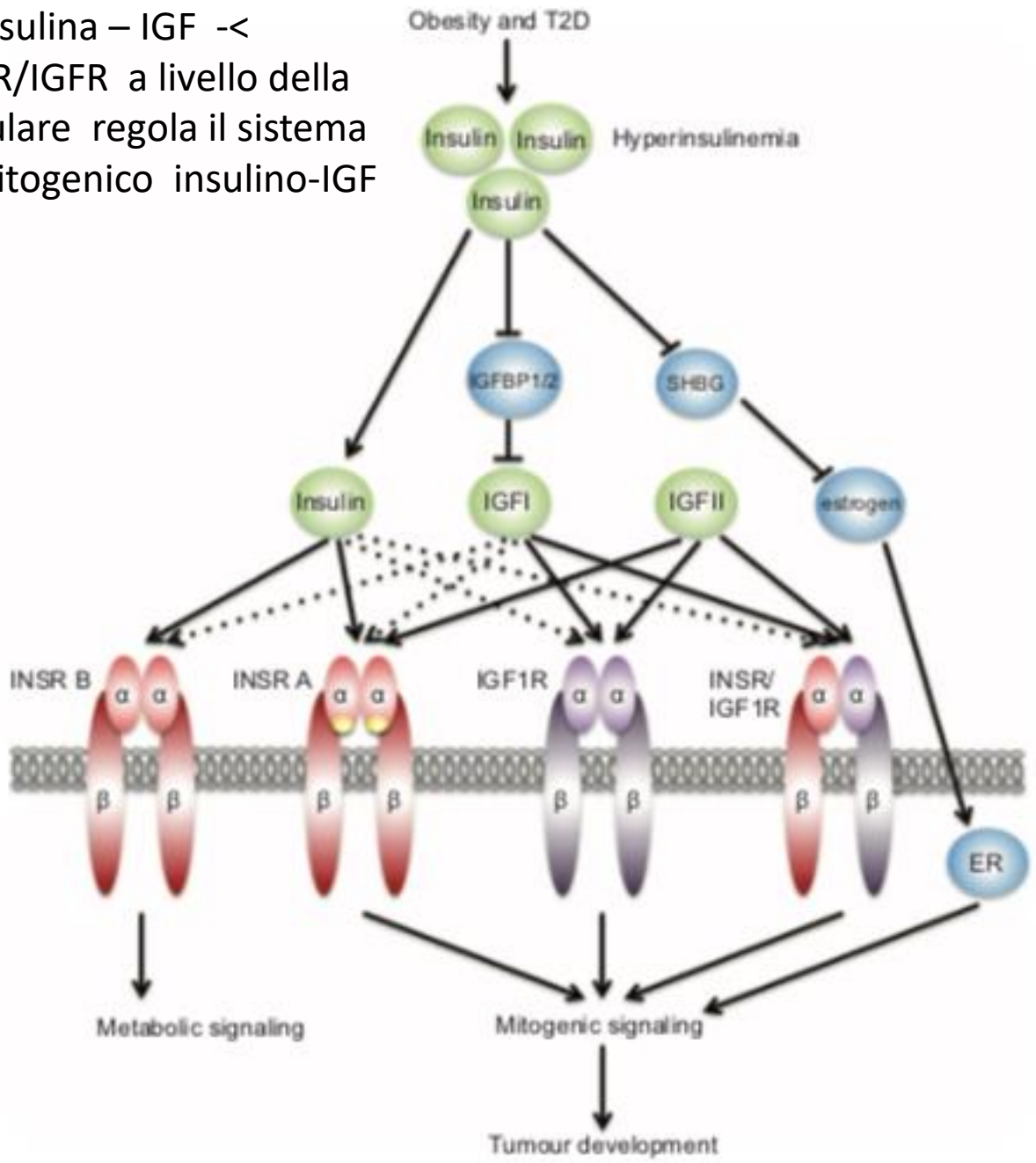
We found a strong independent relationship between both visceral and subcutaneous adiposity with insulin resistance. Increased levels of fat in these depots were signif-

and VAT. In conclusion, we observed that the various fat depots are associated with measures of glucose homeostasis. These findings have important implications for the risk of type 2 diabetes (27) and prevention of diabetes through weight loss programs focused on abdominal fat (23).

