

RESISTENCIA A LA INSULINA LÍPIDOS E INFLAMACIÓN

Adriana Monroy

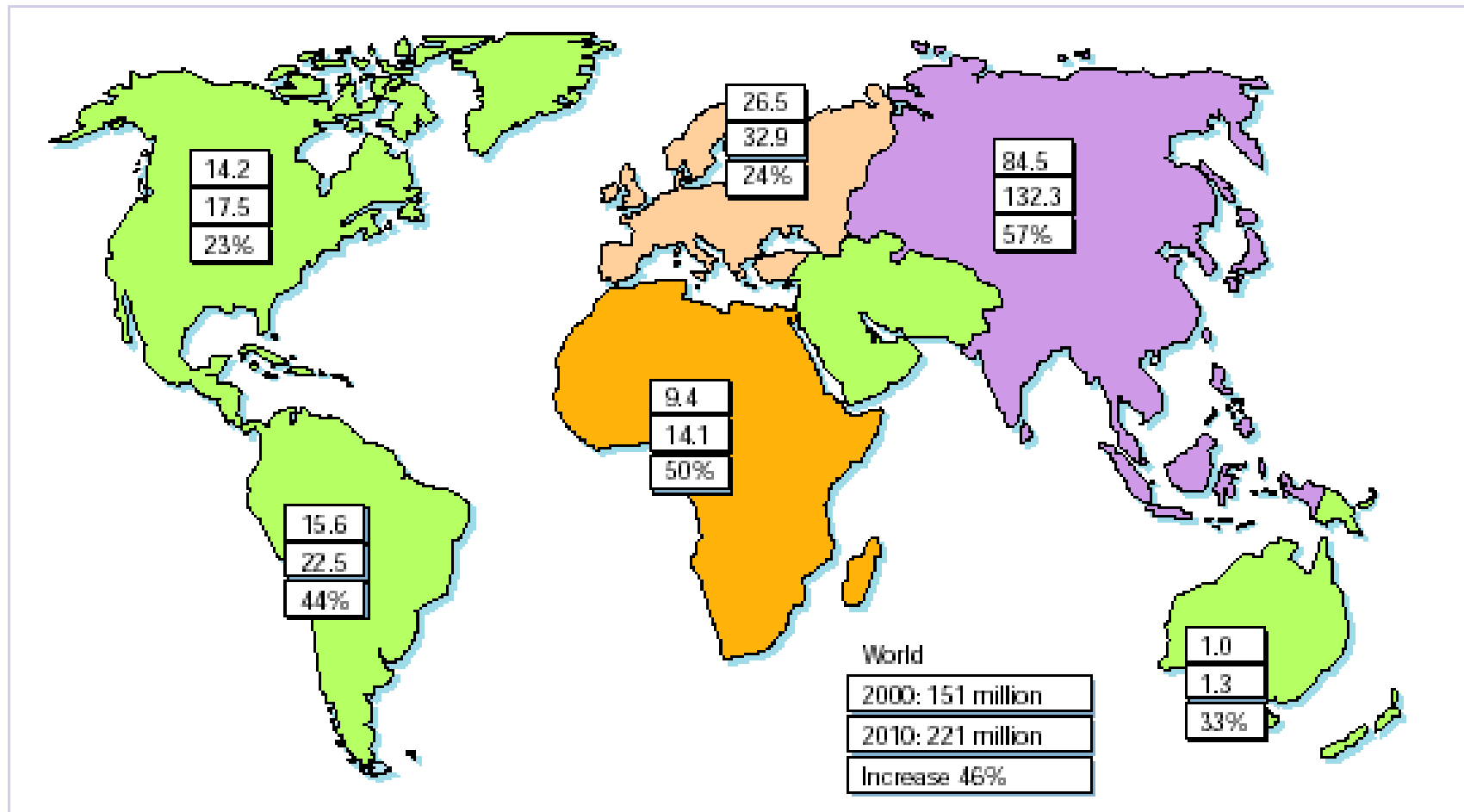
Diabetes Division,

Department of Medicine

University of Texas Health Science Center at San Antonio

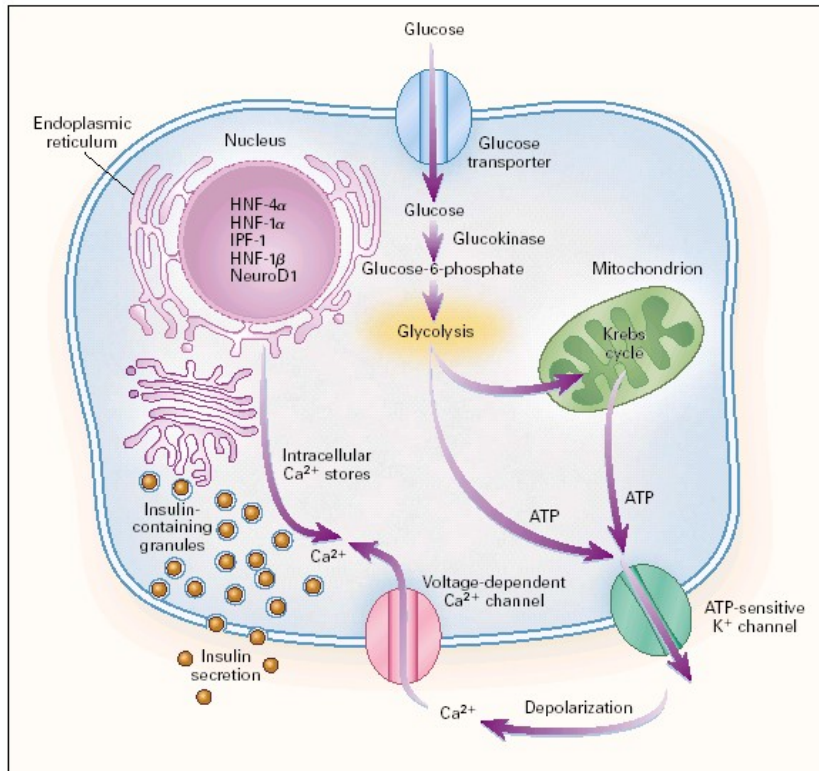
San Antonio, Tx

INCIDENCIA MUNDIAL DE DIABETES

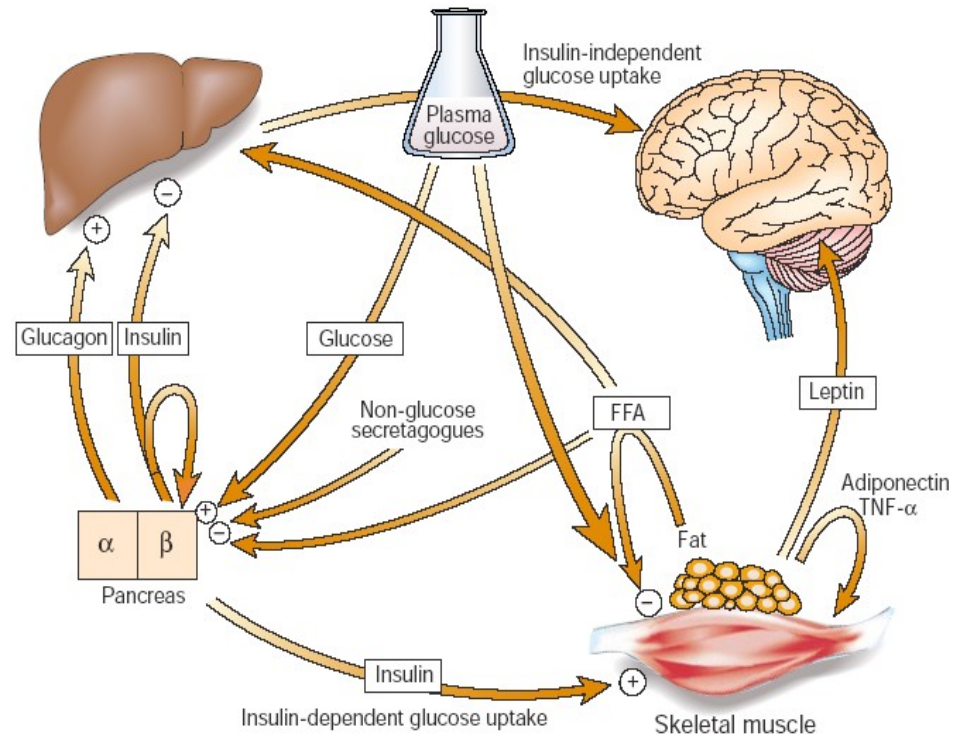


DIABETES MELLITUS TIPO 2

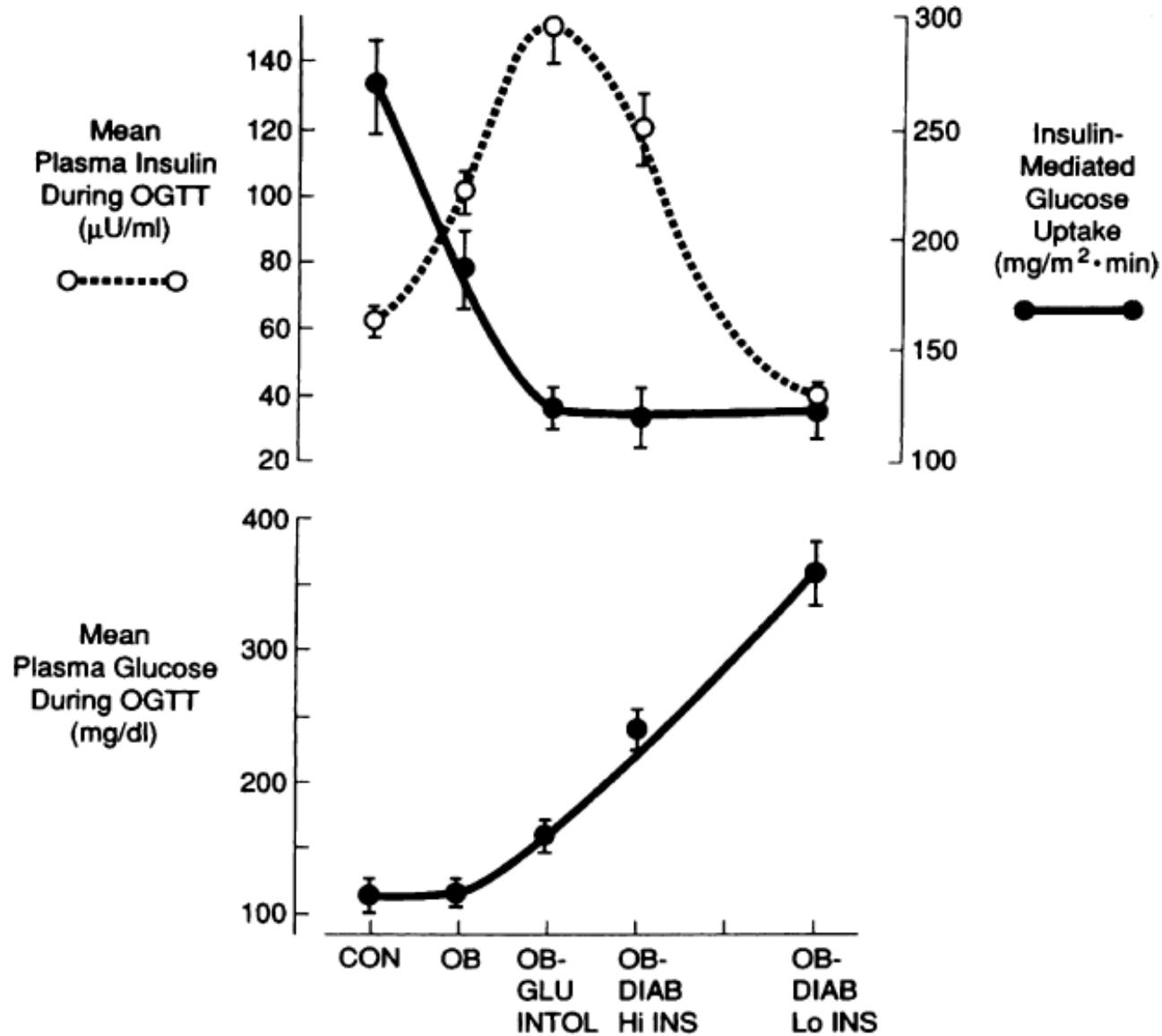
DEFECTOS EN SECRECIÓN DE INSULINA



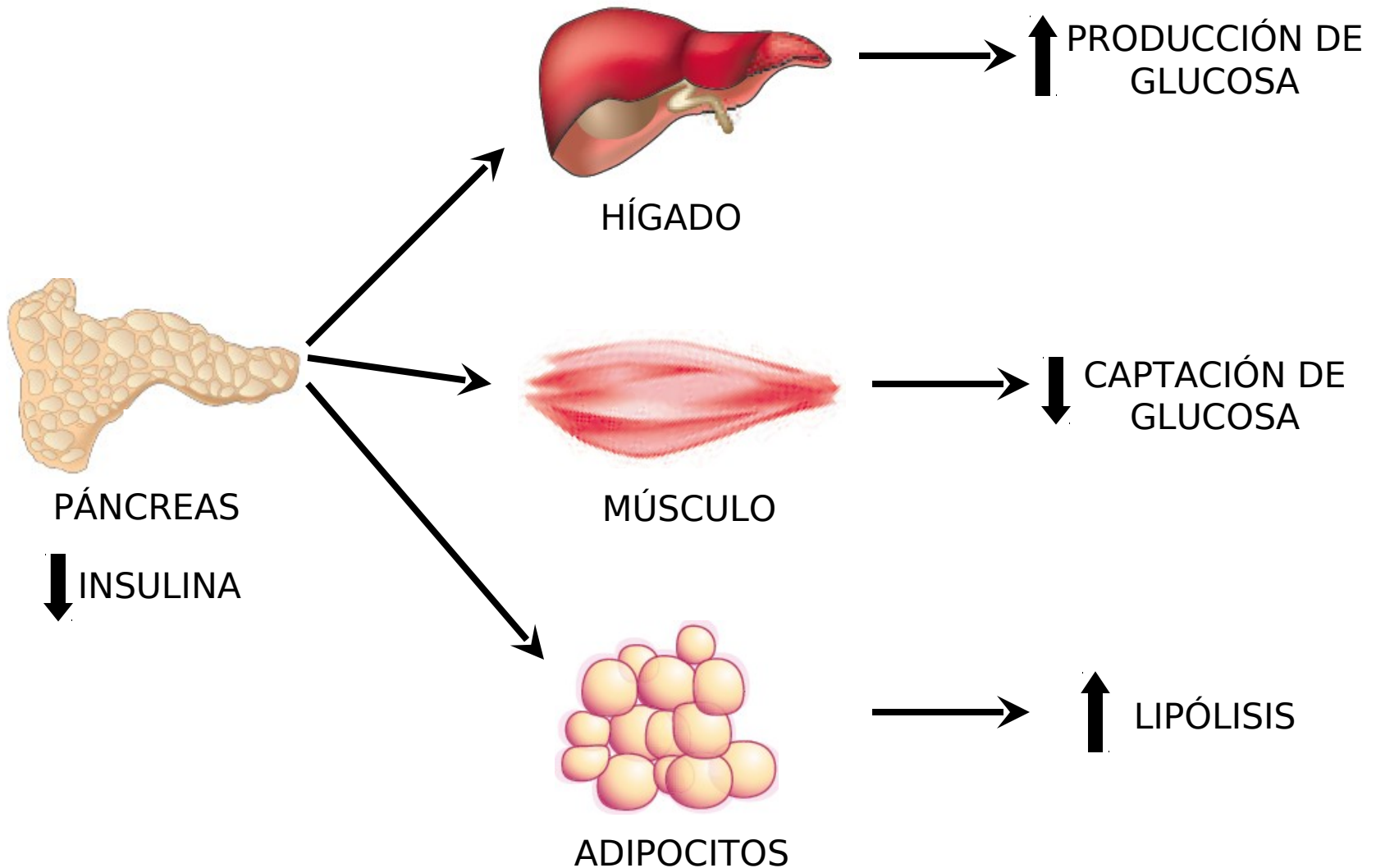
RESISTENCIA A LA INSULINA



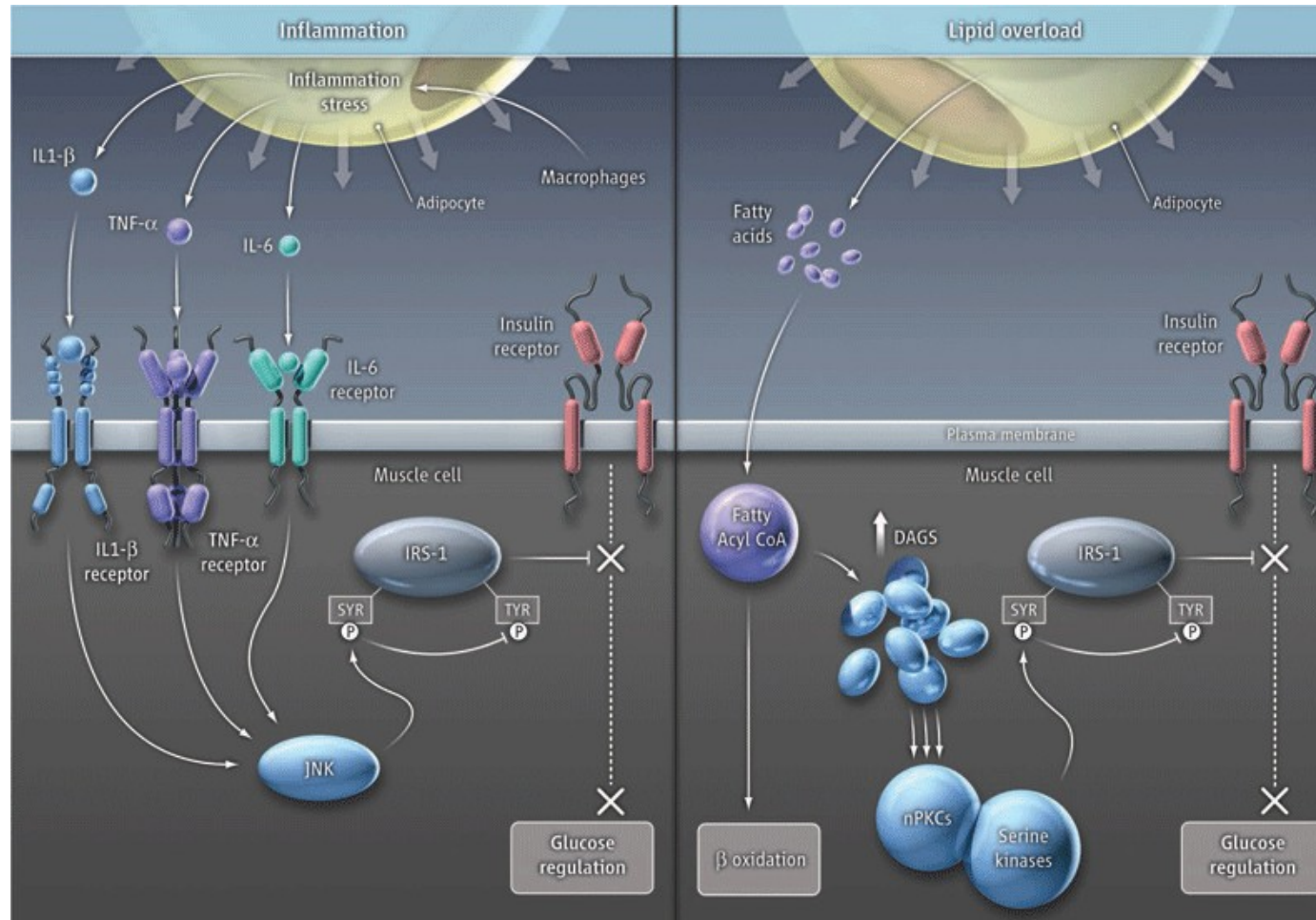
