9 – 11 Marzo 2011

III Sessione

The New Era of Host-Related Genetic Markers in HCV disease and Treatment:

"SOCS SNP and response to antiviral treatment"

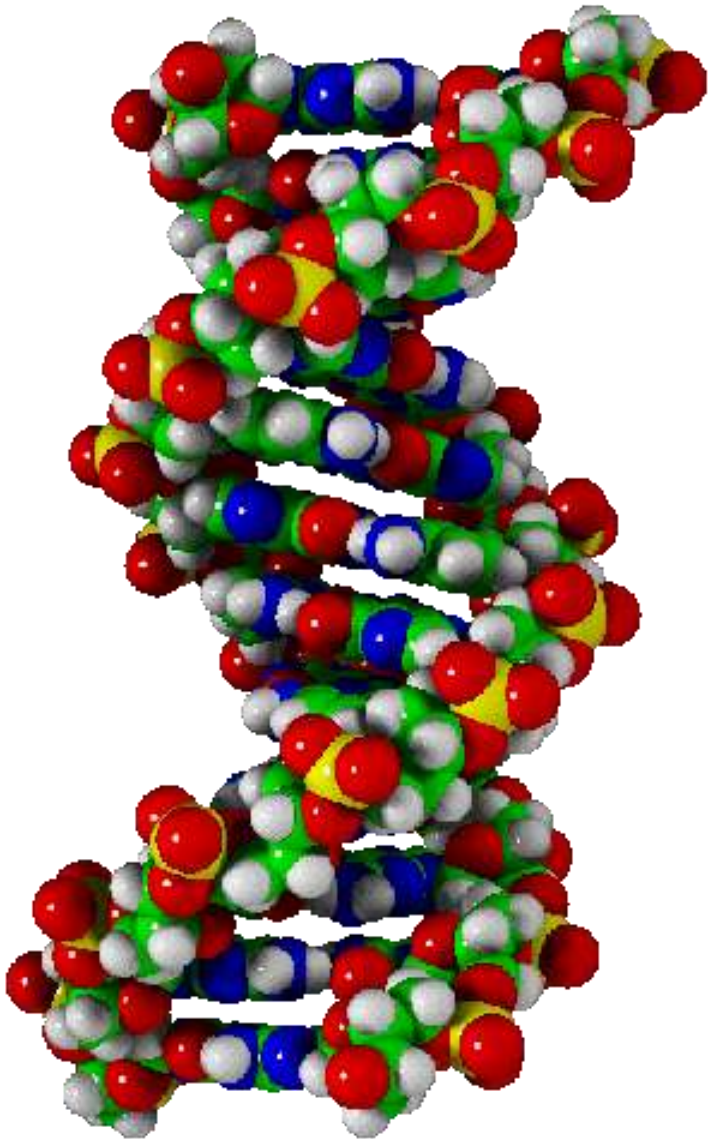
Prof. Marcello Persico

SECONDA UNIVERSITÀ DEGLI STUDI DI NAPOLI

Cattedra di Medicina Interna

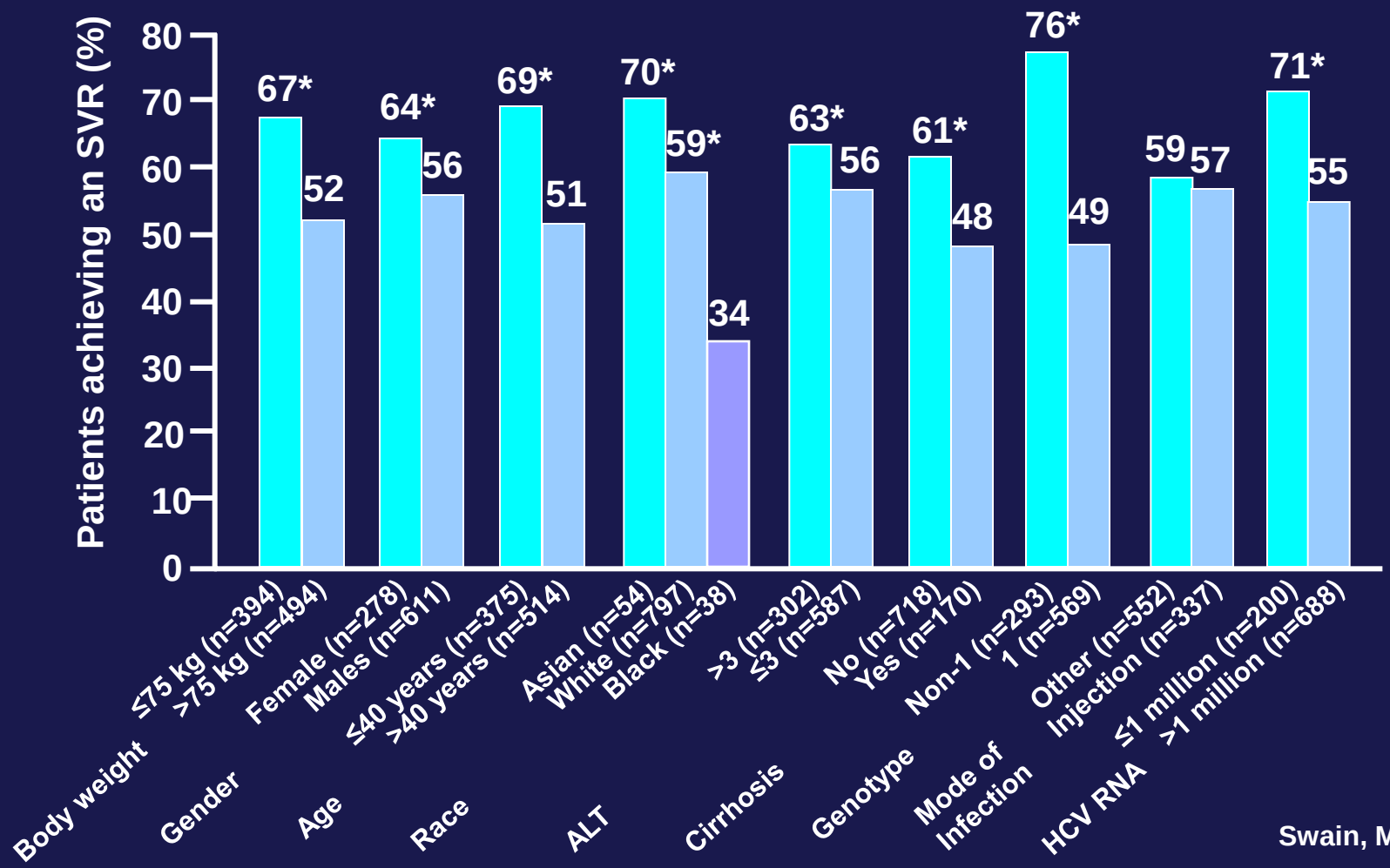
- ***SOCS3***

- IFN-LAMBA3/IL 28



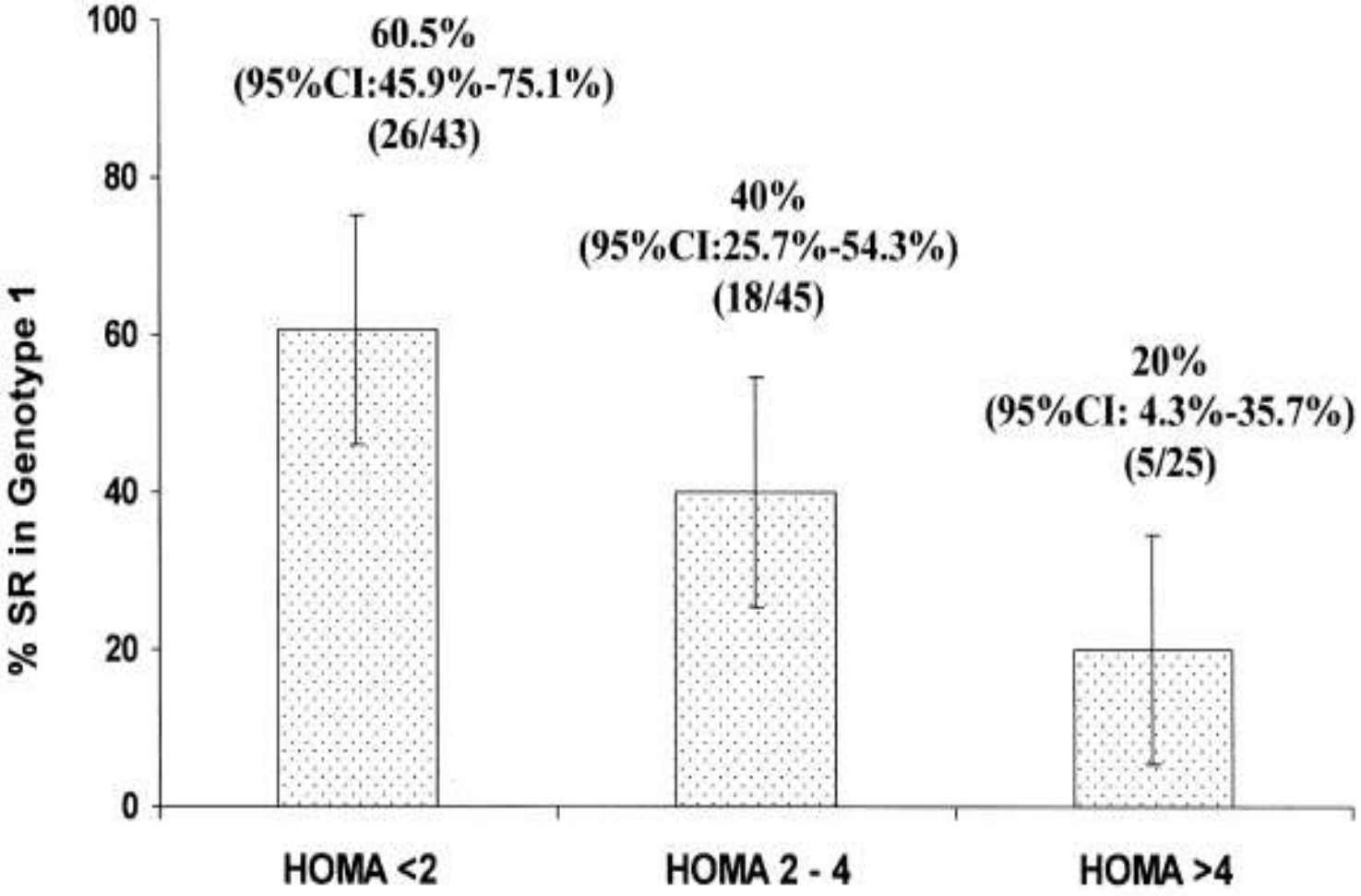
A number of baseline factors have a strong impact on SVR