Diabete tipo II



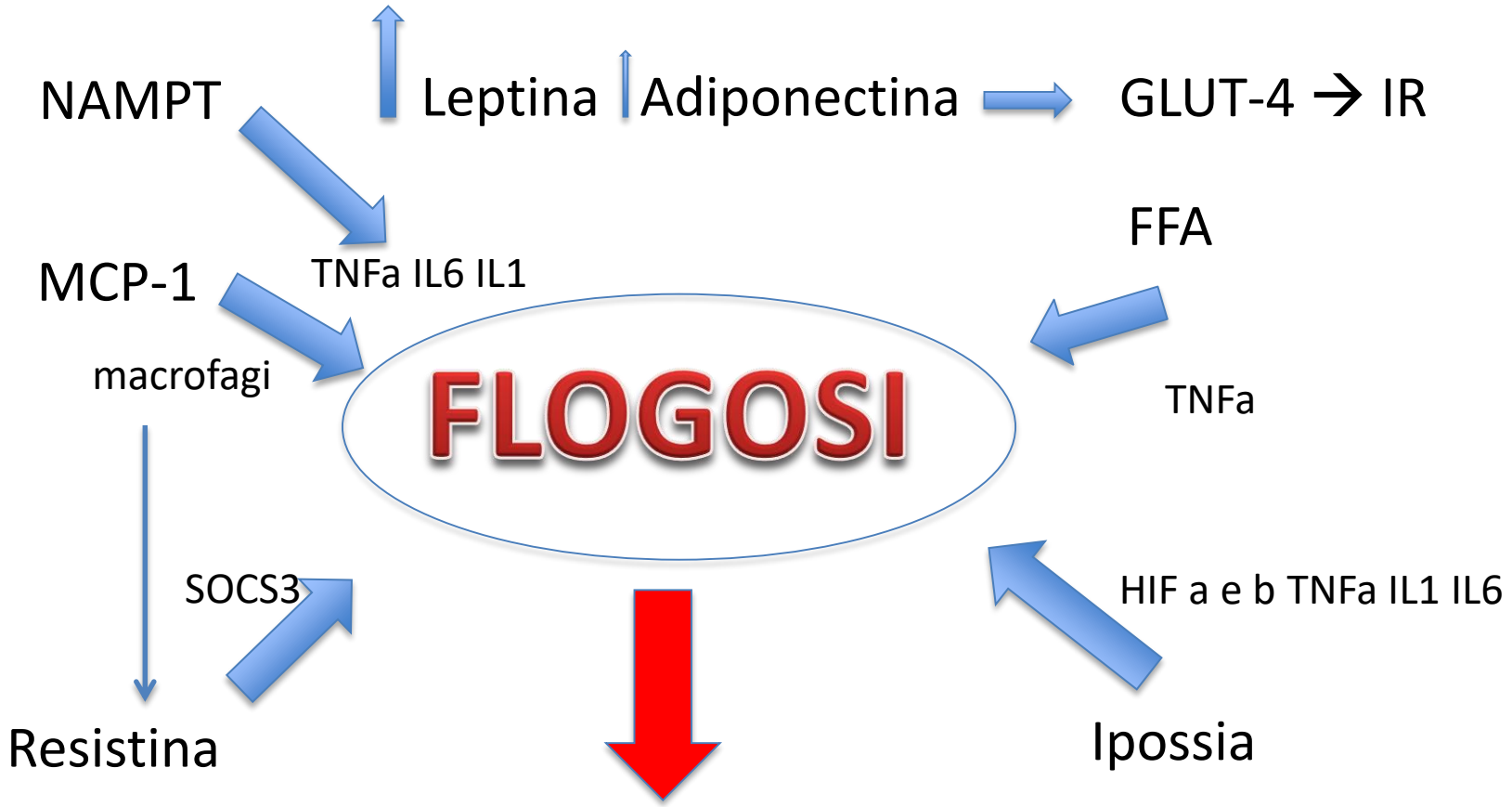
L’interazione insulina – IGF -< INSR-IGFR –INSR/IGFR a livello della membrana cellulare regola il sistema metabolico e mitogenico insulino-IGF dipendente.