HIPERINSULINEMIA Y RESISTENCIA A LA INSULINA PRECEDEN A LA DMT2



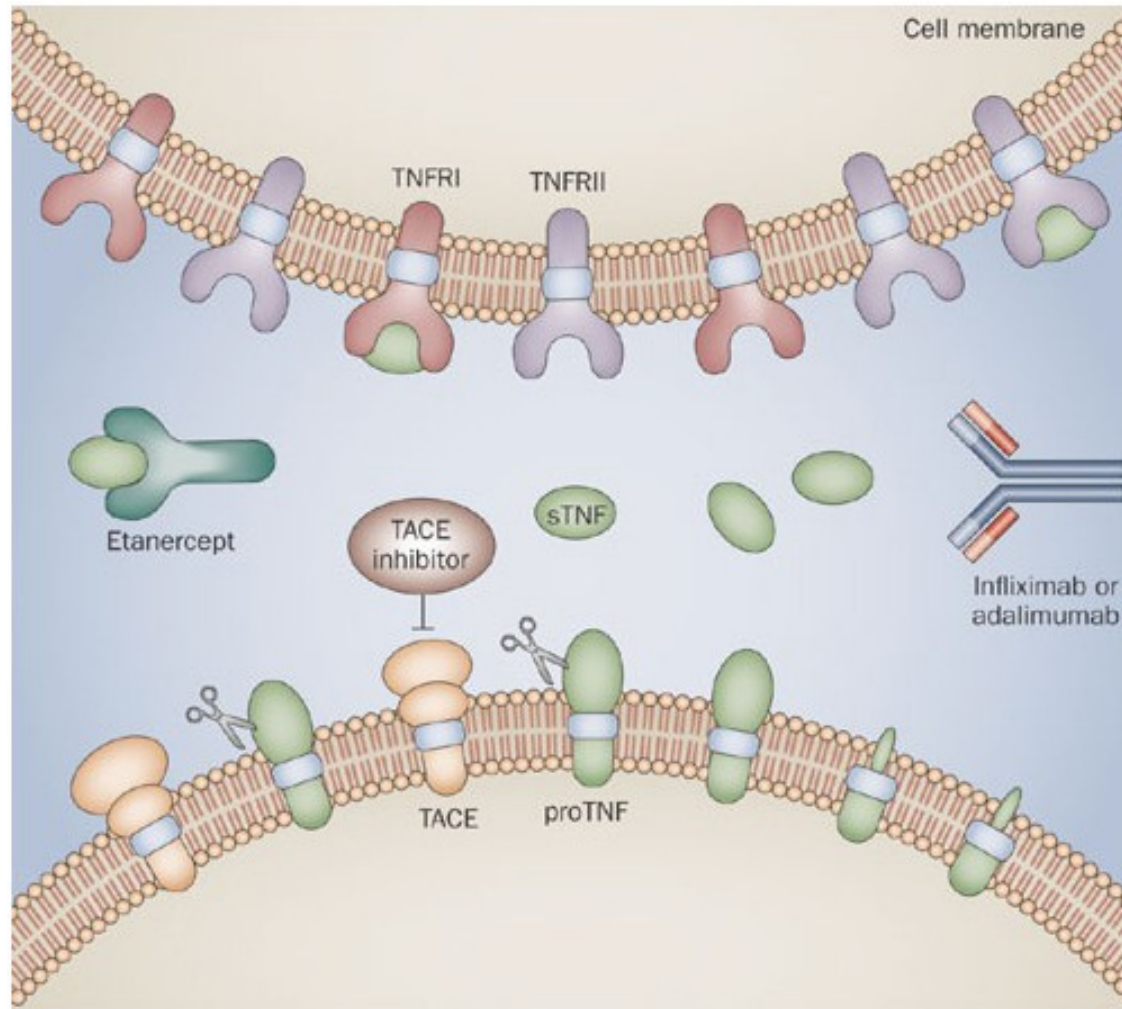
RESISTENCIA A LA INSULINA



MECANISMOS DE RESISTENCIA A LA INSULINA



PROCESAMIENTO PROTEOLÍTICO DE $\text{TNF}\alpha$

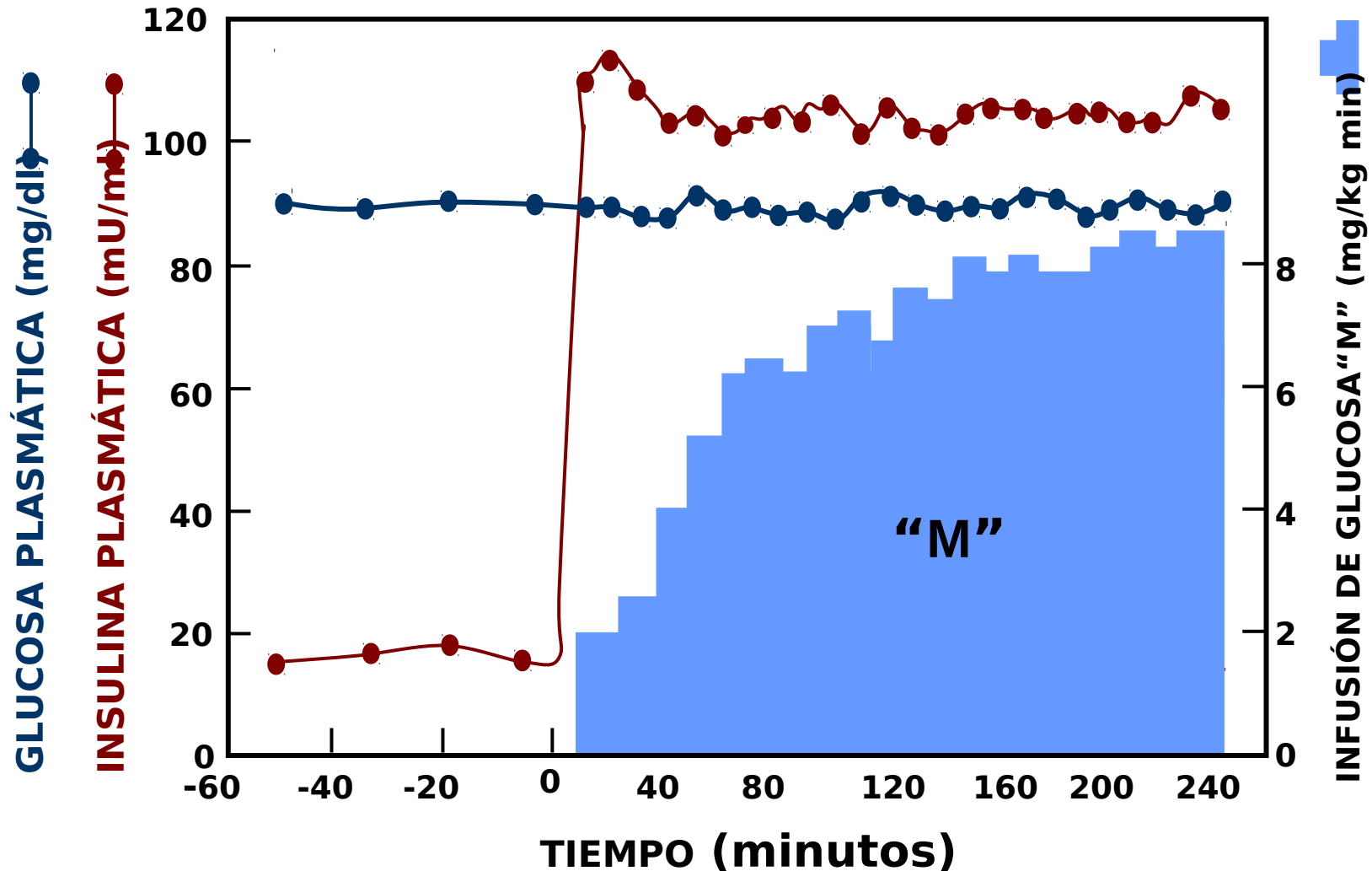


**¿ES LA ACCIÓN Y REGULACIÓN DE
TACE IMPORTANTE EN EL
DESARROLLO DE OBESIDAD Y
DIABETES?**

CARACTERÍSTICAS CLÍNICAS

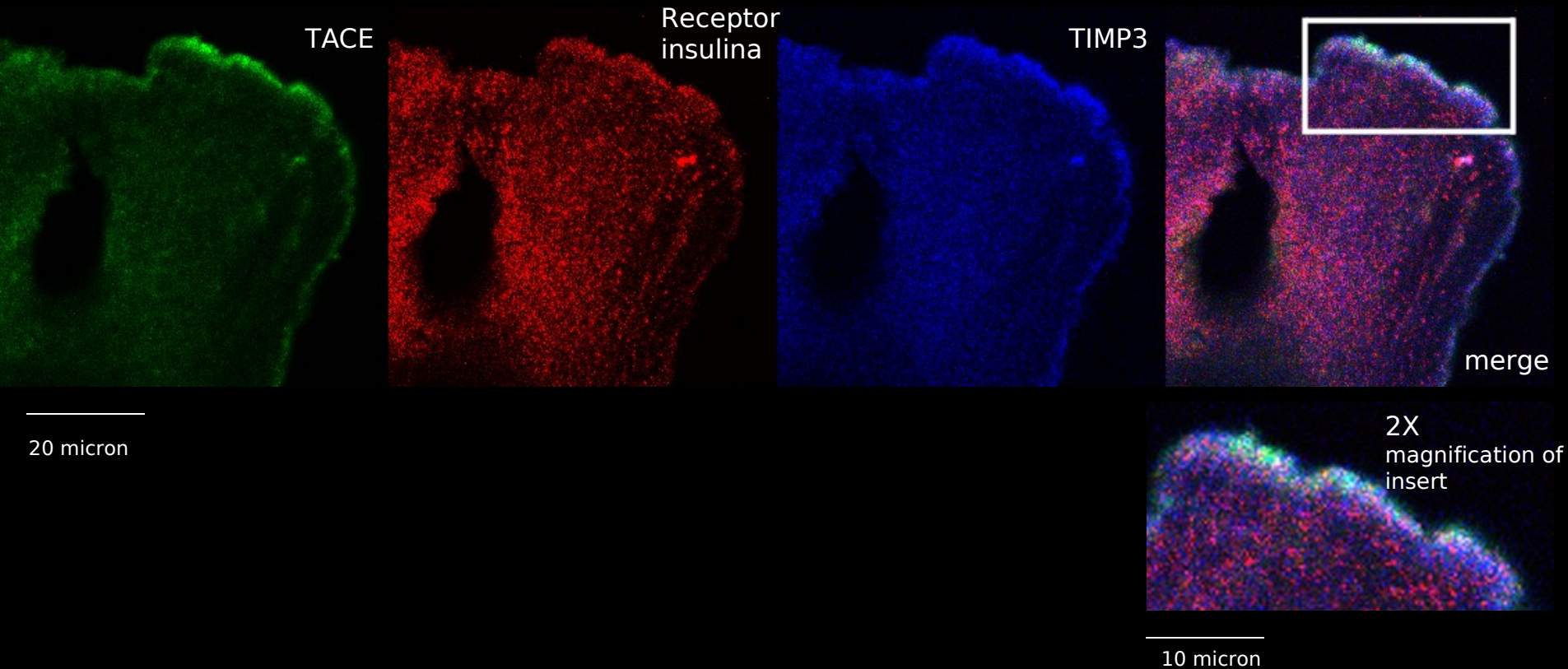
	DELGADOS	OBESOS	DMT2	p
N (M/F)	14 (7/7)	14 (7/7)	14 (7/7)	
Edad (años)	37 ± 3	39 ± 2	42 ± 3	
IMC (kg/m²)	22.3 ± 0.5	30.1 ± 0.7*	31.9 ± 0.8*	* < 0.001