PEGASYS® plus COPEGUS®; * p<0.05



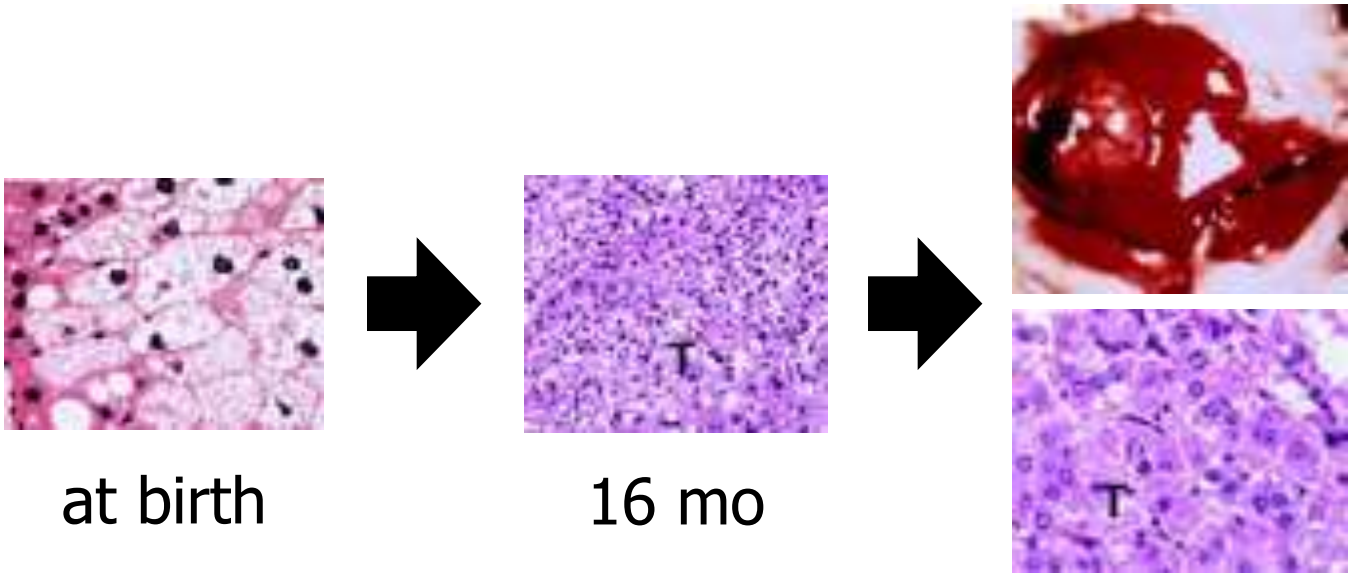
Swain, M et al.

Insulin resistance decreases SVR in chronic hepatitis C



ROMERO-GOMEZ et al, Gastroenterology 2005;128:636-641

HCV Core Protein induces IR, Liver Steatosis and Hepatocellular Carcinoma in Transgenic Mice



at birth

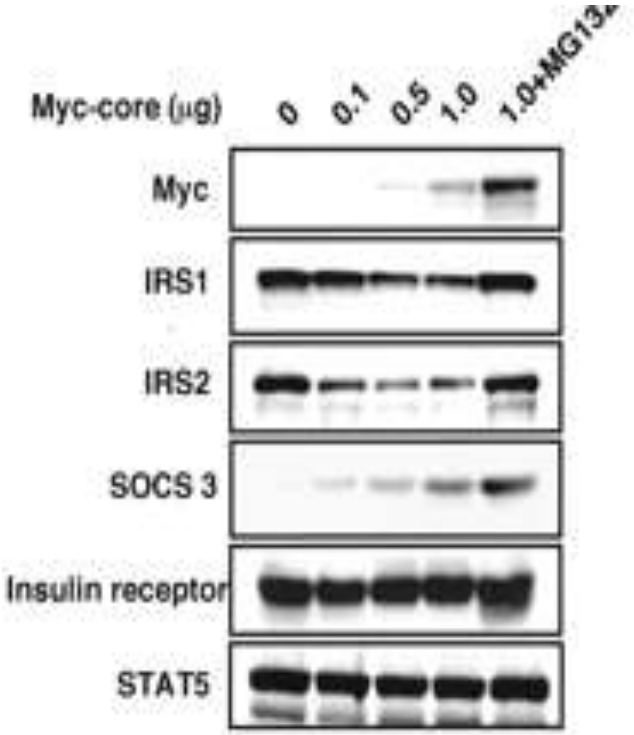
16 mo

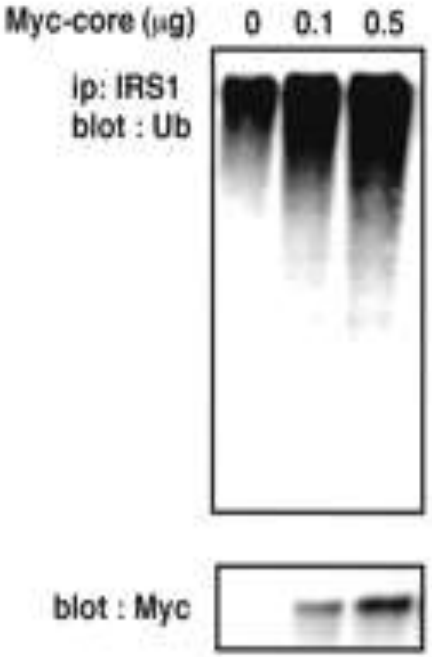
17 mo
"nodule-in-nodule"

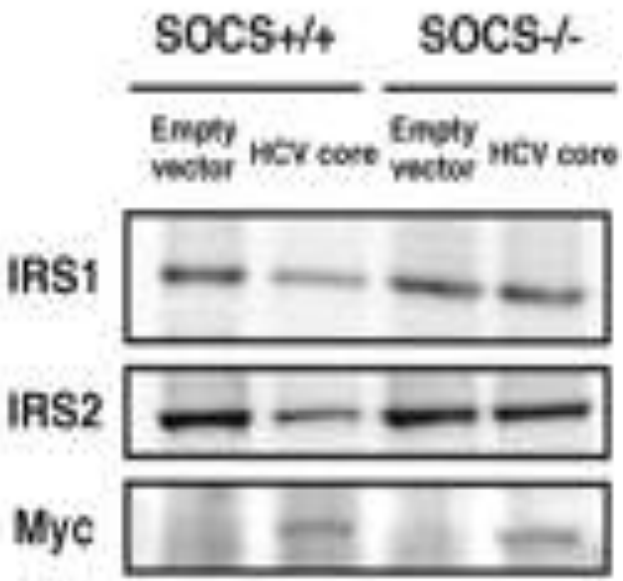
Anti-TNF-α antibody restores insulin sensitivity