Ruolo del tessuto adiposo

- Gli adipociti sono dotati di intensa attività ormonale e metabolica
- Peptidi ormonali : leptina , adiponectina , resistina , lipocalina 2 ,NAMPT
- Mediatori dell’infiammazione : TNFa , IL-6 , IL-1, MCP-1

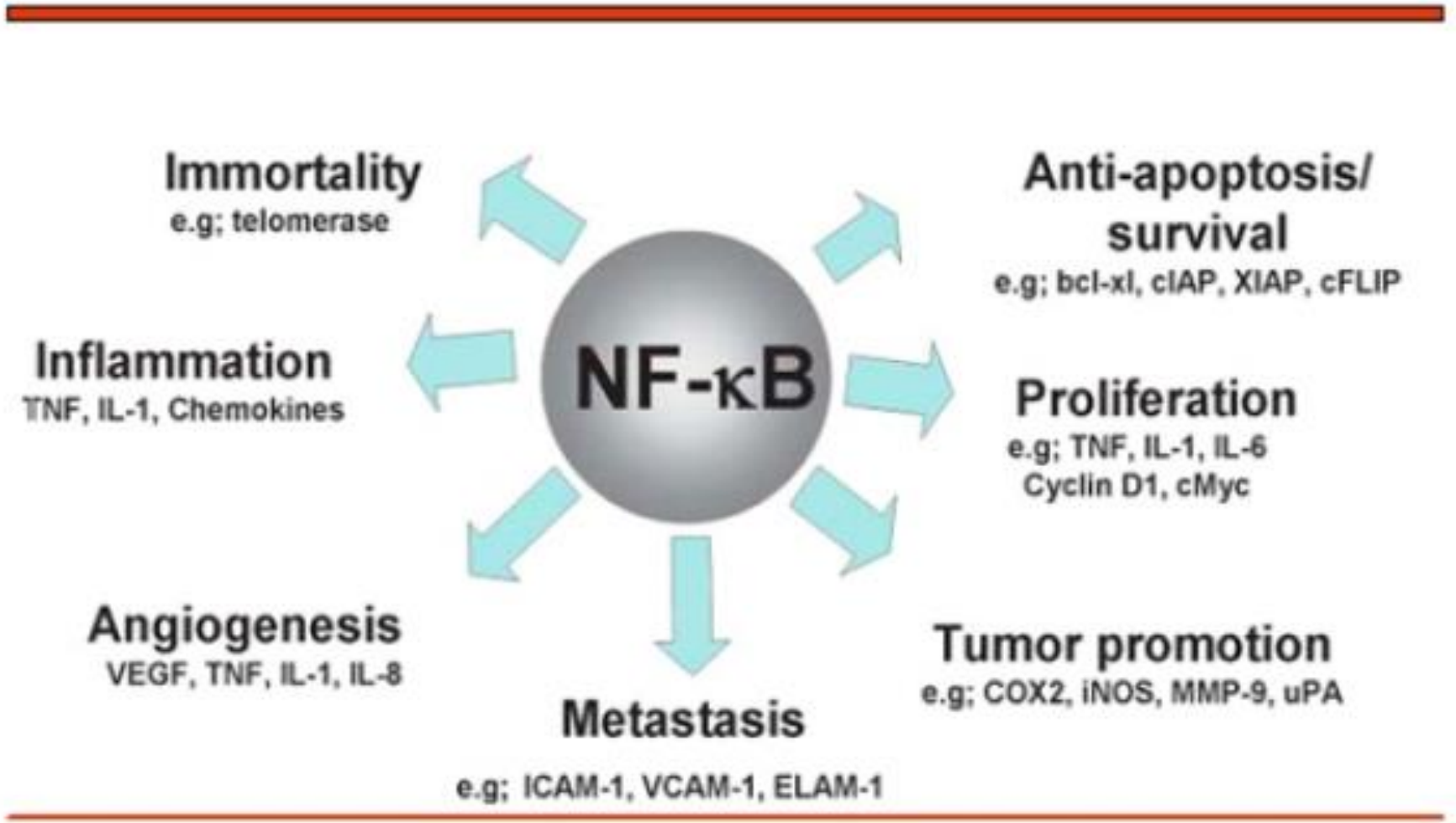
Ruolo del tessuto adiposo