Glucosa (mg/dl)	84 ± 2	94 ± 3*	162 ± 13*	* < 0.001
HbA1c (%)	5.1 ± 0.1	5.2 ± 0.1	8.4 ± 0.3 ‡	‡ < 0.001
Insulina (µU/ml)	3 ± 1	7 ± 1*	17 ± 2*	* < 0.001
M (mg/kg·min)	11.6 ± 0.9	7.4 ± 0.5*	3.4 ± 0.4* ‡	* ‡ < 0.001
Triglicéridos (mg/dl)	92 ± 27	100 ± 13	228 ± 34 ‡	‡ < 0.05
LDL (mg/dl)	114 ± 8	107 ± 8	112 ± 7	
HDL (mg/dl)	52 ± 3	43 ± 3	36 ± 2*	* < 0.001
Ac. grasos (mg/dl)	13 ± 5	16 ± 5	20 ± 7 ‡	‡ < 0.05

CLAMP EUGLICÉMICO HIPERINSULINÉMICO

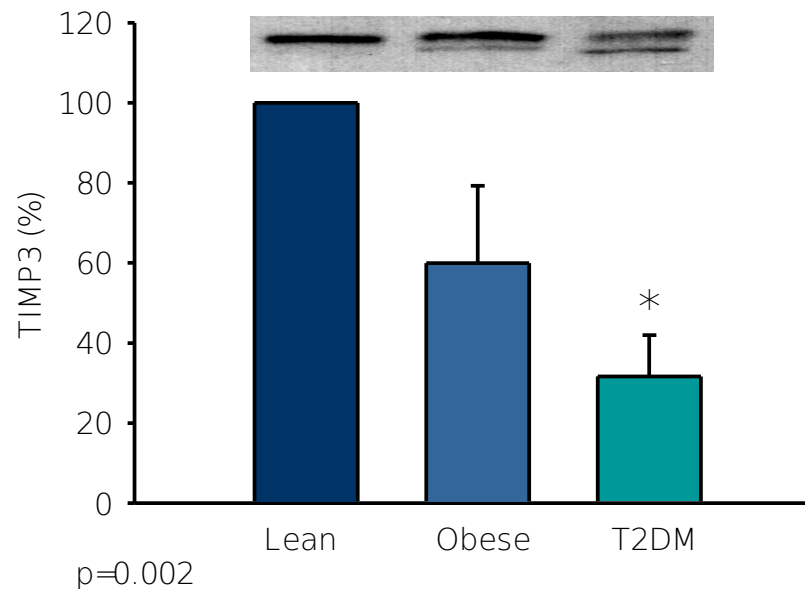
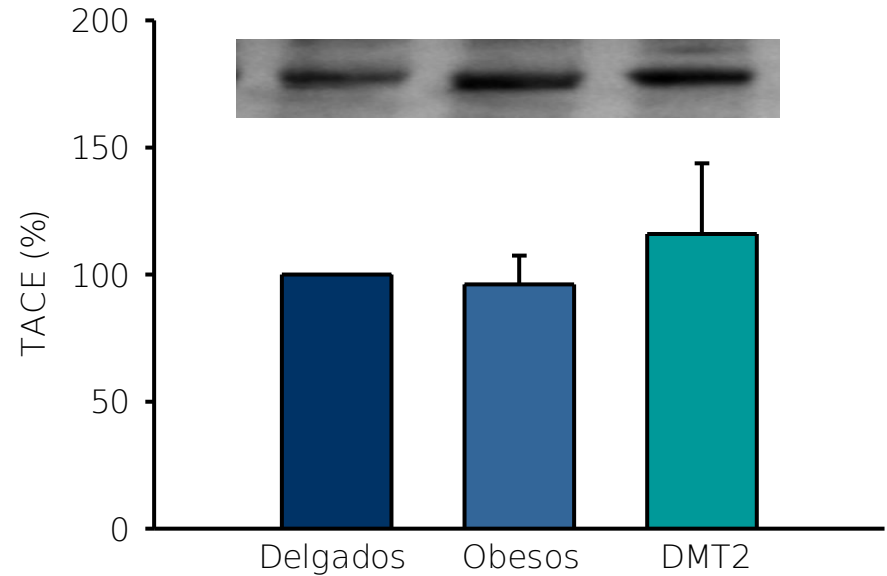
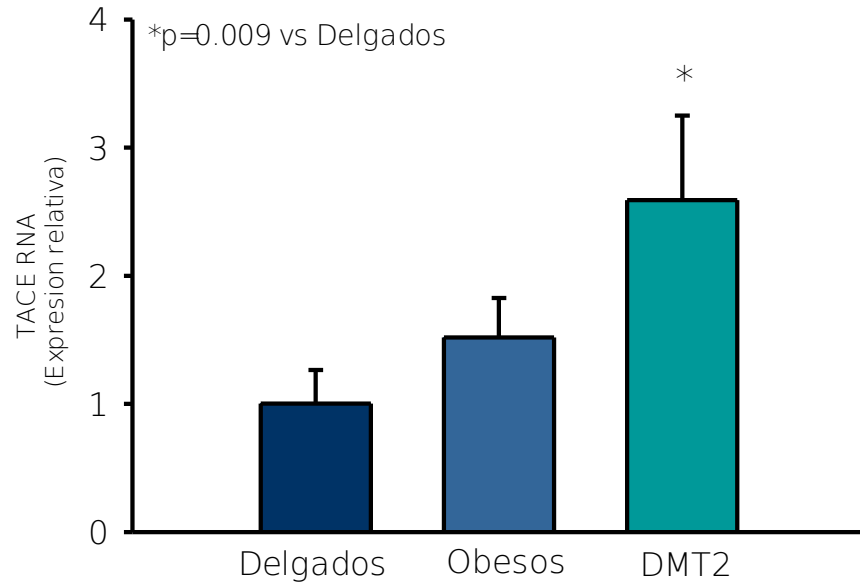