MORIYA et al, Nature Med 1998
SHINTANI et al, Gastroenterology 2004

The HCV Core Protein Decreases IRS1 and IRS2 by Upregulating SOCS-3

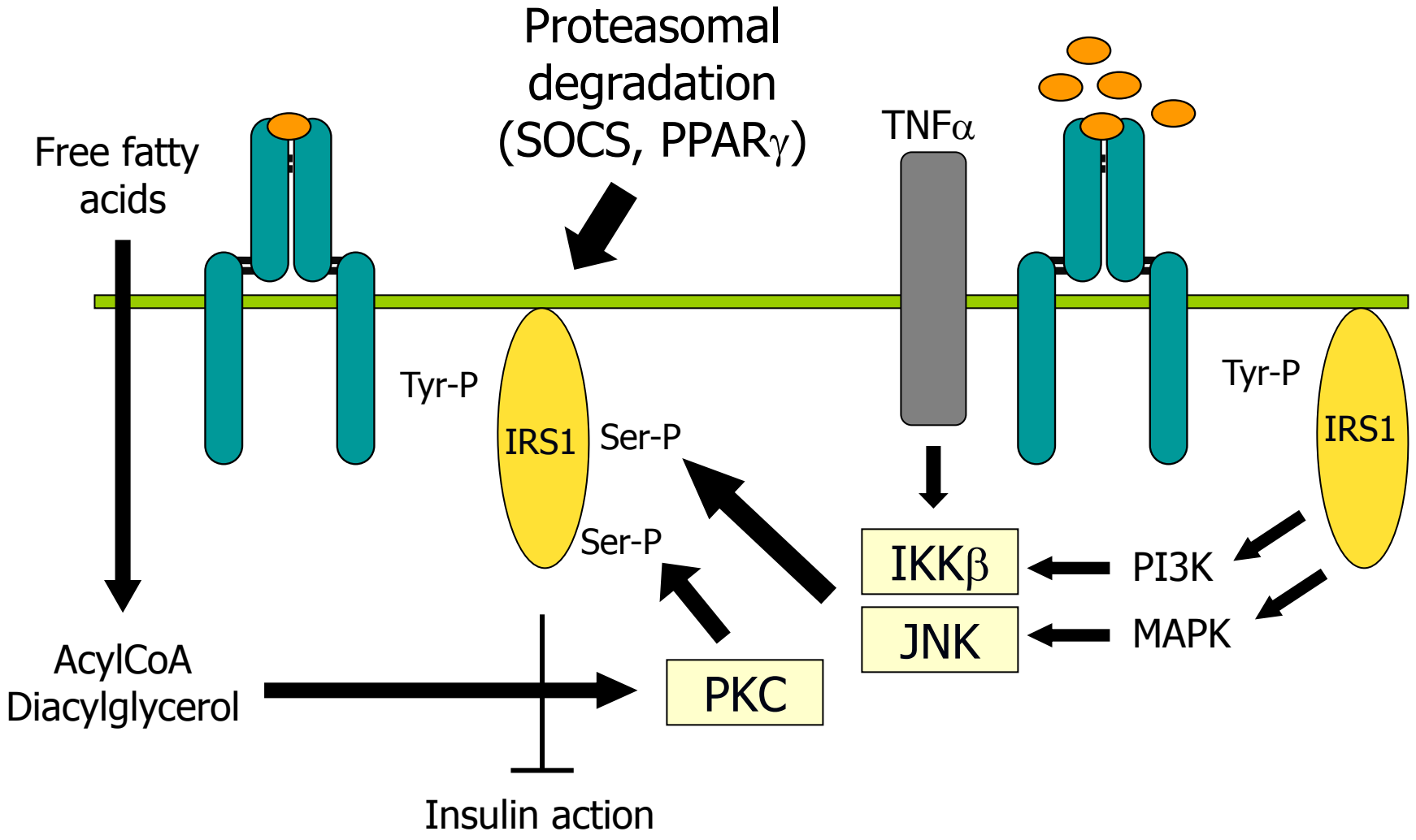




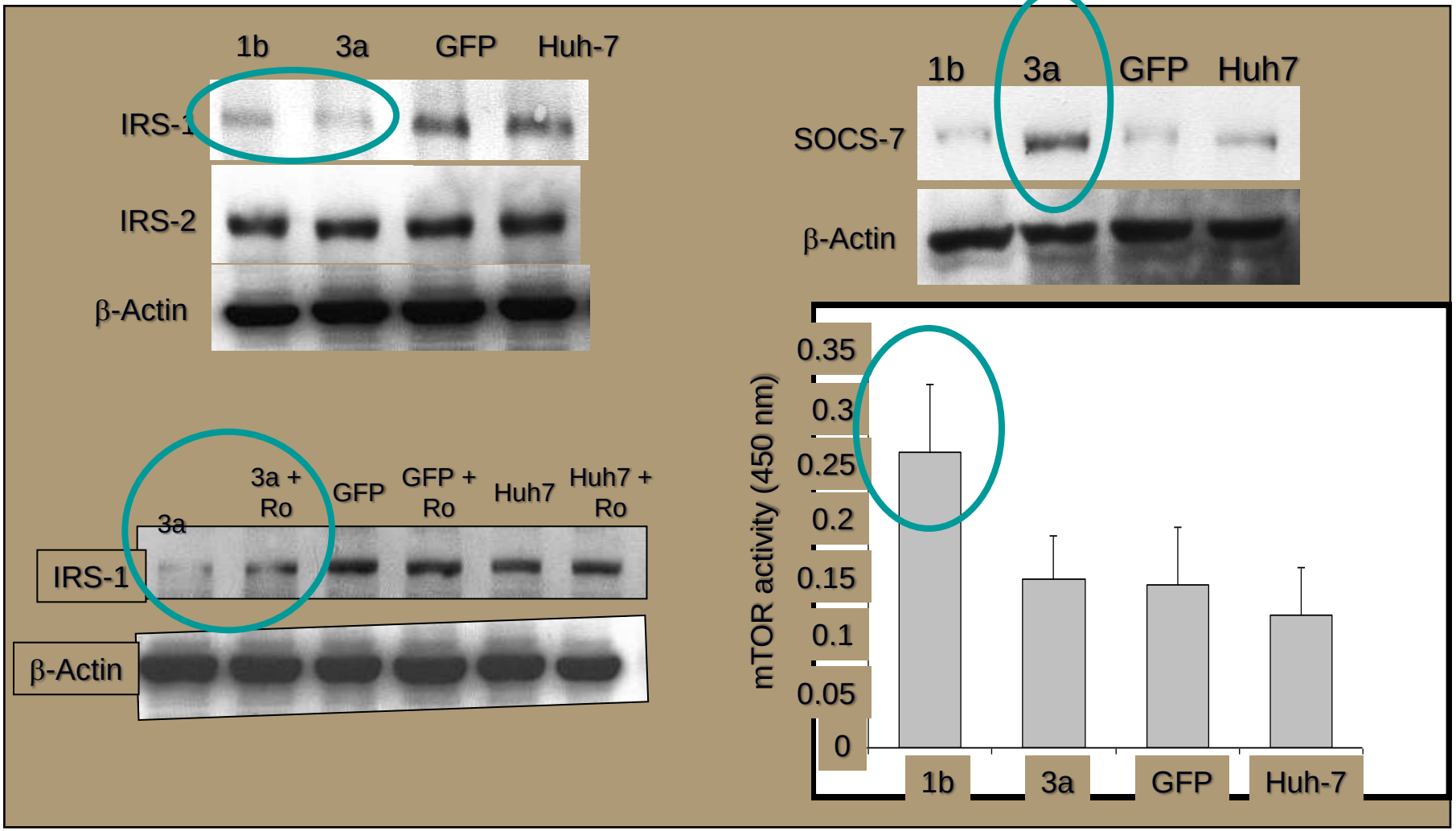


KAWAGUCHI et al, Am J Path 2004;165:1499-1508

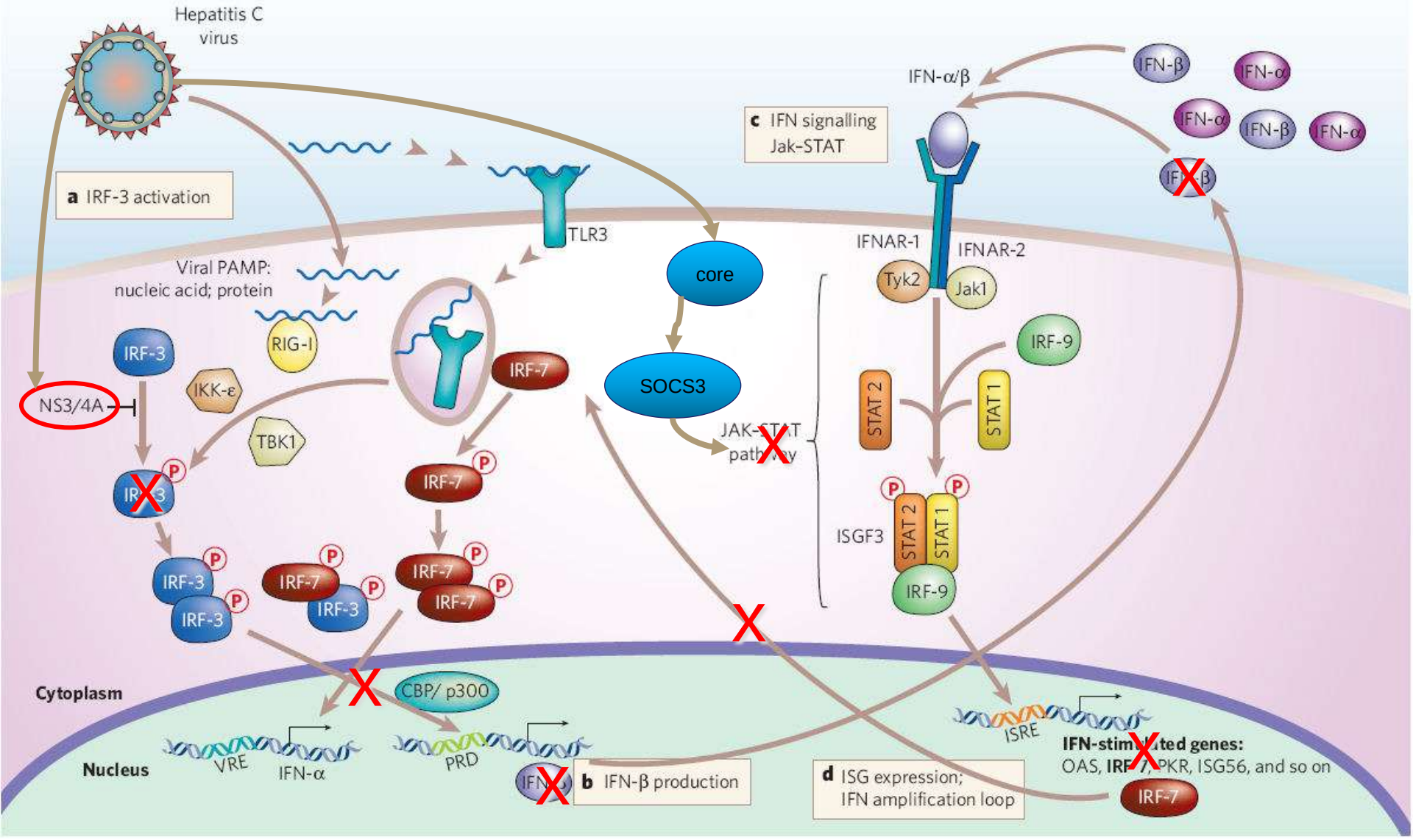
Molecular mechanisms of insulin resistance



Are insulin resistance mechanisms HCV genotype-specific?