NF-kB

Nuclear Factor-k-light chain enhancer of activated B cells

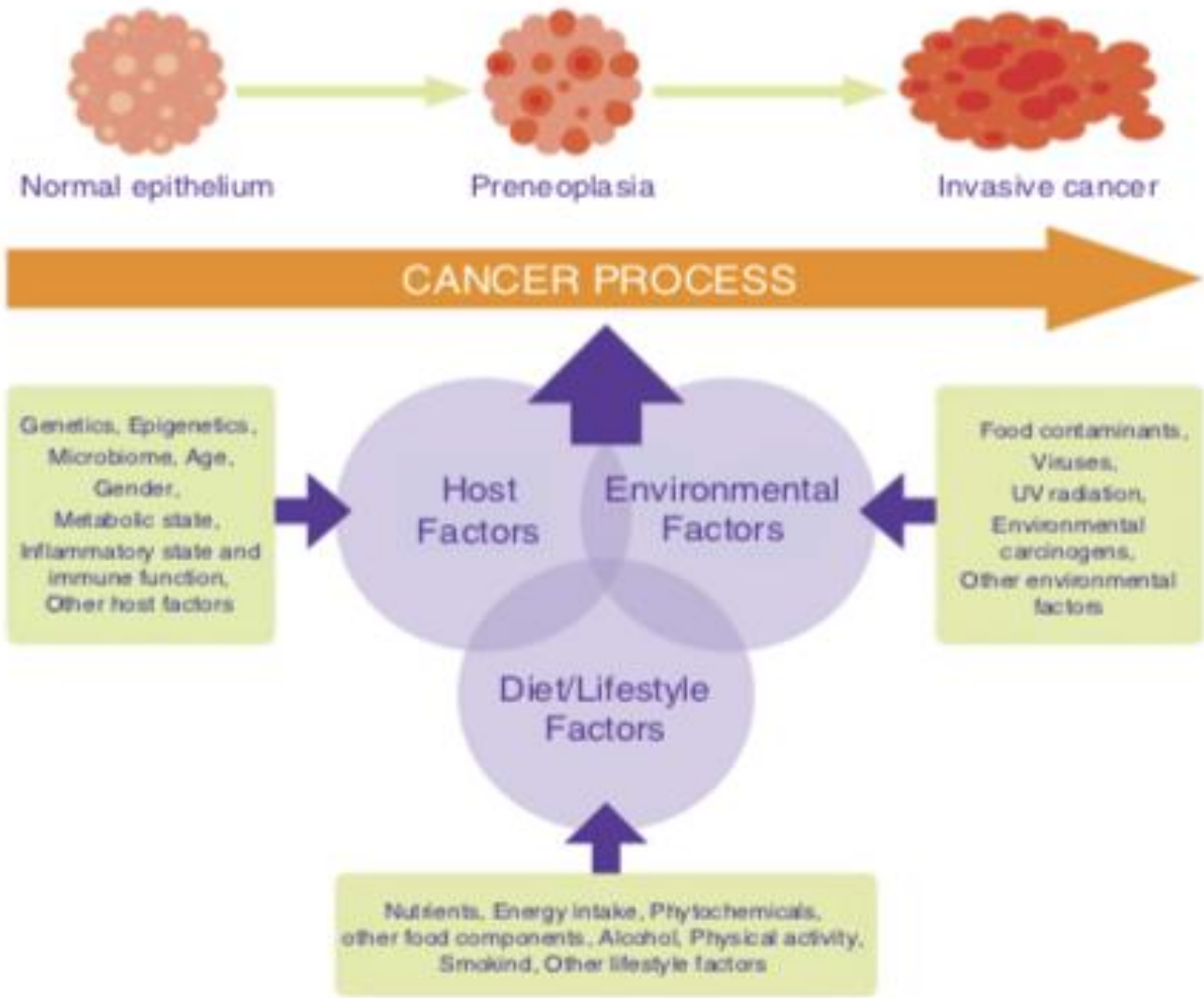
Recettore proteico presente sulla superficie di varie cellule : attivato per eterodimerizzazione da citochine infiammatorie , UV , Rx , radicali liberi , stress ossidativo , virus , batteri ecc