"M" = Índice de infusión de glucosa = Glucosa Metabolizada

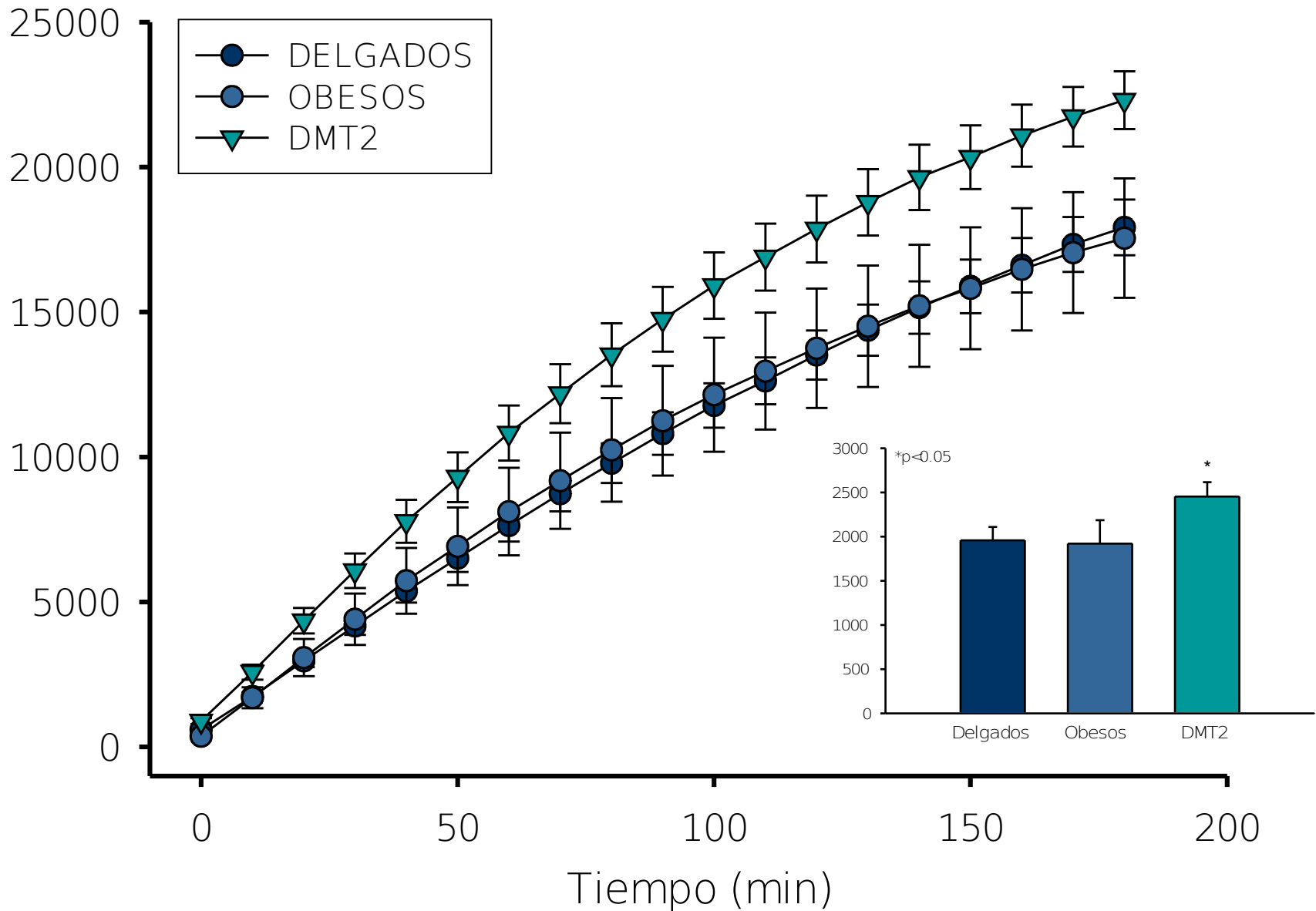
DISTRIBUCIÓN DE TACE, RECEPTOR A INSULINA Y TIMP3 EN MÚSCULO ESQUELÉTICO HUMANO



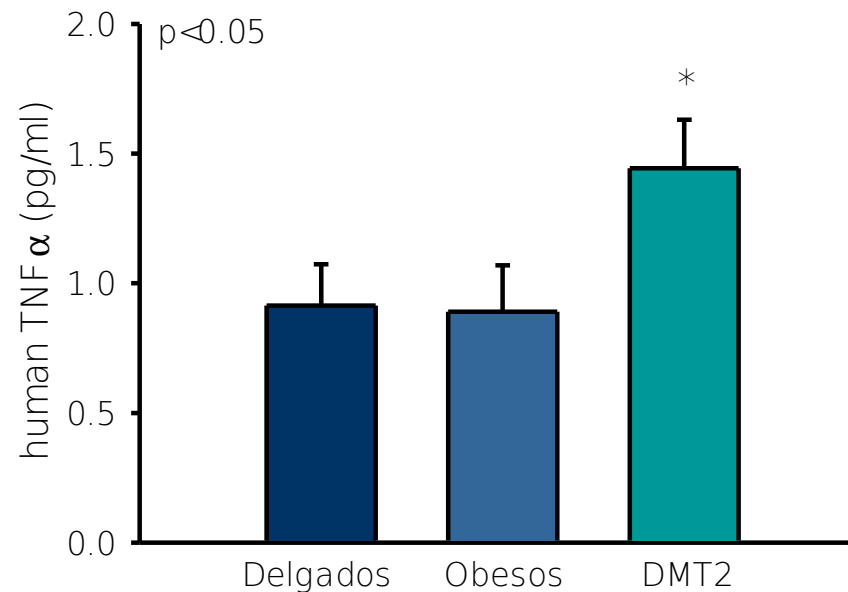
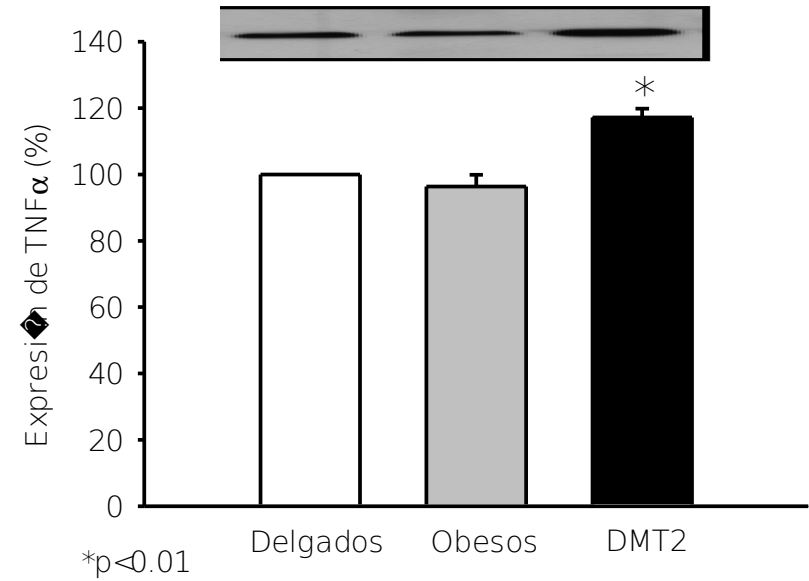
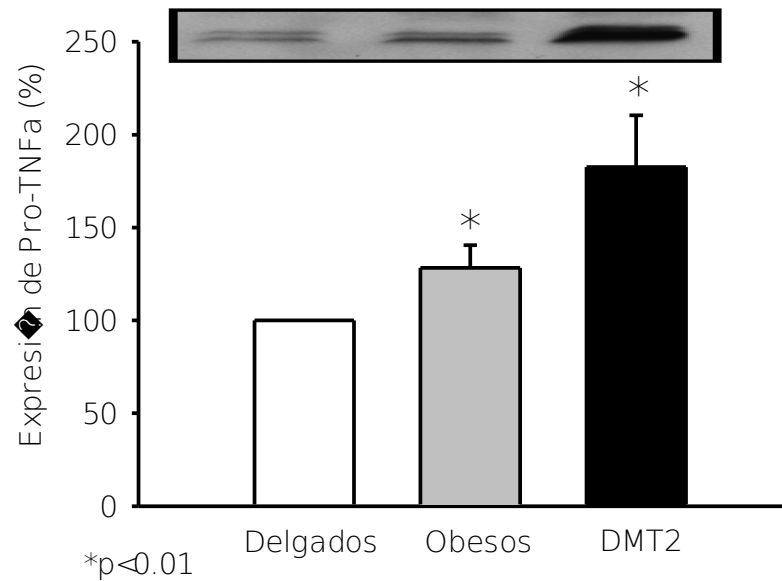
EXPRESIÓN DE TACE/TIMP3 EN MÚSCULO ESQUELÉTICO HUMANO



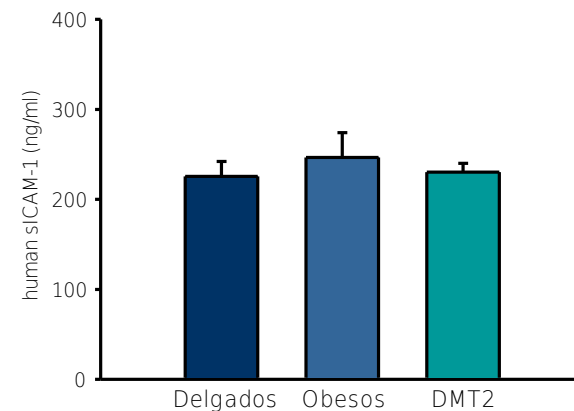
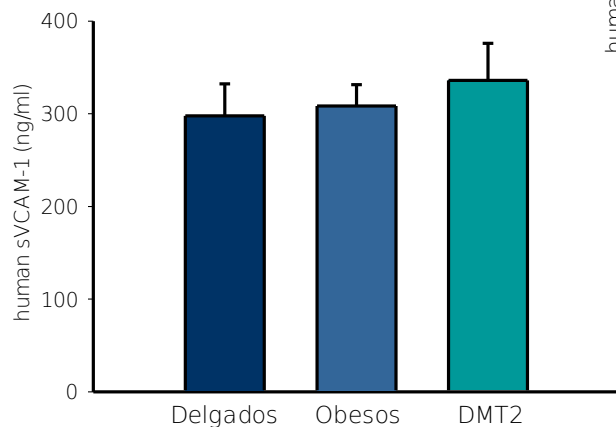
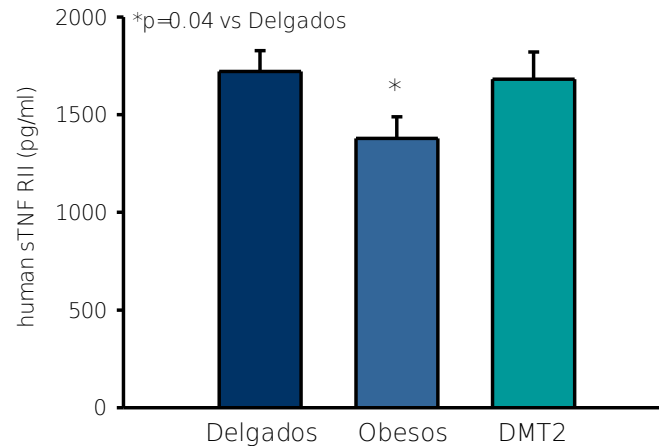
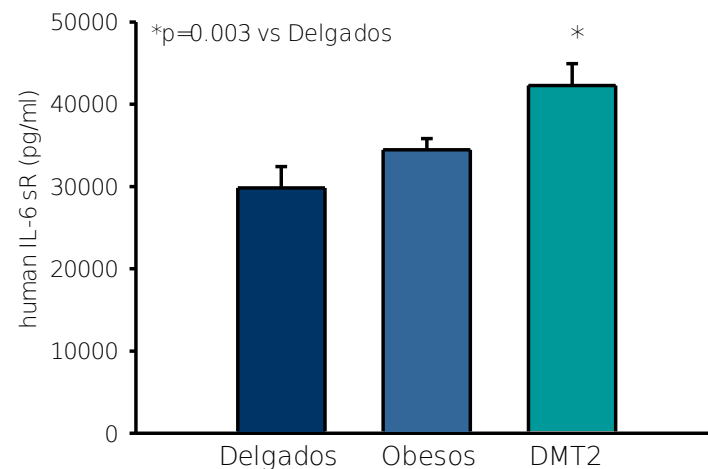
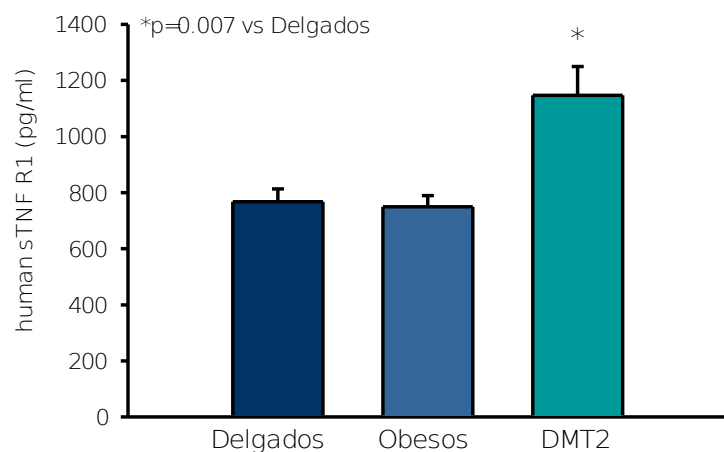
ACTIVIDAD DE TACE EN LISADOS DE MÚSCULO