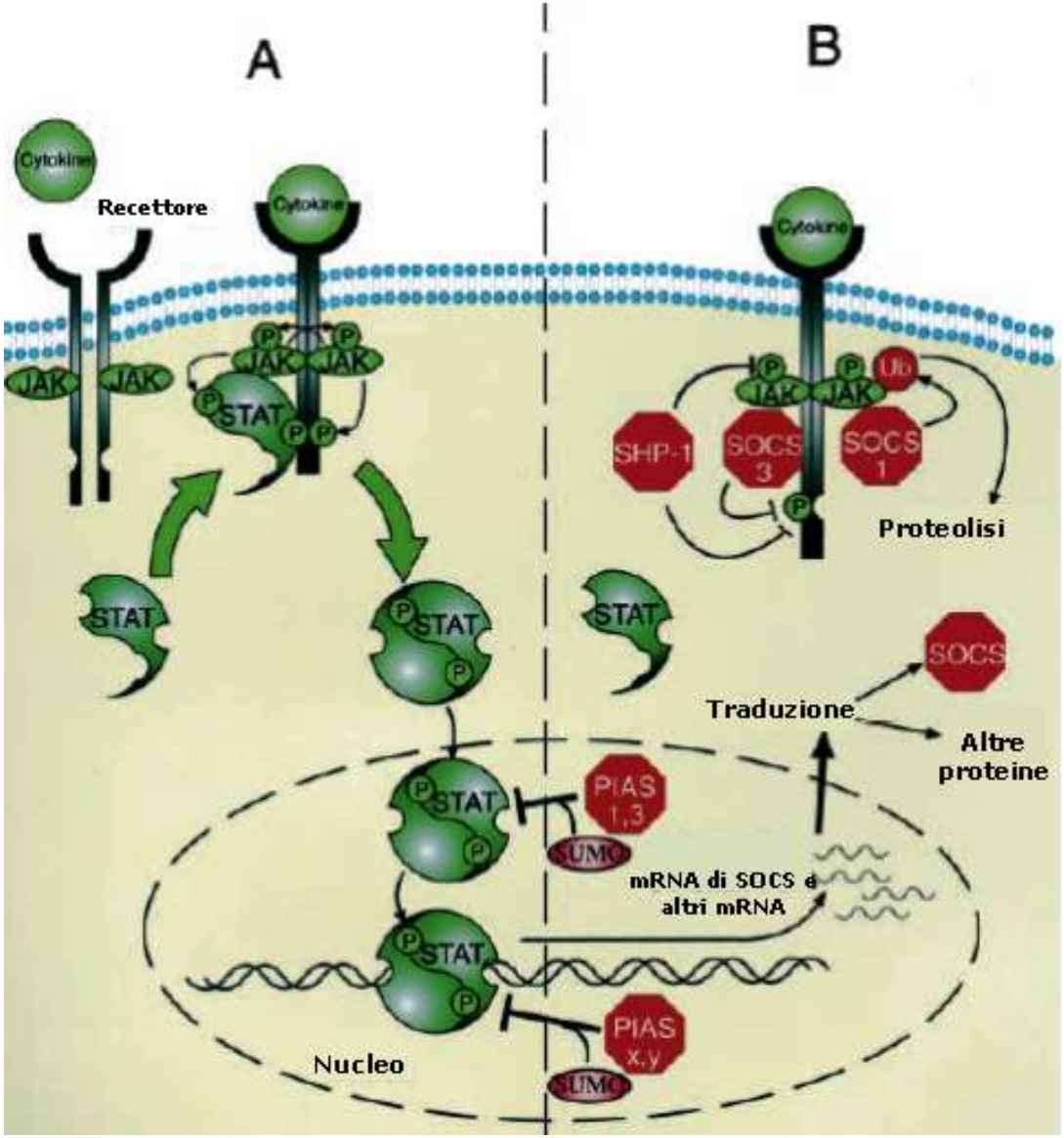


PAZIENZA et al, Hepatology 2007



Gale Nature 2005

Il pathway JAK/STAT



SHP

PIAS

SOCS

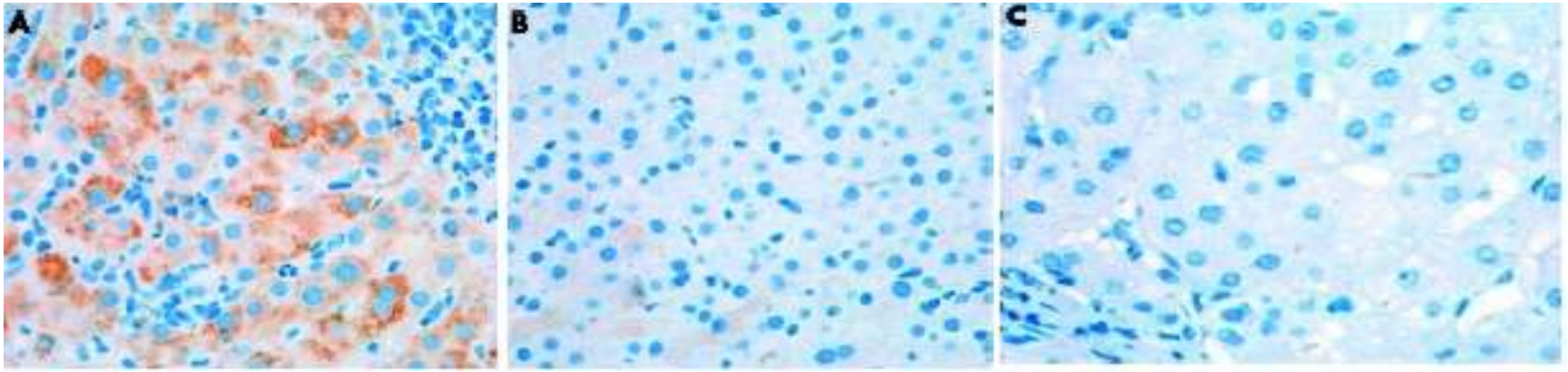
Regolazione negativa

Mx-A

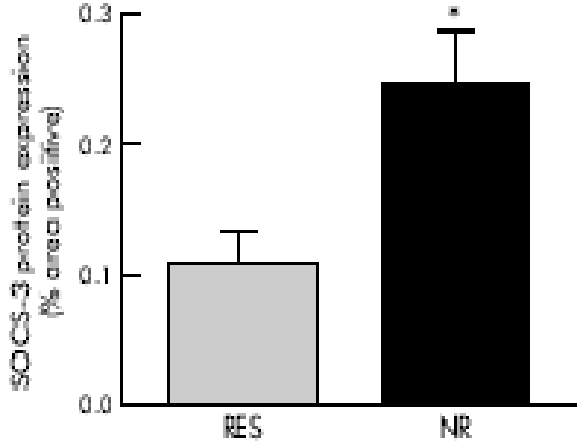
2'-5' OAS

Effettori antivirali

IMMUNOISTOCHIMICA

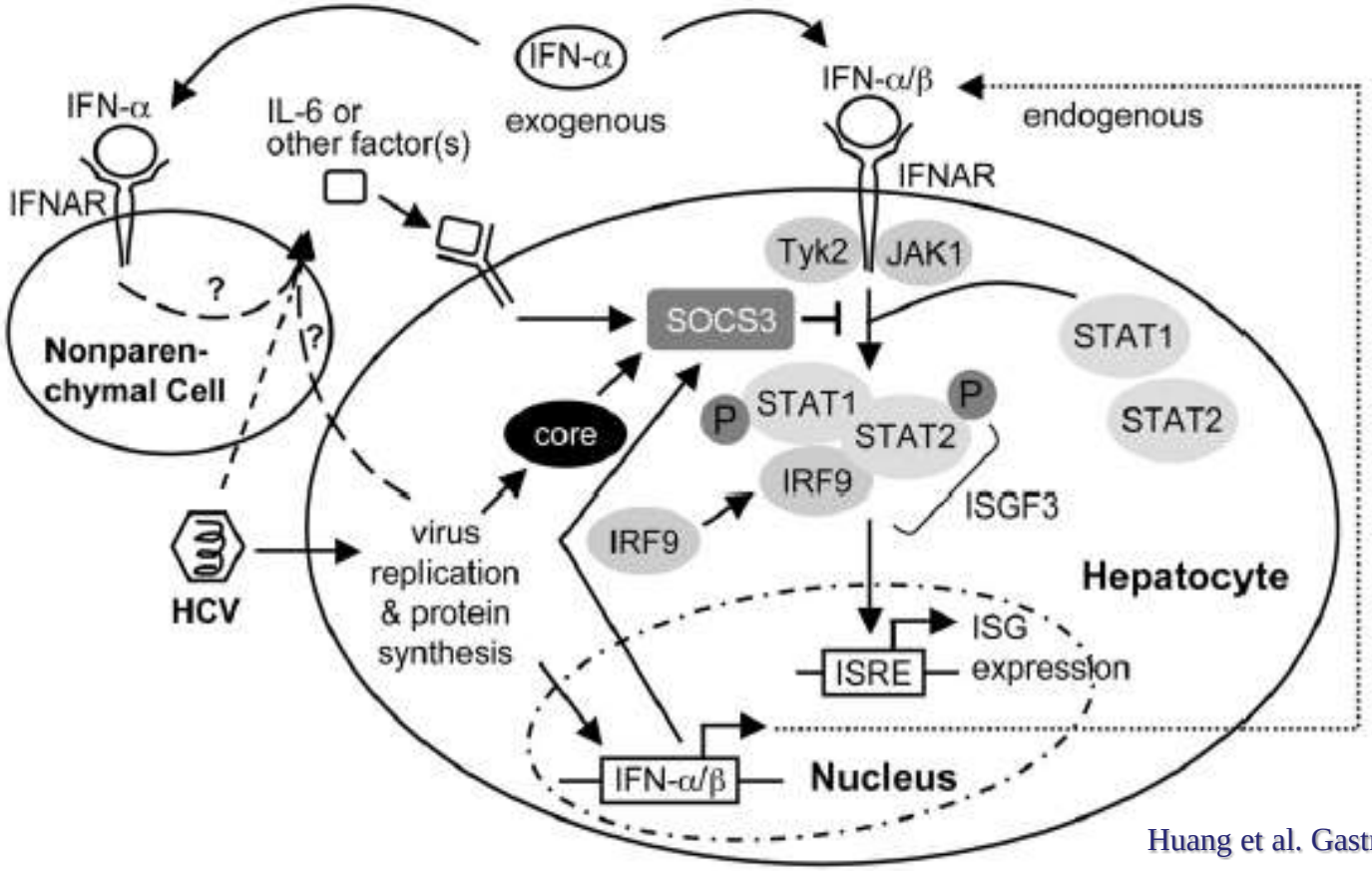


A: obeso non responder; B: responder ; C: controllo negativo



L'espressione epatica di Socs 3 è indotta da citochine e da ormoni associati all'obesità ed all'insulino resistenza. Una marcata riduzione di SOCS3 è stata notata in ratti obesi mancanti del TNF-α.