Strategie per la riduzione del rischio oncologico

- Controllo farmacologico dell'iperglicemia
- Controllo del BMI (22-25 kg/h2)
- Attività fisica
- Alimentazione

Diet, nutrition and physical activity, other environmental exposures and host factors interact to affect the cancer process



British Journal of Nutrition, (2019), 122, 481–487 doi:10.1017/S0007114518002222

Nutrition and cancer: prevention and survival

Martin J. Wiseman[1,2]*

Exposure	Systemic impact	Cell function	Hallmarks possibly affected
Greater body fatness	Hyperinsulinaemia	mTOR/PI3K/AKT, MAPK	Reduced apoptosis; increased proliferation; genome instability
	Increased oestradiol	MAPK/ERK/PI3K	Increased proliferation in ER-positive tissues; genome instability
	Inflammation	STAT3/NF-κB	Reduced apoptosis; increased cell division; altered macrophage function; genome instability
		WNT, P53	Cellular energetics
Greater height	Higher IGF-I	mTOR/PI3K/AKT, MAPK	Reduced apoptosis; increased proliferation
Greater physical activity	Reduction in insulin	mTOR/PI3K/AKT, MAPK	Increased apoptosis; reduced proliferation; less genome instability
	Reduction in oestradiol and testosterone	MAPK/ERK/PI3K	Reduced proliferation in ER-positive tissues; reduced genome instability
	Reduced inflammation (long term); improved immune function	STAT3/NF-κB	Increased apoptosis; increased cell division; altered macrophage function; reduced genome instability
		WNT, P53	Cellular energetics
Greater intake of red and processed meat	Elevated exposure to nitrites; endogenous *N*-nitroso compound formation	DNA adduct formation → mutations in p53, KRAS	Reduced apoptosis; increased proliferation; genomic instability
		Oxidative stress, inflammation	Increased inflammation; genomic instability
Greater intake of dairy foods	Higher IGF-I	mTOR/PI3K/AKT, MAPK	Reduced apoptosis; increased proliferation
Lower vegetables and fruit intake	Folate deficiency	DNA uracil misincorporation	Genome instability
	Low dietary fibre intake	Low butyrate	Reduced apoptosis; increased proliferation
	Low levels of carotenoids, vitamins A, C, E	Oxidative stress, inflammation	Increased inflammation; genomic instability; reduced apoptosis; increased proliferation
Greater alcohol intake	Elevated acetaldehyde	Oxidative stress, lipid peroxidation	Increased inflammation; genomic instability
	Increased oestradiol	MAPK/ERK/PI3K	Increased proliferation in ER-positive tissues
	Inflammation	STAT3/NF-κB	Reduced apoptosis; increased cell division; altered macrophage function
	Folate deficiency; interference with 1-carbon metabolism	DNA uracil misincorporation	Genome instability

American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Prevention

Be physically active

- Adults should get at least 150 minutes of moderate intensity or 75 minutes of vigorous intensity activity each week (or a combination of these), preferably spread throughout the week.
- Children and teens should get at least 1 hour of moderate or vigorous intensity activity each day, with vigorous activity on at least 3 days each week.
- Limit sedentary behavior such as sitting, lying down, watching TV, and other forms of screen-based entertainment.
- Doing some physical activity above usual activities, no matter what one's level of activity, can have many health benefits.

Nutrizione

- Rispettare i fabbisogni energetici
- Limitare la carne rossa
- Almeno 5 porzioni di frutta e/o verdura al giorno
- Prediligere i cereali non raffinati
- Prediligere i legumi
- Olio EVO
- Limitare alcolici al minimo (max 24 gr/die per gli uomini , 12 per le donne)

…se fossimo in grado di fornire a ciascuno la giusta dose di nutrimento ed esercizio fisico, né in difetto né in eccesso, avremmo trovato la strada per la salute…

Ippocrate (460-377 a.C.)