EXPRESIÓN DE $\text{TNF}\alpha$ EN MÚSCULO Y SUERO



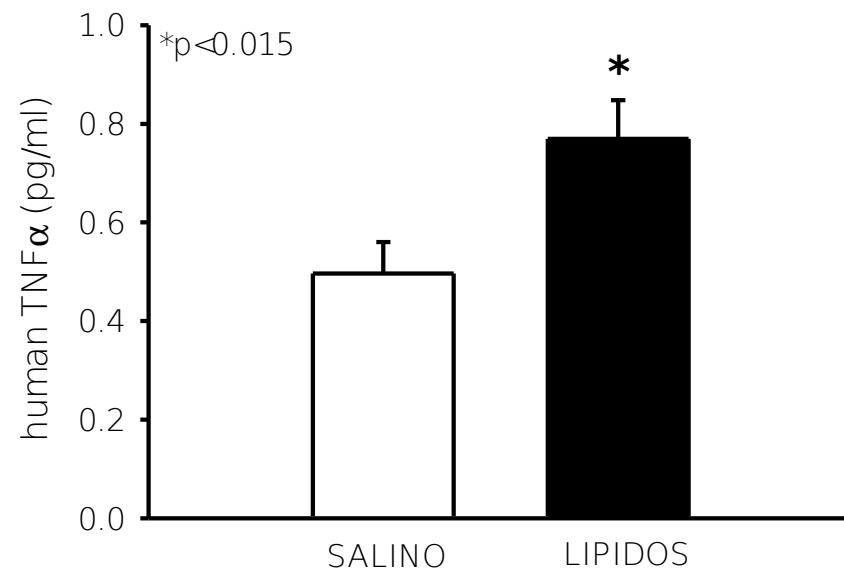
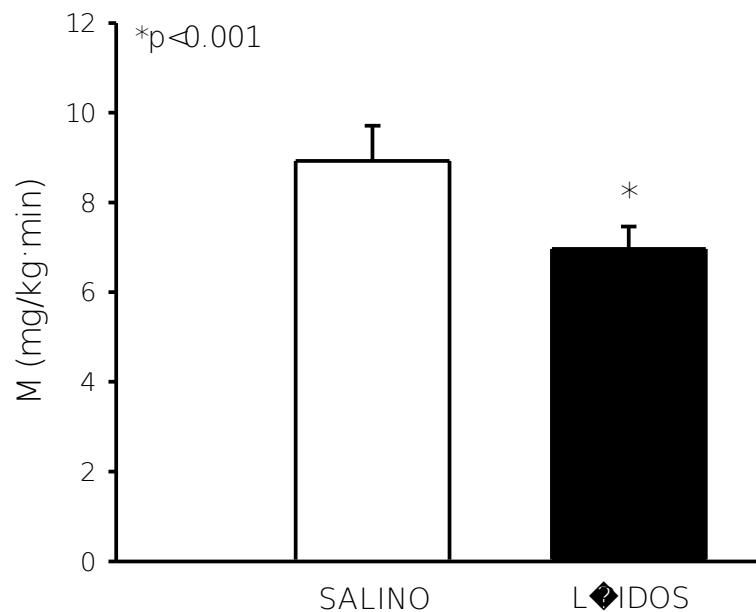
NIVELES EN SUERO DE LOS RECEPTORES DE IL-6 Y $\text{TNF}\alpha$



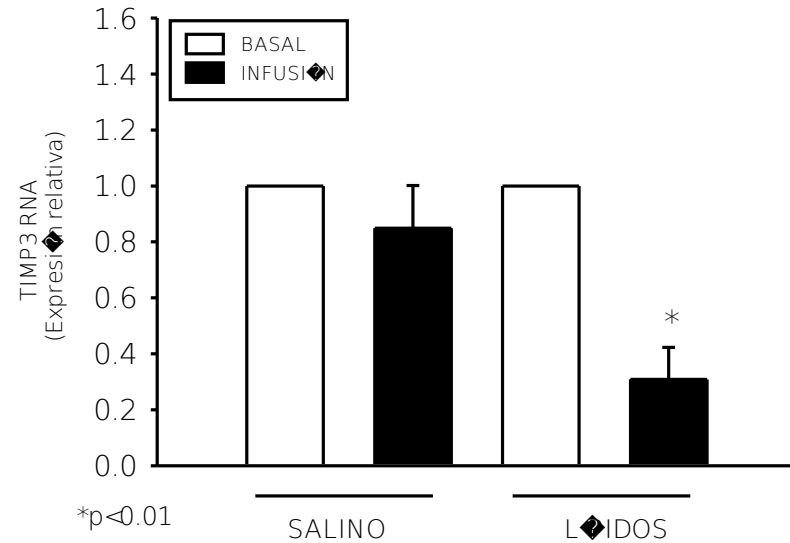
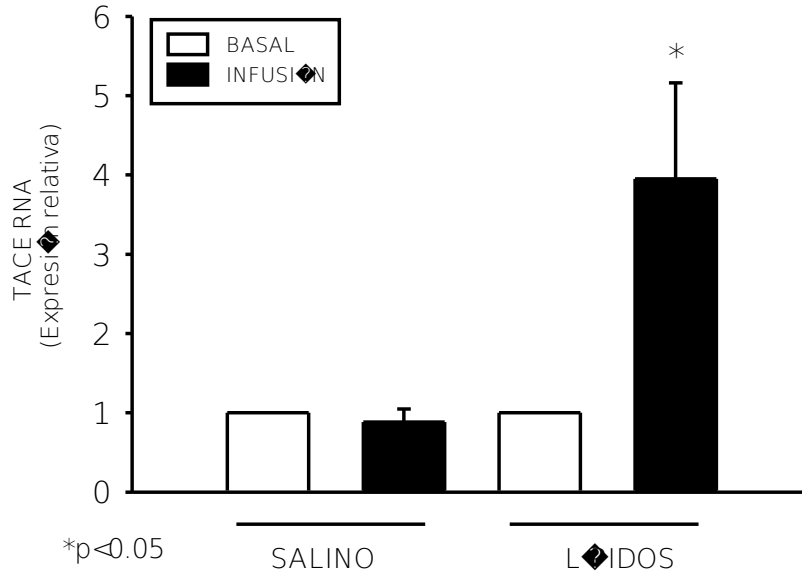
CORRELACIÓN ENTRE FACTORES SOLUBLES Y PARÁMETROS METABÓLICOS

	IMC (kg/m ²)		M (mg/kg.min)		HbA1C (%)	
	r	p	r	p	r	p
Ac. grasos	0.117	0.479	0.384	0.017	0.331	0.04
TNF α	0.467	0.009	0.451	0.014	0.672	<0.0001
sTNFRI	0.502	0.001	0.519	0.003	0.680	<0.0001
sTNFRI	0.204	0.22	-0.262	0.16	0.354	0.047
sIL-6R	0.341	0.04	0.441	0.015	0.376	0.034
sVCA _M	0.127	0.45	-0.271	0.15	0.220	0.23
sICA _M	0.235	0.16	-0.215	0.25	0.058	0.55

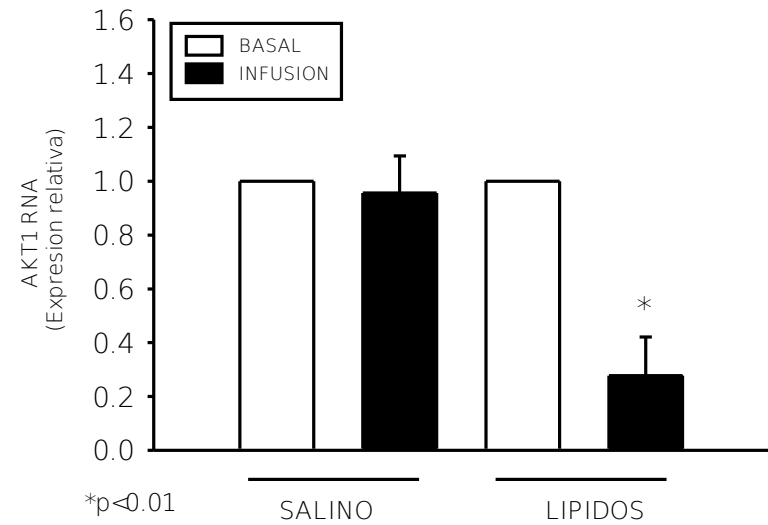
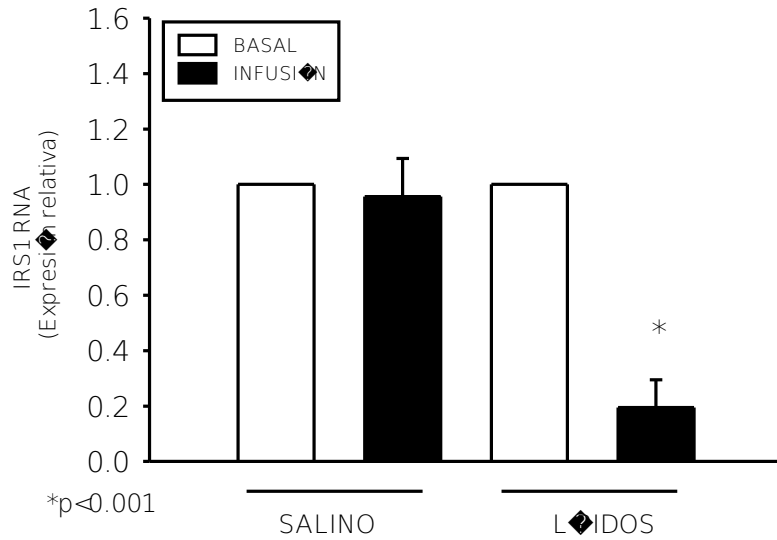
SENSIBILIDAD A LA INSULINA Y NIVELES DE $\text{TNF}\alpha$ DESPUÉS DE INFUSIÓN DE LÍPIDOS



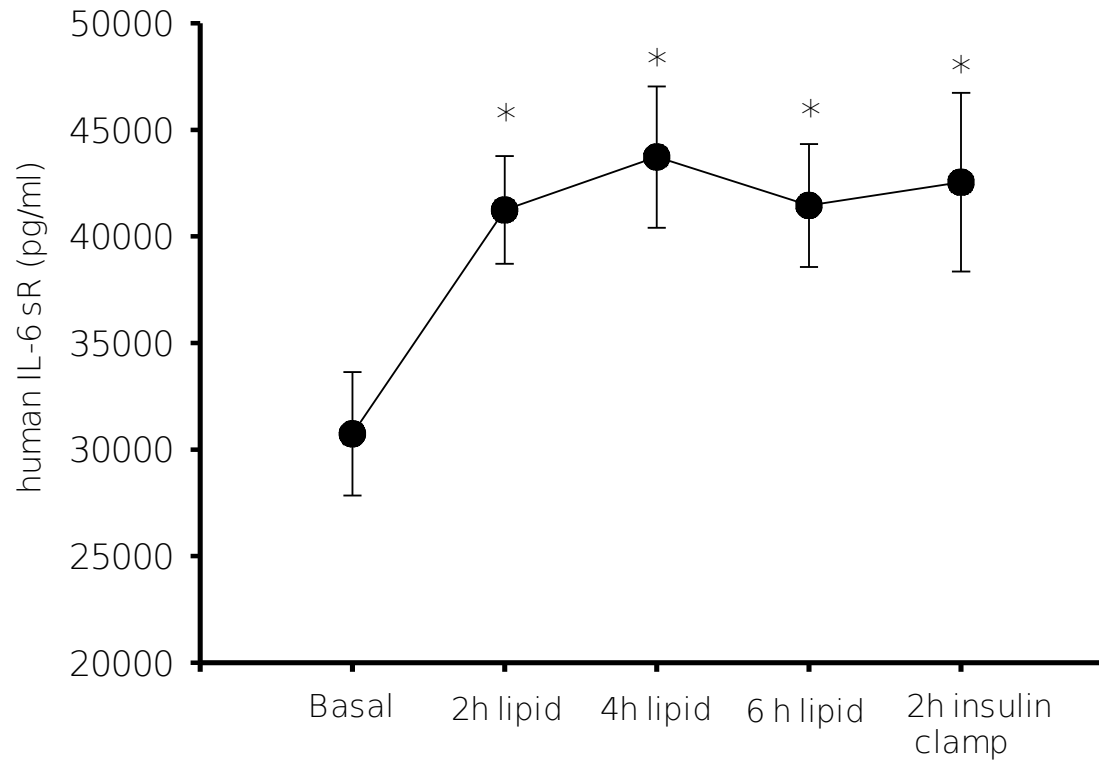
EXPRESIÓN DE TACE/TIMP3 DESPUÉS DE INFUSIÓN DE LÍPIDOS