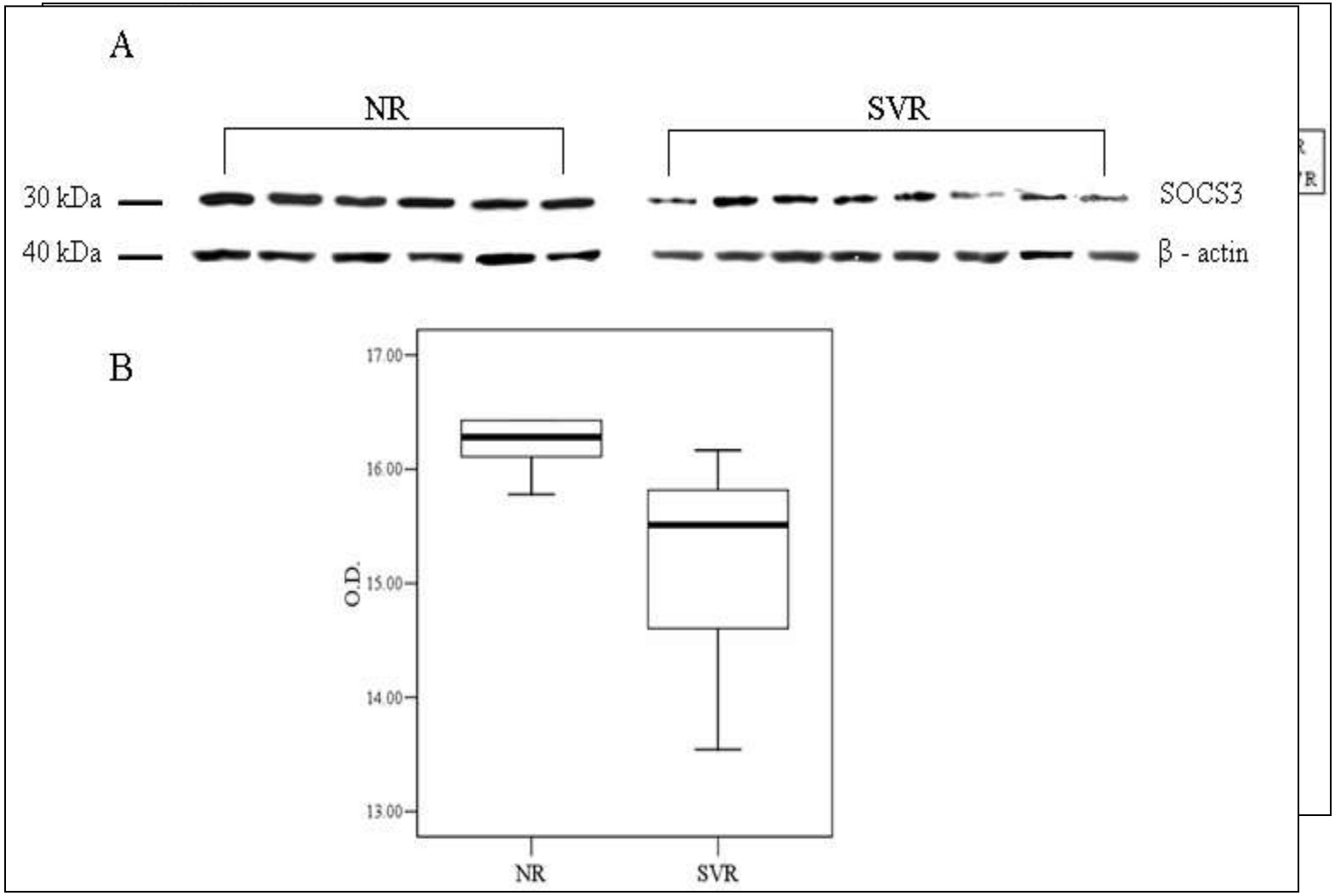
Model of IFN resistance in chronic HCV infection



Huang et al. Gastro 2007

HCV infection leads to endogenous IFN production and also to increased expression of SOCS3, either directly by a viral protein or indirectly by an IFN inhibitory factor (IL-6 or other soluble factors). SOCS3 can suppress JAK-STAT signaling by blocking the IFN-induced formation of ISGF3. With exogenous IFN treatment, SOCS3 is induced, preventing further ISG activation and markedly blunting the IFN response

Analisi di espressione genica su pazienti con epatite cronica HCV-correlata

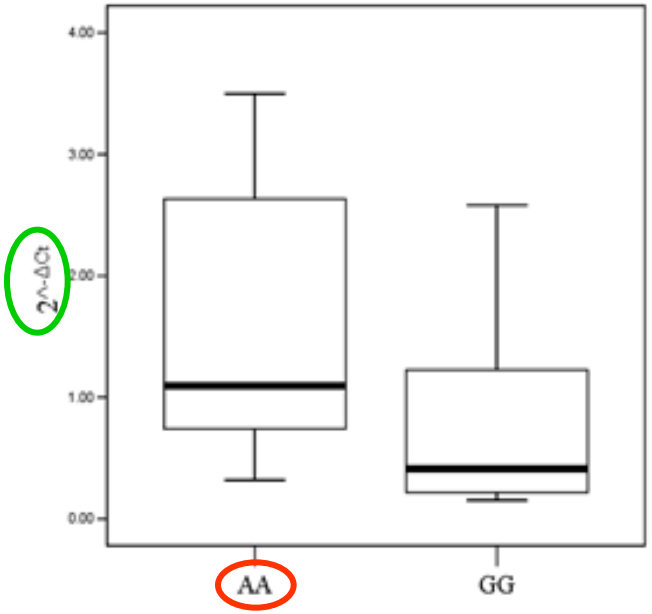


Mann Whitney test; P<0.05

First International Course of Translational Hepatology, Florence, 2011

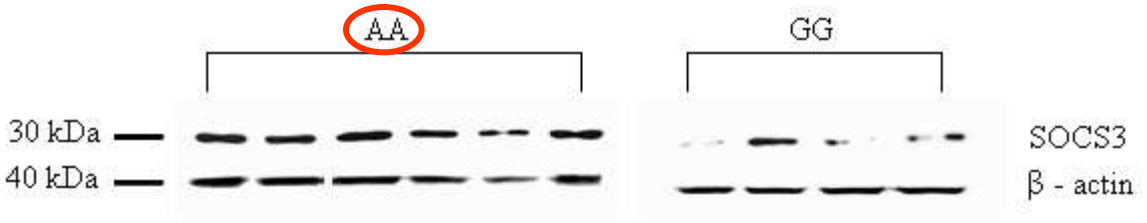
Persico et al, GUT, 2008

La variante allelica -4874 A è associata ad elevati livelli di espressione di SOCS3



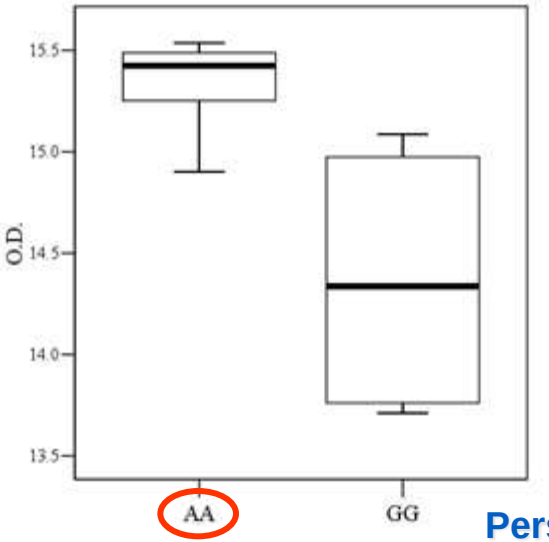
QRT-PCR:
- 12 AA (1.1; 1.60 ± 0.31)
- 16 GG (0.40; 0.81 ± 0.20)

Mann Whitney test; P<0.05



Western blotting, 10 HCV NR:
- 6 AA: (15.42; 15.34 ± 0.10)
- 4 GG: (14.34; 14.37 ± 0.35)

Mann Whitney test; P<0.05



Persico et al, GUT, 2007

Suppressor of Cytokine Signaling 3 (SOCS3) Expression and Hepatitis C Virus–Related Chronic Hepatitis: Insulin Resistance and Response to Antiviral Therapy

b,[1] Monica
asutti,[3] Rol

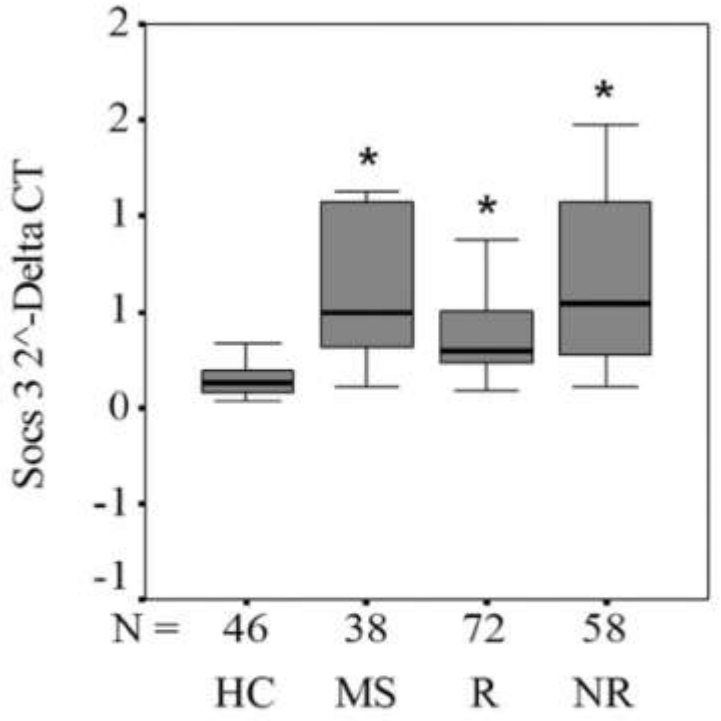
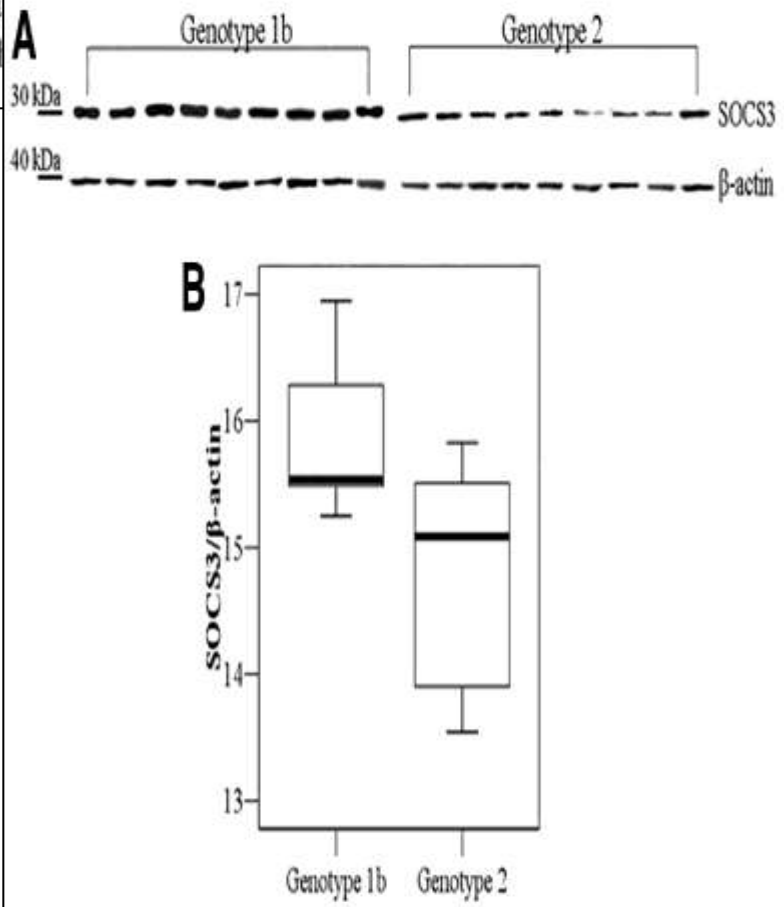
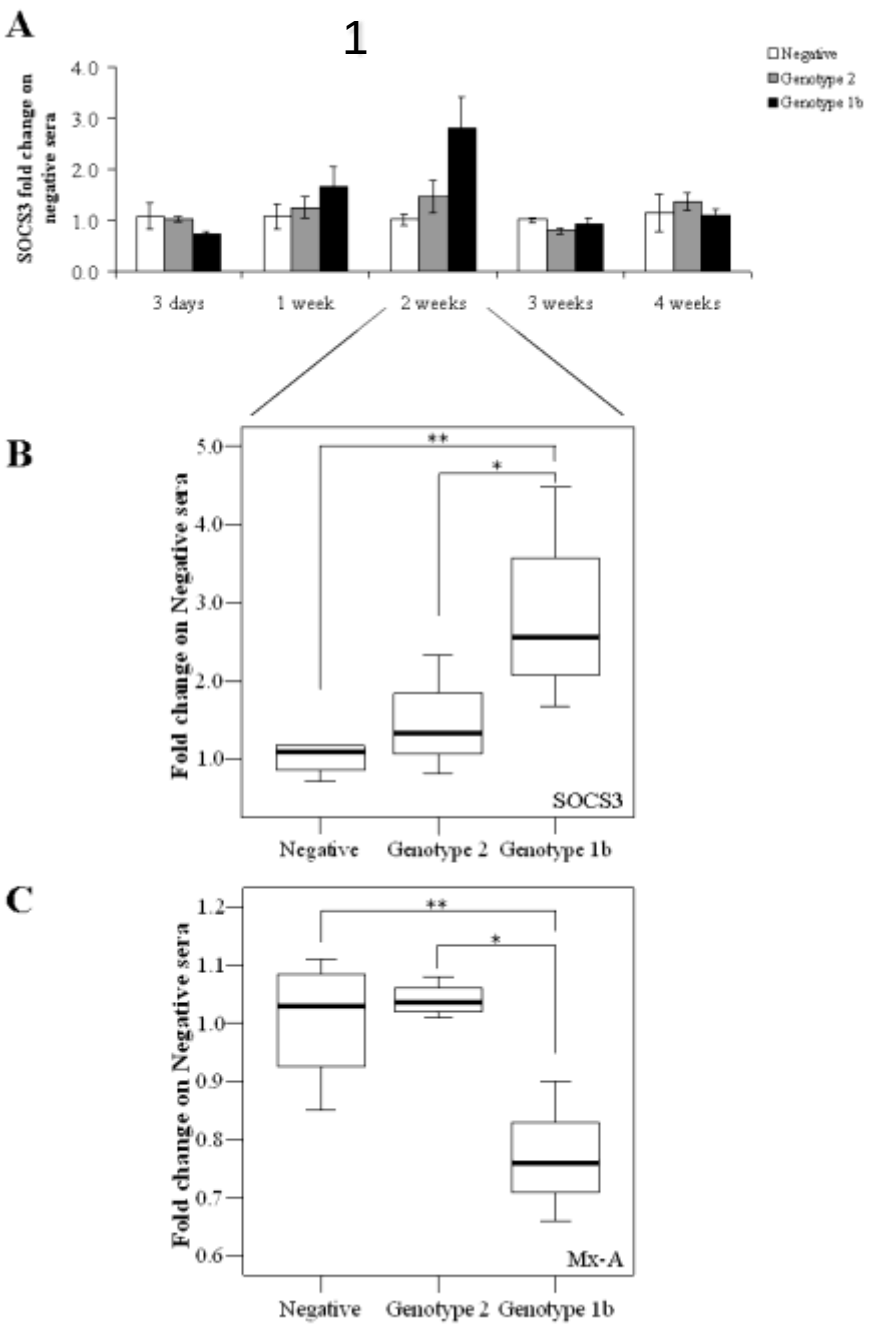
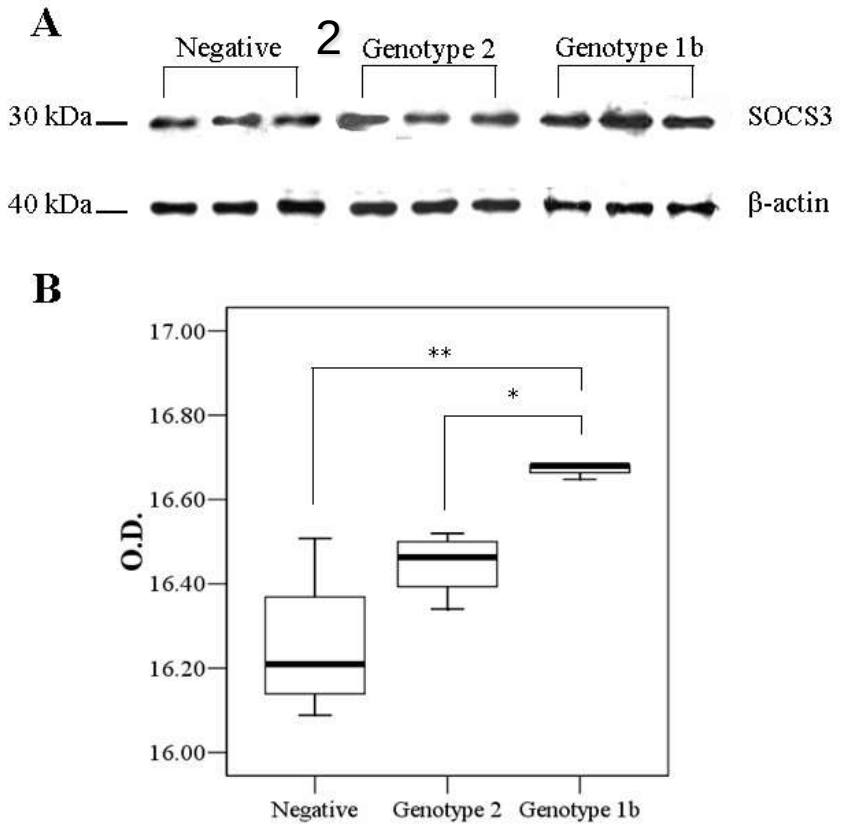


Fig. 1. Correlation between the SOCS3 expression, response to antiviral therapy, and metabolic syndrome. The box plot shows the median values of $2^{-\Delta CT}$ in healthy controls (HC), all patients with metabolic syndrome (MS), responder patients (R), and nonresponder patients (NR). *$P < 0.001$ for HC versus R.*$P < 0.01$ for R versus NR. *$P < 0.01$ for HC versus MS.



Hepatology 2007Oct;46(4):1009-15.