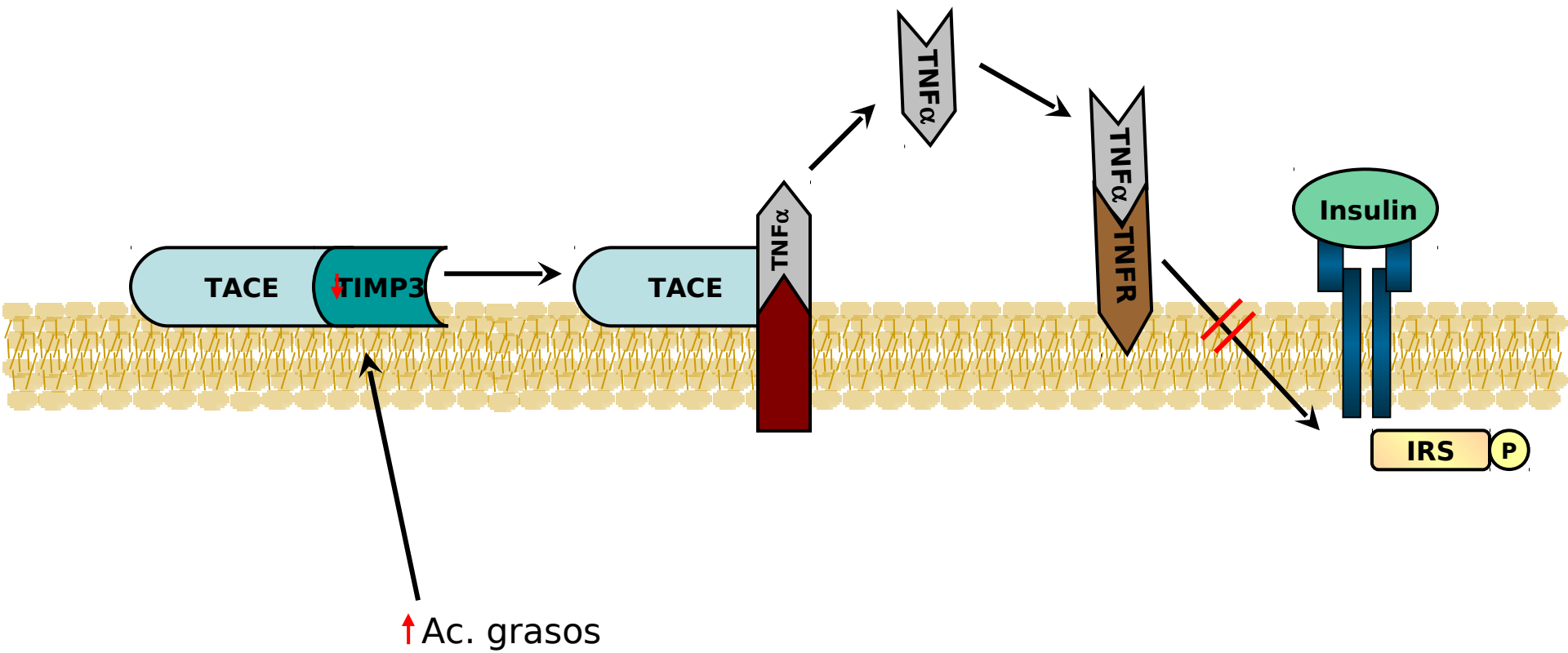
EXPRESIÓN DE IRS1 Y AKT1 DESPUÉS DE INFUSIÓN DE LÍPIDOS



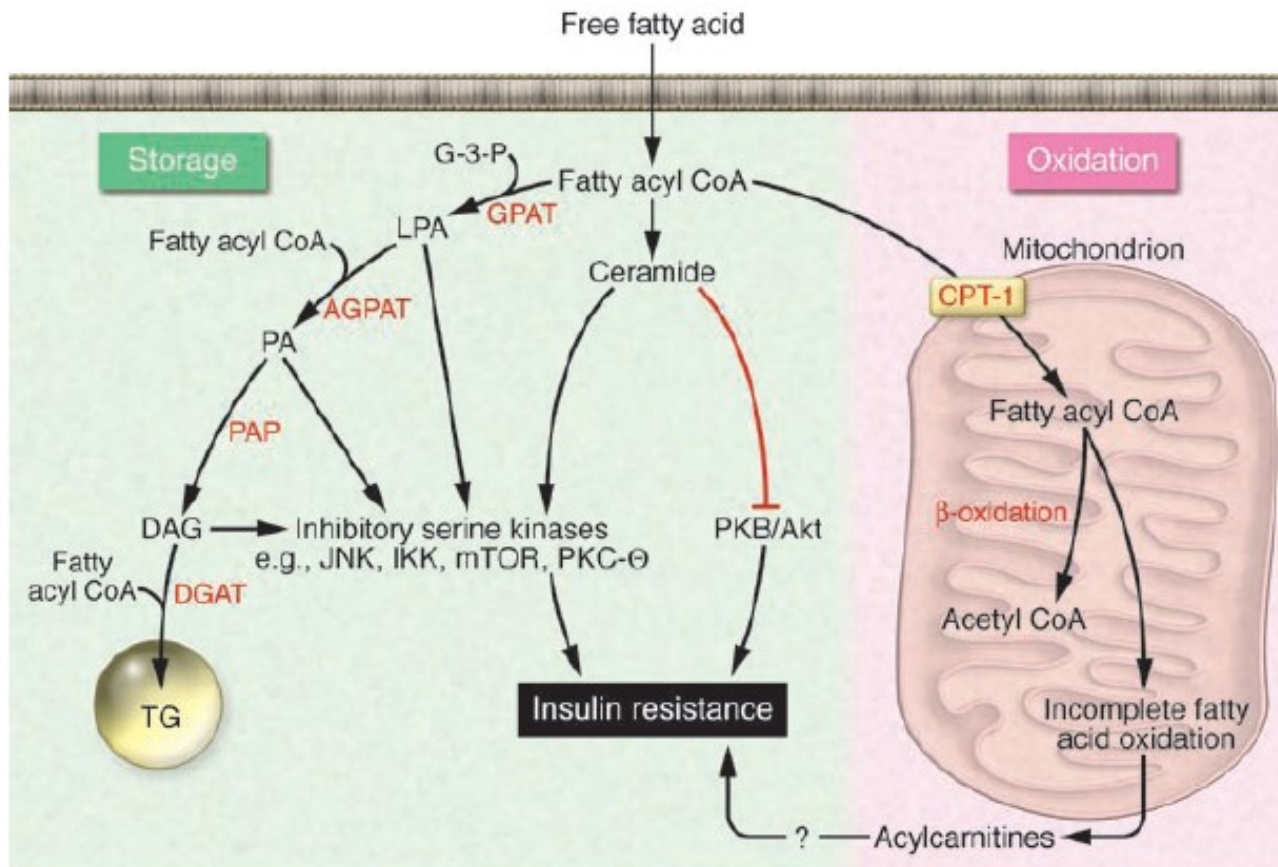
NIVELES DEL RECEPTOR DE INTERLEUCINA 6 SOLUBLE DURANTE LA INFUSIÓN DE LÍPIDOS



*p<0.02 vs Basal



OXIDACIÓN DE AC. GRASOS, DISFUNCIÓN MITOCONDRIAL Y RESISTENCIA A LA INSULINA

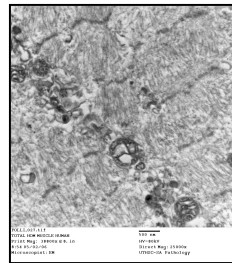


¿ES POSIBLE IDENTIFICAR MARCADORES PROTEÍCOS DE DISFUNCIÓN MITOCONDRIAL EN OBESIDAD Y DIABETES?

CARACTERÍSTICAS CLÍNICAS

	NGT	T2DM
M/F	4/4	4/4
Edad (años)	36 ± 5	50 ± 3
IMC (kg/m ²)	25.6 ± 1.7	35.6 ± 1.9
HbA1c (%)	5.1 ± 0.1	9.0 ± 0.7
M (mg/kg.min)	9.8 ± 1.1	2.9 ± 0.5
Insulina (pg/ ml)	5.16 ± 1.5	9.7 ± 1.9
Duración Diabetes		2.7 ± 1.3

FRACCIONAMIENTO CELULAR DE MUESTRAS DE MÚSCULO HUMANO



HOMOGENADO TOTAL

Centrifugar 700xg 10 min 4°C

Sobrenadante

Botón (Núcleo, Membranas y desechos celulares)
Re-Homogenizar en un homogenizador de Dounce (II)
Centrifugar 700xg 10 min. 4°C

Botón
10,000xg 30 min. 4°C

Botón
Resuspender en sol. homogenización
Colocar en gradiente de
Sacarosa 1.0M/1.5M
80,000xg 1 h 4°C

Recuperar interfase
Lavar con sol. homogenización
Mitocondria

Sobrenadante
Fracción post-mitochondrial
(citoplasma, ER, lisosomas)
100,000xg 1h 4°C

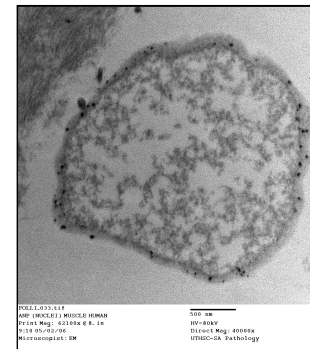
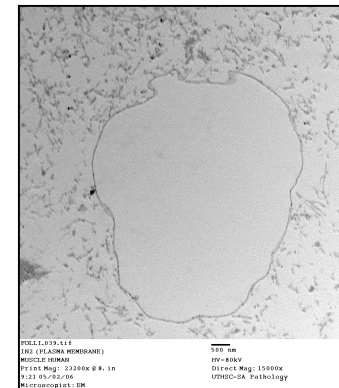
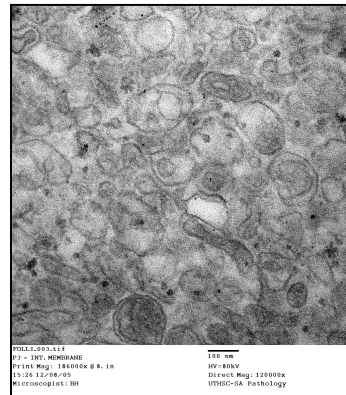
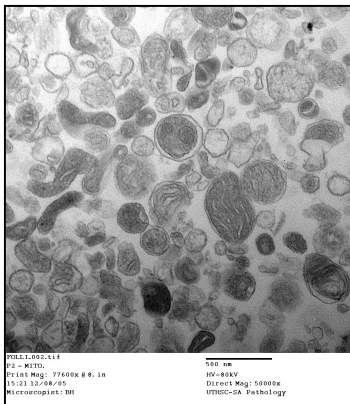
Botón
10,000xg 10 min. 4°C
Membranas
Intracelulares

Sobrenadante
Citoplasma

Botón
(Núcleo, Membranas y desechos celulares)
Resuspender en sol. Sacarosa I
Colocar sobre sol. sacarosa II
30,000xg 45 min. 4°C