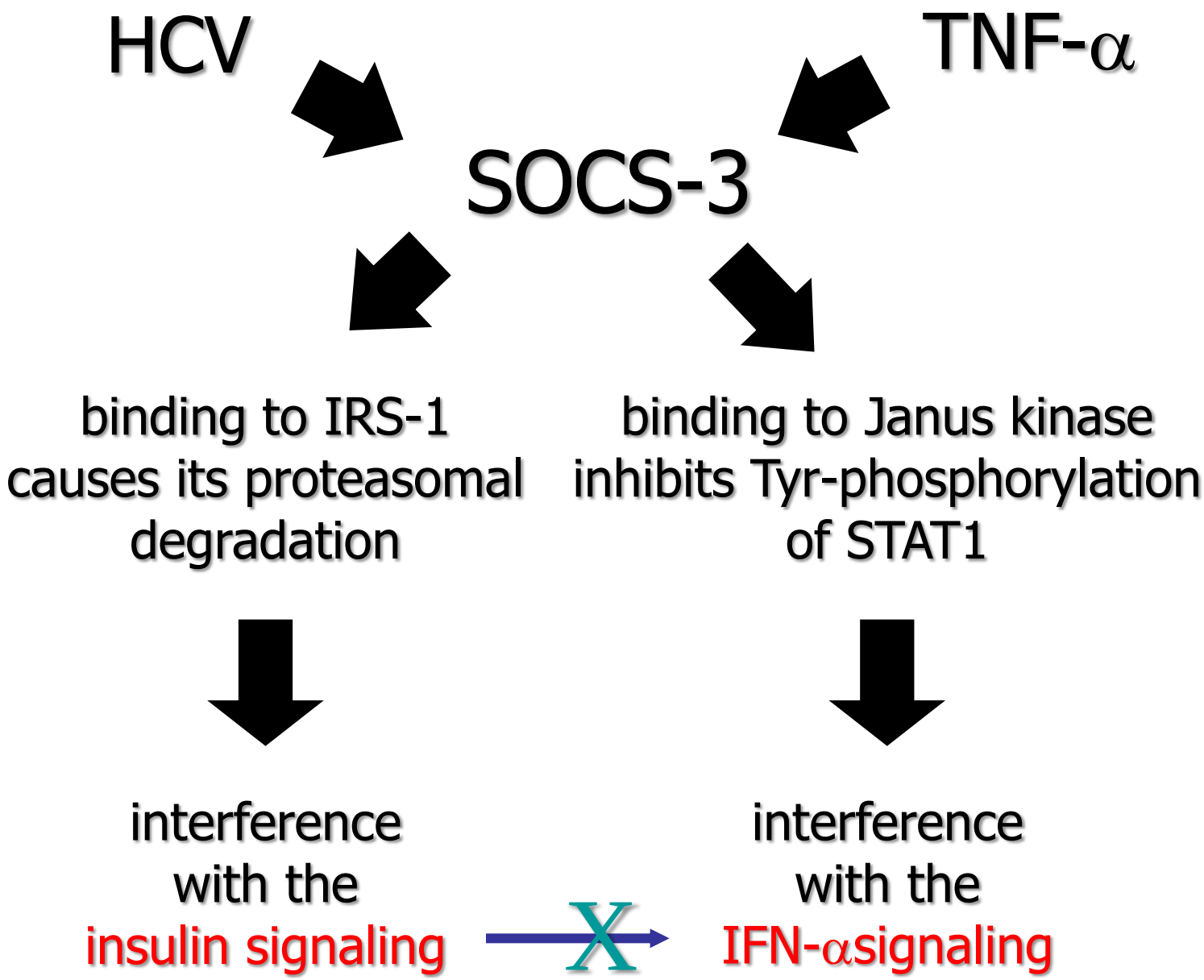


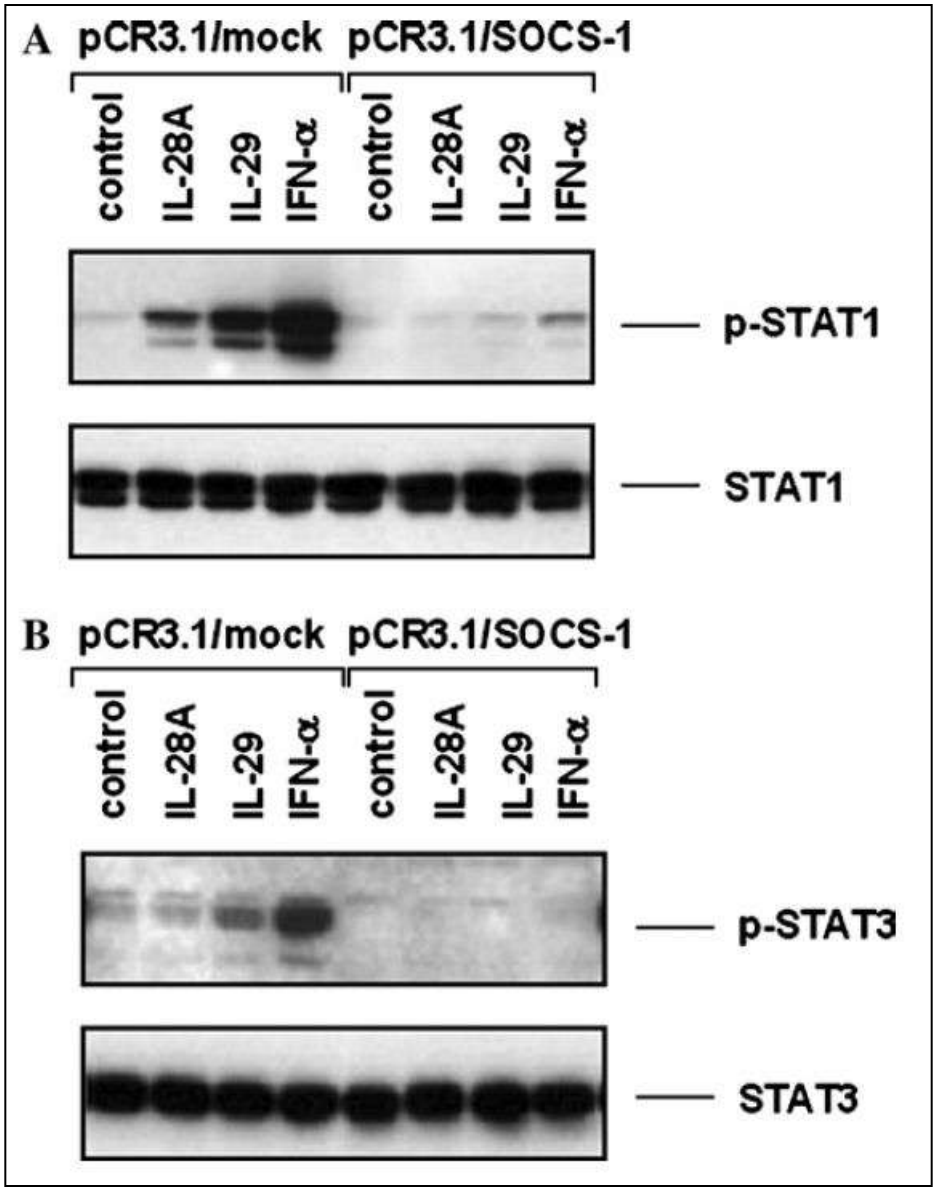


1: Andamento di Socs3 ai vari tempi e nei diversi genotipi, con particolare sulla seconda settimana a cui si osserva il picco di espressione.

2: Western blotting della proteina socs3 al tempo in cui si osserva il picco di espressione genica

Persico et al. CCLM, 2009


HCV
TNF-α
SOCS-3
binding to IRS-1
causes its proteasomal
degradation
binding to Janus kinase
inhibits Tyr-phosphorylation
of STAT1
interference
with the
insulin signaling
X
interference
with the
IFN-αsignaling



IFN-Lambdas induced STAT1 and STAT3 phosphorylation.

A control HepG2 clone (pCR3.1/mock) and SOCS-1 (pCR3.1/SOCS-1) overexpressing clone were incubated with 1000 U/ml IFN-a, 100 ng/ml IL-28A, and 100 ng/ml IL-29 for 15 min, respectively.

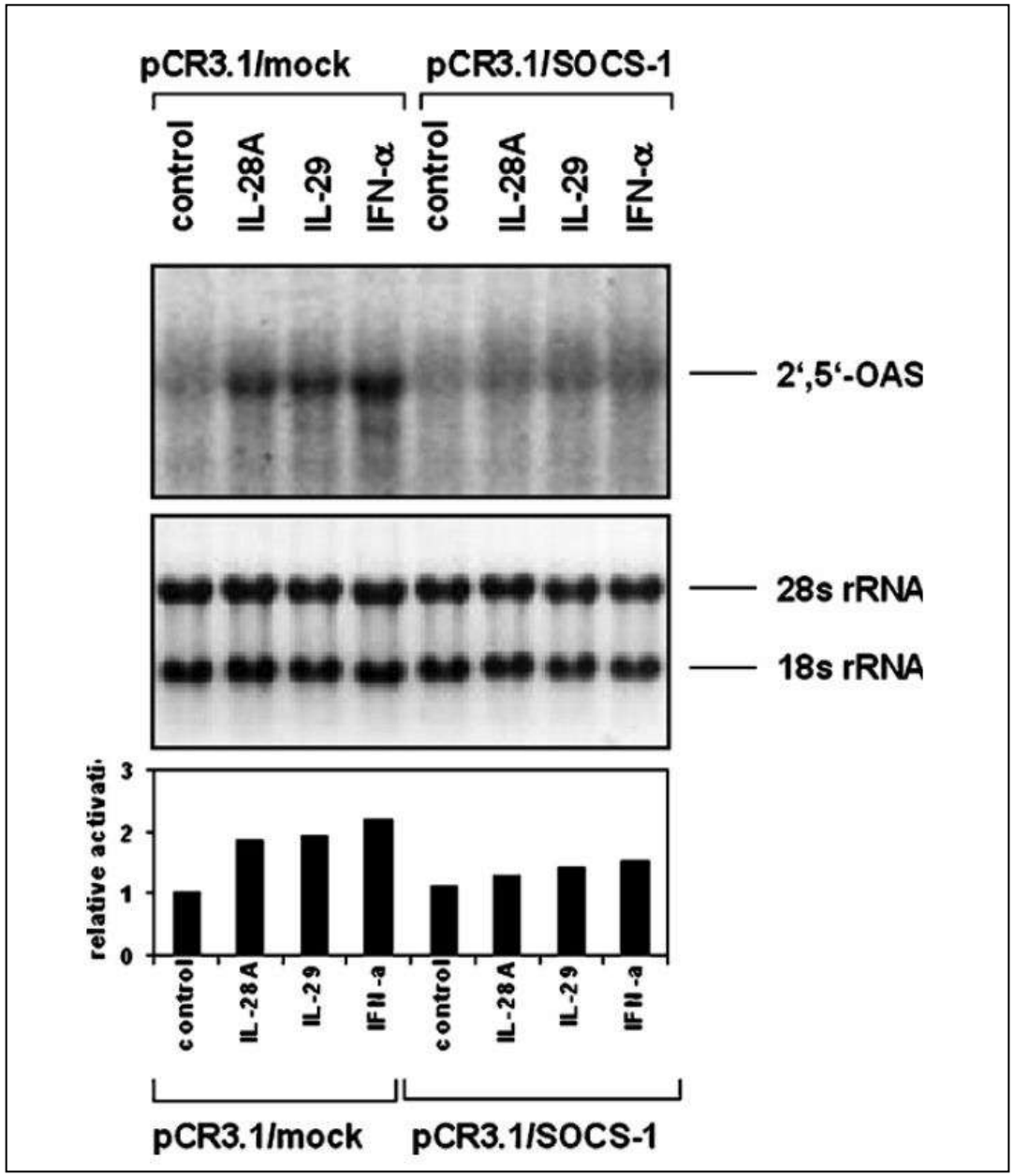
(A) Tyrosine phosphorylation of STAT1 (pSTAT1) in mock-transfected cells was diminished in SOCS-1 overexpressing cells.

(B) Tyrosine phosphorylation of STAT3 (pSTAT3) after stimulation with IFN-a or IFN-lambdas.

SOCS-1 overexpression completely abolished STAT3 phosphorylation.

Shown is one representative Western blot out of four performed experiments.

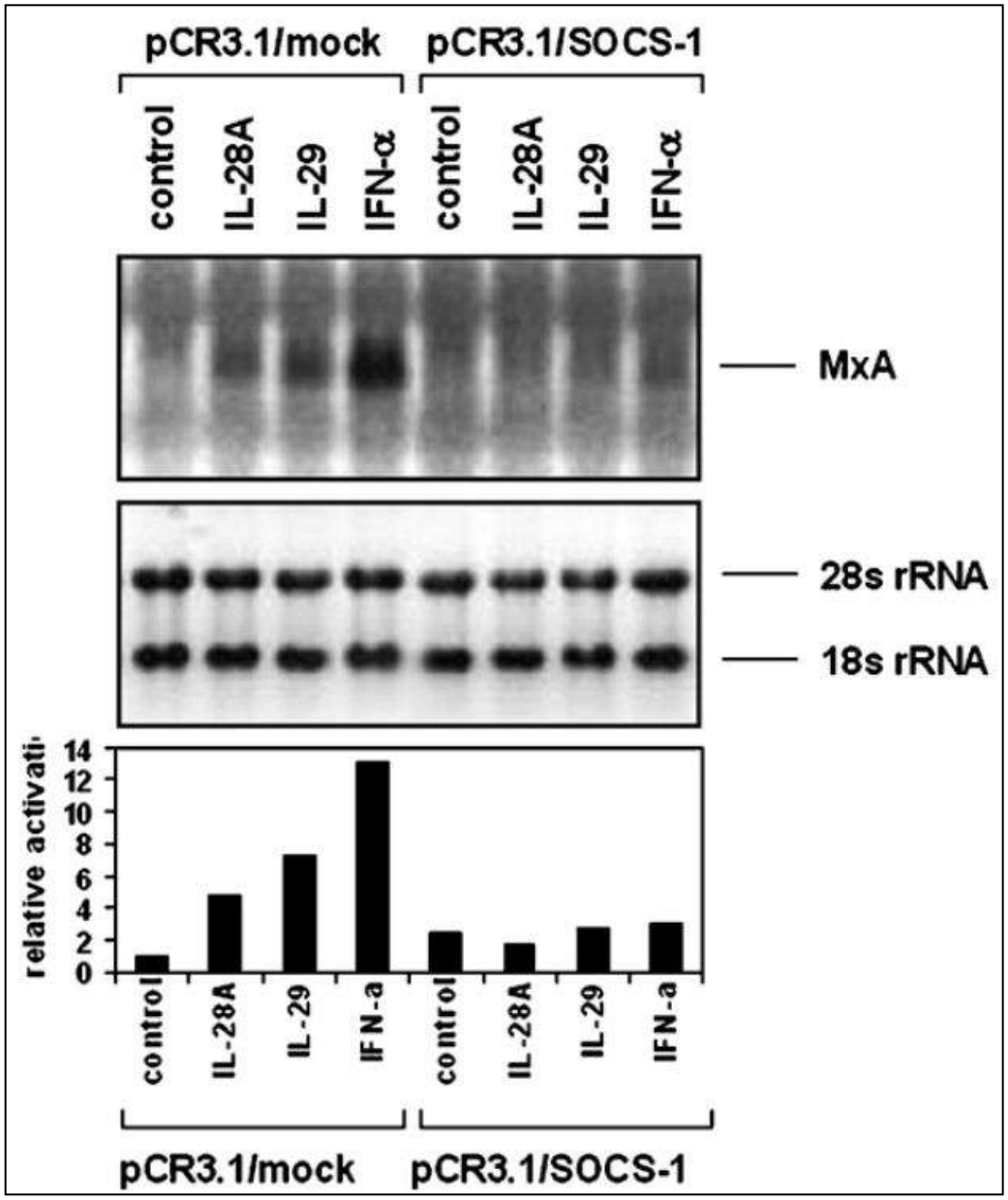
S. Brand et al. - Biochemical and Biophysical Research Communications 331 (2005) 543–548



IFN-lambdas induced 20,50-OAS gene expression which was inhibited by SOCS-1 over expression.

A control HepG2 clone (pCR3.1/mock) and SOCS-1 (pCR3.1/SOCS-1) overexpressing clone were incubated with 1000 U/ml IFN-a, 10 ng/ml IL-28A or 10 ng/ml IL-29 for 5 h, respectively. 20,50-OAS mRNA expression was determined by Northern blot analysis (upper panel). Equal loading is confirmed by ethidium bromide staining of 28s and 18s rRNA (middle panel). Baseline mRNA level in the control pCR3.1/mock clone was set as 1.0. Baseline and stimulus induced 20,50-OAS mRNA levels in all other groups were calculated as -fold increase in comparison to this control group (lower panel). Shown is one representative Northern blot out of three performed experiments.

S. Brand et al. - Biochemical and Biophysical Research Communications 331 (2005) 543–548

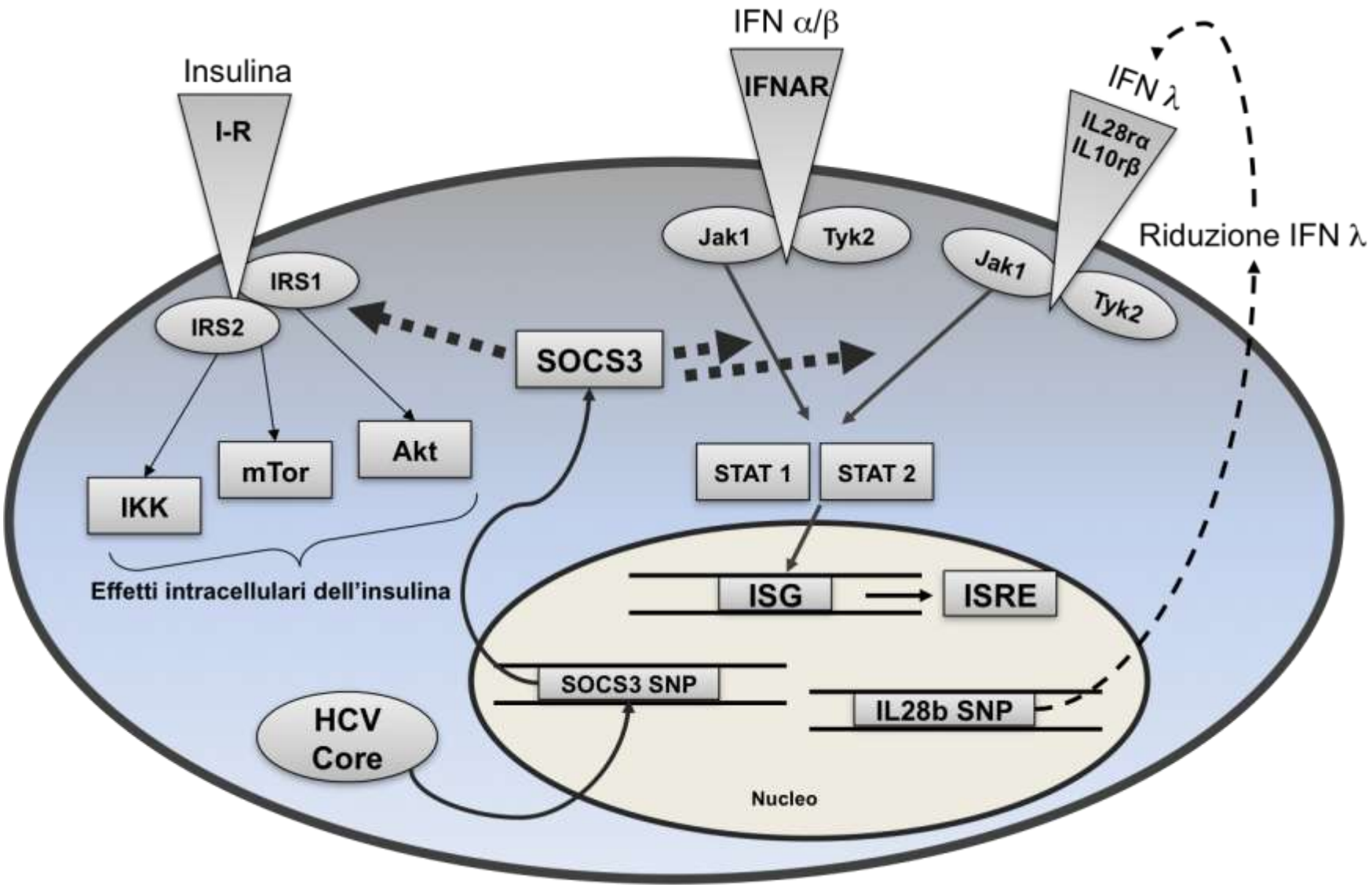


IFN-lambdas induced MxA gene expression which was inhibited by SOCS-1 overexpression.

A control HepG2 clone (pCR3.1/mock) and SOCS-1 (pCR3.1/SOCS-1) overexpressing clone were incubated with 1000 U/ml IFN-a, 10 ng/ml IL-28A or 10 ng/ml IL-29 for 5 h, respectively. MxA mRNA expression was determined by Northern blot analysis (upper panel). Equal loading is confirmed by ethidium bromide staining of 28s and 18s rRNA (middle panel). Baseline mRNA level in the control pCR3.1/mock clone was set as 1.0. Baseline and stimulus induced MxA mRNA levels in all other groups were calculated as -fold increase in comparison to this control group (lower panel). Shown is one representative Northern blot out of three performed experiments.

S. Brand et al. / Biochemical and Biophysical Research Communications 331 (2005) 543–548

SOCS 3



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