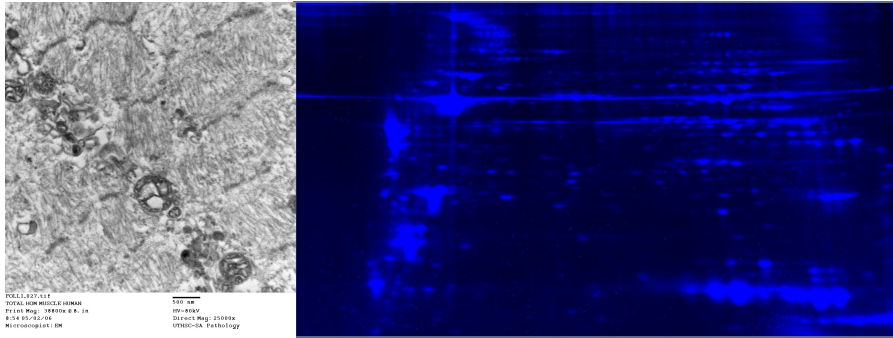
Interfase
Membrana
Plasmática

Botón
Núcleo

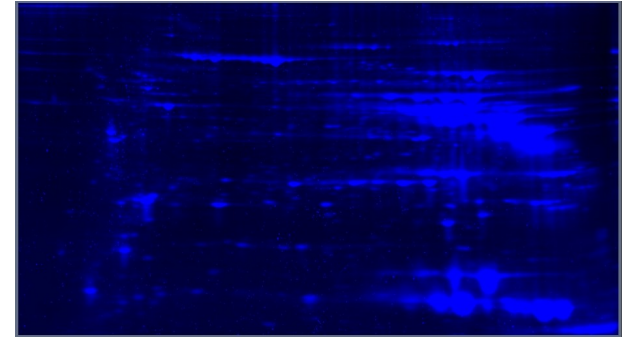


FRACCIONES CELULARES DE MÚSCULO HUMANO

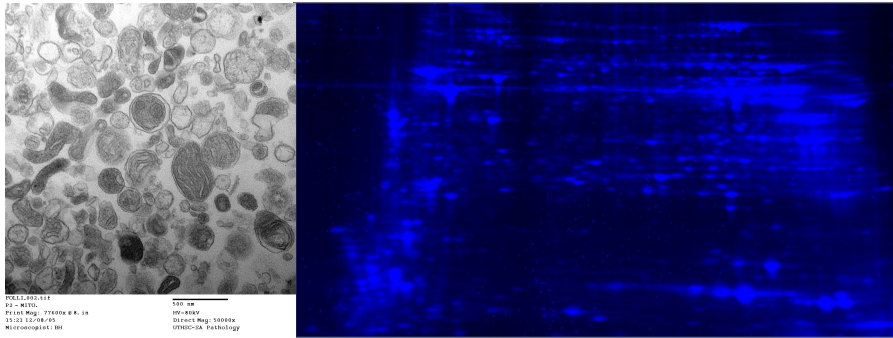
Homogenizado Total



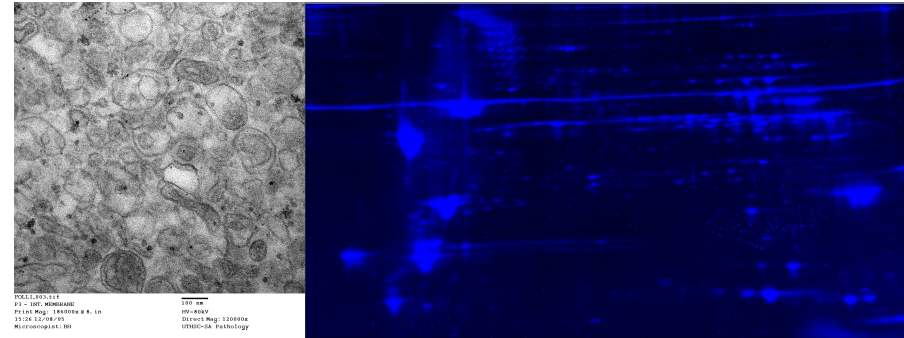
Citoplasma



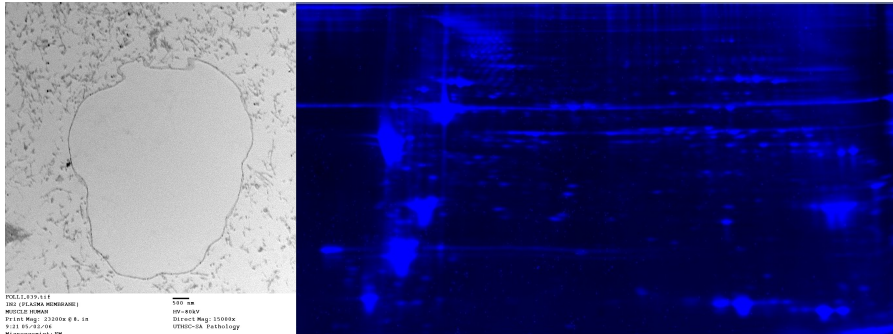
Mitocondria



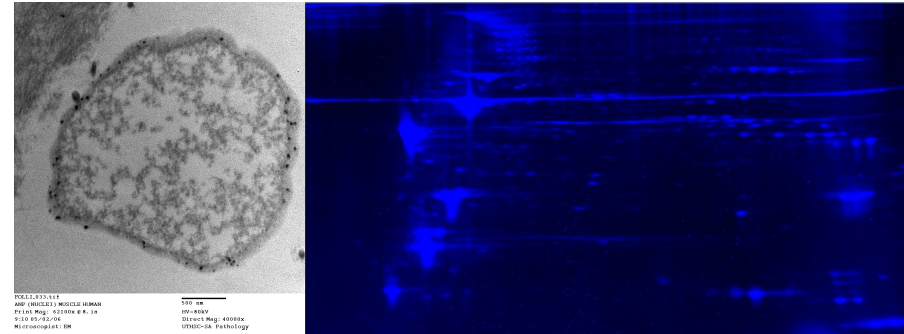
Membranas Intracelulares



Membrana Plasmática

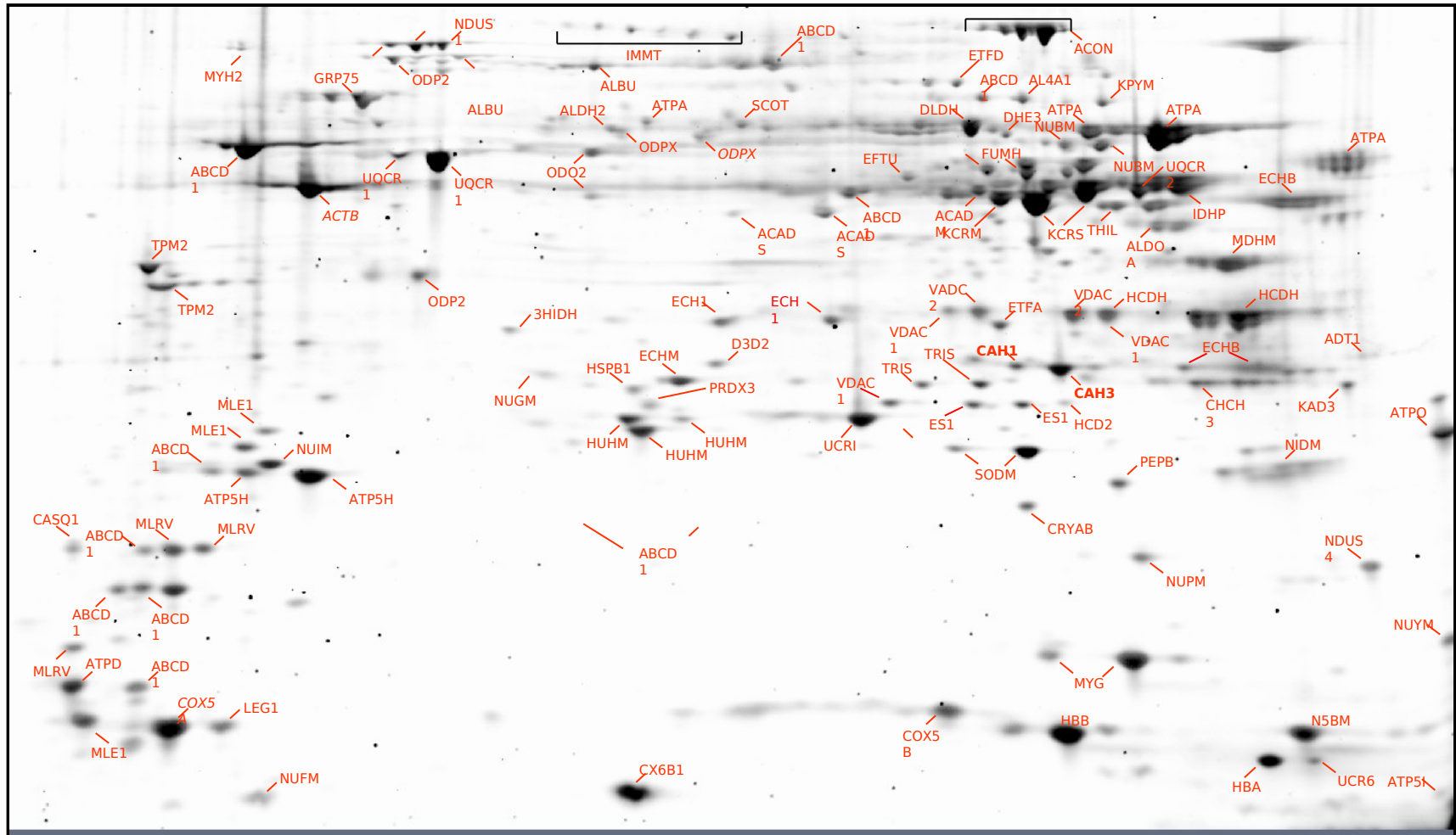


Núcleo



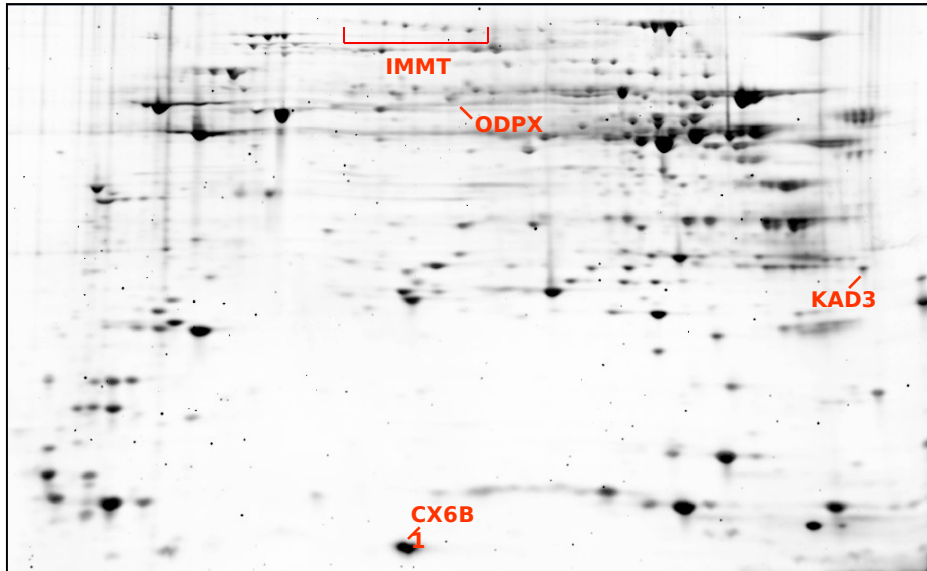
3

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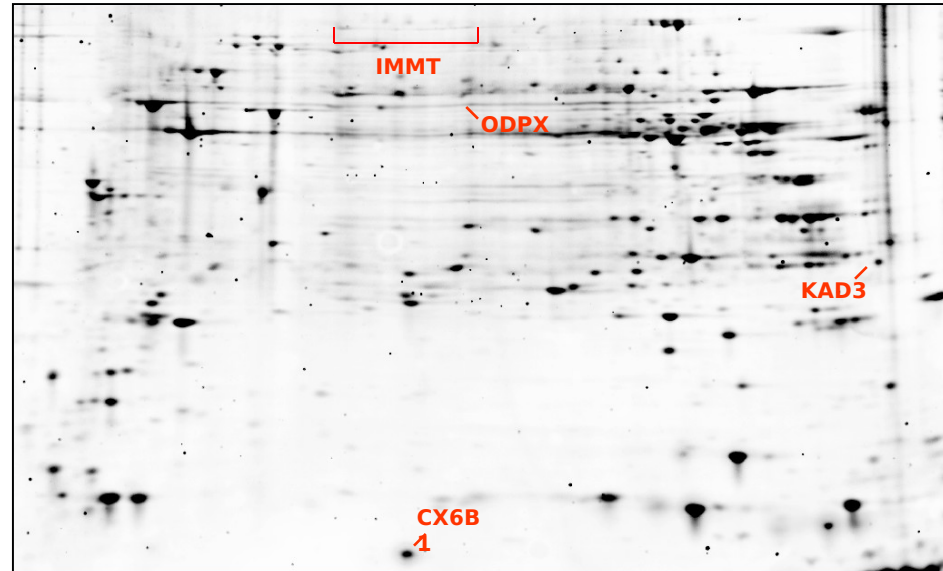


EXPRESIÓN DIFERENCIAL DE PROTEÍNAS MITOCONDRIALES EN DMT2

NGT



DMT2



EXPRESIÓN DIFERENCIAL DE PROTEÍNAS MITOCONDRIALES EN DMT2

	NGT	T2DM	p
Mitofilina	3.5±0.9	2±0.4	<0.01
Piruvato deshidrogenasa proteína X	7±1.8	4±1	<0.05
Citocromo C oxidasa subunidad VIb	1.6±0.4	1±0.2	<0.05
Adenilato cinasa 3	5.9±1.6	8.9±2.5	<0.01

CARACTERÍSTICAS CLÍNICAS

M/F

4/0

**Edad
(años)**

**45[±]
11**

**IMC
(kg/m²)**

**26.7[±]
1.8**

**HbA1c
(%)**

**5.7[±]
0.05**

**M
(mg/kg.min)**

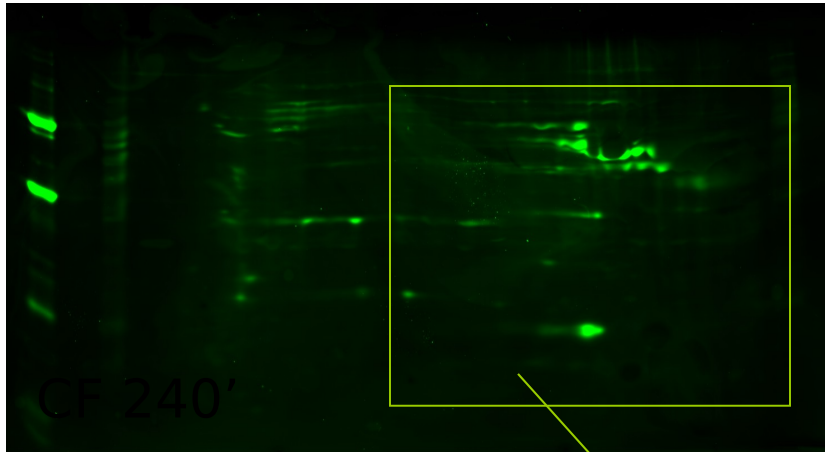
**8.2[±]
1.7**

**Insulina (pg/
ml)**

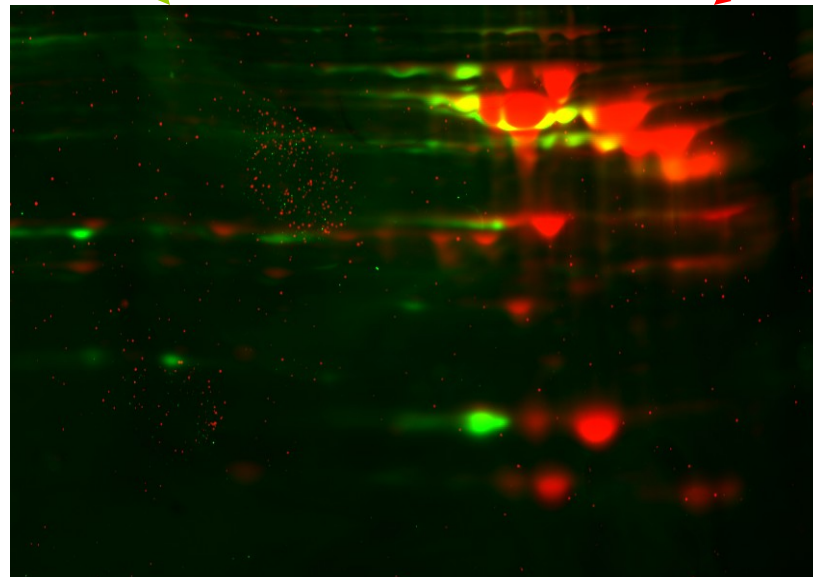
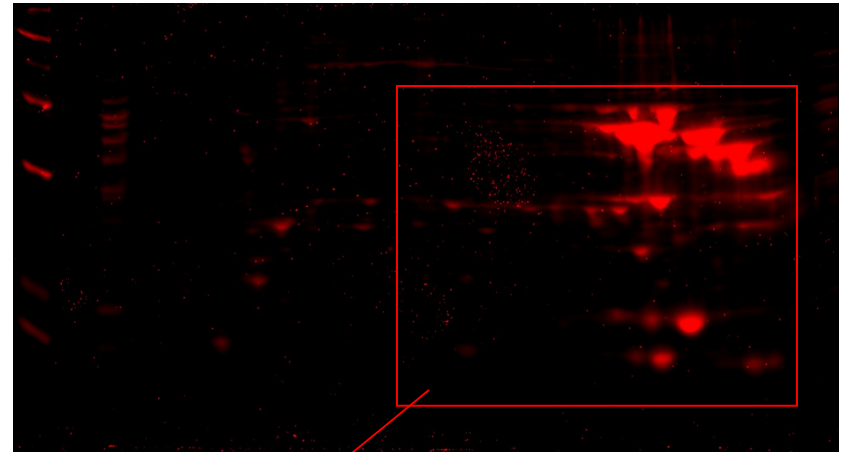
**5.57[±]
0.95**

RESULTADOS

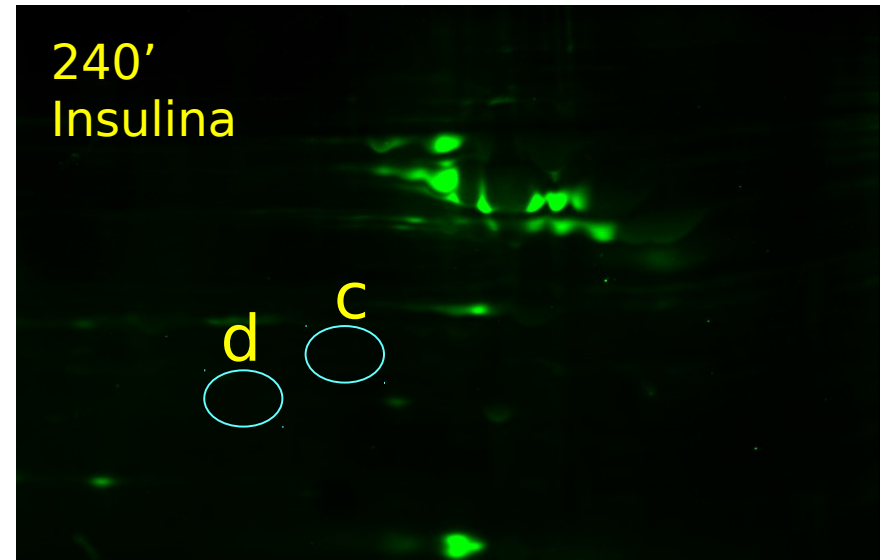
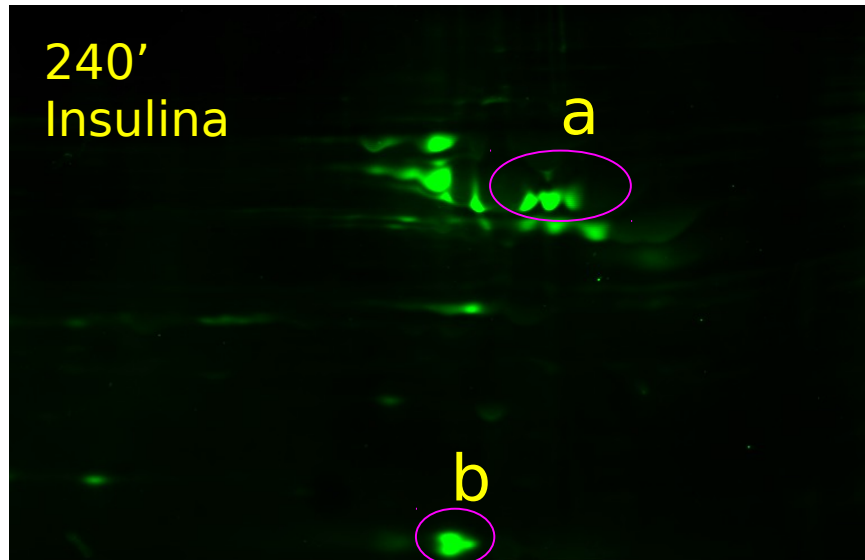
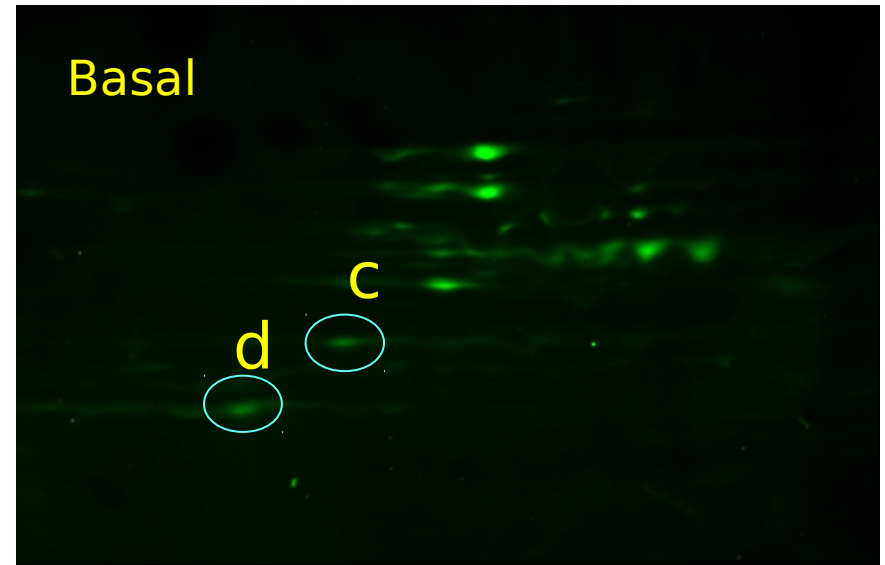
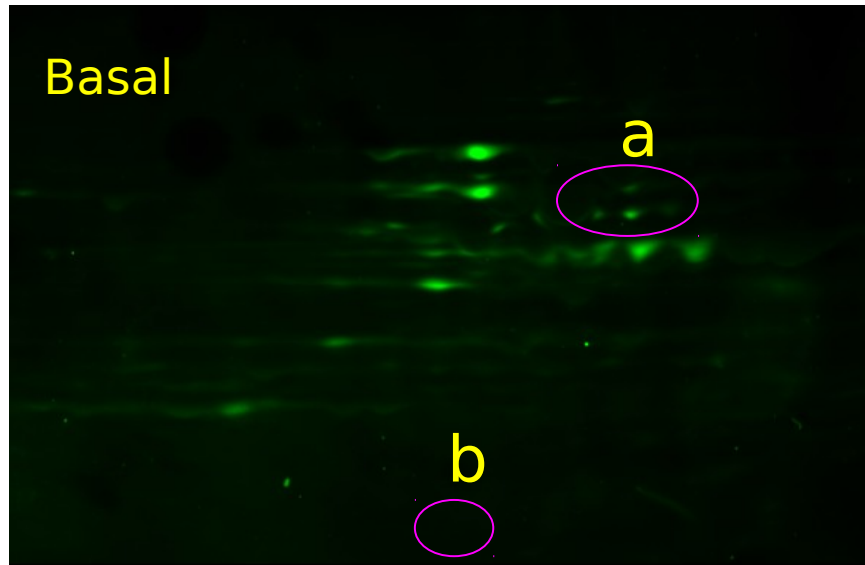
Proteínas fosforiladas
(Pro-Q Diamond)



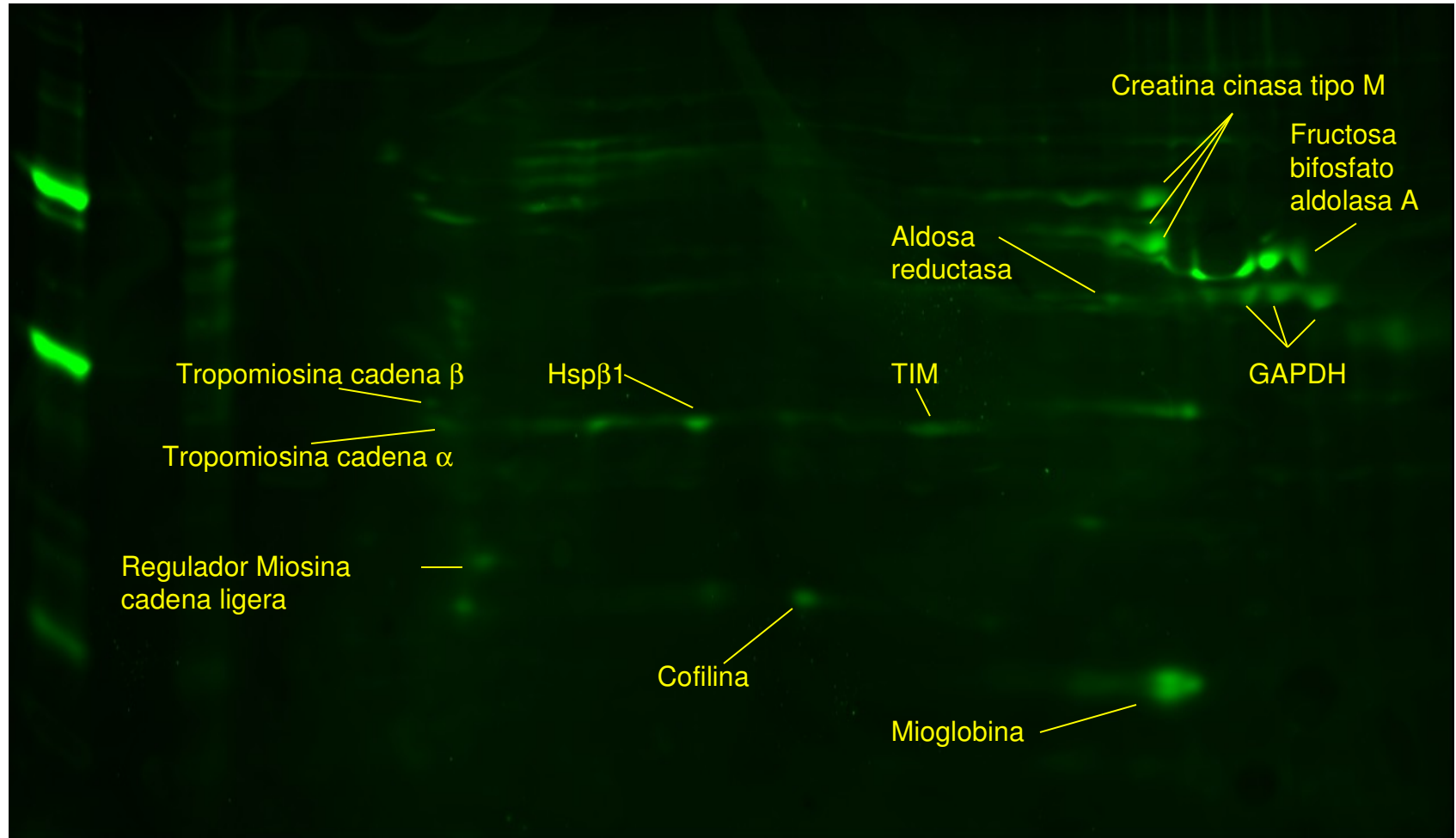
Proteínas totales
(Sypro Ruby)



FOSFORILACIÓN/DEFOSFORILACIÓN ESTIMULADA POR INSULINA



FOSFORILACIÓN ESTIMULADA POR INSULINA



FUTUROS PROYECTOS

- Modificación del estado de fosforilación de proteínas mitocondriales en células β estimuladas con insulina