

CONCLUSIONES

Primera: El RA induce la aparición de TrkB y TrkC catalíticamente activos en células SH-SY5Y. De acuerdo con este patrón de expresión, BDNF, NT-3 y NT-4/5 pero no NGF inducen la supervivencia y crecimiento neurítico en células SH-SY5Y pre-tratadas con RA.

Segunda: BDNF, NT-3 y NT-4/5 pero no NGF activan las vías MEK/MAPK y PI 3-K/Akt en células SH-SY5Y pre-tratadas con RA. La activación de MAPK y Akt se puede prevenir mediante el inhibidor de MEK, PD98059 y el de PI 3-K, LY294002, respectivamente.

Tercera: La vía MEK/MAPK es necesaria para el crecimiento neurítico y la expresión de GAP-43 inducidos por BDNF. La inhibición de la vía no tiene ningún efecto sobre la supervivencia celular.

Cuarta: La vía PI 3-K/Akt es necesaria para la supervivencia celular inducida por BDNF. La retirada de BDNF, o el bloqueo de la vía PI 3-K/Akt, induce una muerte de morfología apoptótica.

Quinta: El tratamiento de células SH-SY5Y con RA a tiempos largos no permite su diferenciación homogénea hacia un fenotipo neuronal. El tratamiento secuencial con RA y BDNF (este último en medio libre de suero), provoca la diferenciación homogénea de estas células hacia un fenotipo neuronal.

Sexta: Las células diferenciadas con RA y BDNF se hallan detenidas en la fase G1 del ciclo celular. Consistentemente, el grado de fosforilación de pRb va disminuyendo a lo largo de los días de tratamiento.

Séptima: La retirada del BDNF en células SH-SY5Y diferenciadas con RA y BDNF, causa un incremento de la síntesis de DNA y la fosforilación de pRb, concomitante a una muerte morfológica y bioquímicamente apoptótica.

Octava: Las células diferenciadas con RA y BDNF expresan diferentes marcadores neuronales y son negativas para GFAP. El patrón de expresión de MAP2 y Tau sugiere que éstas se hallan polarizadas.

Novena: Las motoneuronas espinales de pollo expresan *in vivo* e *in vitro* todos los componentes de los receptores para GFLs (Ret y GFR α -1, -2 y -4). Estos receptores forman un complejo funcional capaz de autofosforilarse en presencia de ligando.

Décima: Los GFLs promueven la supervivencia de las motoneuronas *in vitro*, de manera dependiente de GFR α s. A concentraciones subsaturantes, la combinación de GFLs tiene un efecto aditivo sobre la supervivencia.

Decimoprimera: Los GFLs promueven la activación de las vías MEK/MAPK y PI 3-K/Akt en motoneuronas de pollo. La activación de MAPK y Akt se puede prevenir mediante el inhibidor de MEK, PD98059 y el de PI 3-K, LY294002, respectivamente.

Decimosegunda: La actividad PI 3-K es necesaria para la supervivencia de motoneuronas de pollo mediada por GFLs, mientras que la inhibición de MEK no causa ningún efecto sobre ella. La muerte observada tras el bloqueo de la PI 3-K es de carácter apoptótico y mimetiza la retirada de GFLs.

Decimotercera: La actividad Src es necesaria para el crecimiento neurítico y la supervivencia mediados por GDNF en células Neuro 2a y neuronas granulares del cerebelo, respectivamente.

Decimocuarta: p60Src, pero no Fyn o Yes, coinmunoprecipita con Ret en presencia de ligando en células Neuro 2a o neuronas del ganglio cervical superior estimuladas con GDNF. p60Src se fosforila en su loop de activación tras estimulación con GDNF en células Neuro2a.

Decimoquinta: La actividad Src es necesaria para la activación de las vías MEK/MAPK y PI 3-K/Akt mediada por GDNF en células Neuro 2a y SH-SY5Y.

p60Src promueve la supervivencia de neuronas granulares del cerebelo a través de un mecanismo dependiente de PI 3-K.

Decimosexta: La actividad Src no es necesaria para la supervivencia mediada por NGF en neuronas granulares del cerebelo y neuronas del ganglio cervical superior.

COMUNICACIONES A CONGRESOS

Autores: Encinas M., Iglesias M., Llecha N. y Comella J.X.
Título: Las ERK MAPK y la PI 3-K están involucradas en la supervivencia y la neuritogénesis inducida por BDNF en la línea celular de neuroblastoma humano SH-SY5Y
Tipo de participación: Comunicación oral
Congreso: 15º Seminari Conjunt de les seccions de Biologia Molecular i Biologia del Desenvolupament de la Societat Catalana de Biologia
Lugar de celebración: Sitges (Barcelona) **Fecha:** 1998

Autores: Encinas M., Iglesias M., Llecha N. and Comella J.X.
Título: ERK MAPKs and PI 3-K are involved in BDNF mediated survival and neuritogenesis of the neuroblastoma cell line SH-SY5Y
Tipo de participación: Póster
Congreso: 25th Silver Jubilee FEBS meeting
Lugar de celebración: Copenhage **Fecha:** 1998

Autores: Encinas M.
Título: Implicació de la PI 3-K i les MAPK en la supervivència i diferenciació de neuroblastomes humans induïda per neurotrofines
Tipo de participación: Comunicación oral
Congreso: Mort Neuronal i Neurodegeneració. 1ª Reunió de la xarxa temàtica de neurodegeneració
Lugar de celebración: La Seu d'Urgell (Lleida) **Fecha:** 1998

Autores: Encinas M., Iglesias M., Llecha N. and Comella, JX.
Título: Implicació de les MAPK de tipus ERK i de la PI 3-K en la neuritogènesi i supervivència induïda per BDNF en la línia de neuroblastoma humà SH-SY5Y
Tipo de participación: Comunicación oral
Congreso: II Simposi de Neurobiologia Experimental de la Societat Catalana de Biologia
Lugar de celebración: Barcelona **Fecha:** 1998

Autores: Dolcet X, Soler RM, Encinas M., Egea J, Bayascas JR, Comella JX
Título: Els receptors dels factors neurotròfics de la família del GDNF influeixen la supervivència de motoneurons espinals mitjançant l'activació de la fosfatidil inositol cinasa.
Tipo de participación: Comunicación oral
Congreso: Seccions de Biologia Molecular i Biologia del Desenvolupament de la Societat Catalana de Biologia: Seminario conjunto.
Lugar de celebración: Sitges (Barcelona) **Fecha:** 1999

Autores: Bayascas JR, Comella JX, Soler RM, Espinet C, Dolcet X, Encinas M., Egea J
Título: PI 3-kinase pathway mediate survival effects of the GDNF-related neurotrophic factors
Tipo de participación: Póster
Congreso: Sociedad Española de Biología del Desarrollo: II Congreso Nacional.
Lugar: Barcelona **Fecha:** 1999

Autores: Dolcet X, Soler RM, Encinas M., Egea J, Bayascas JR, Comella. JX
Título: Los receptores de los factores neurotróficos de la familia del GDNF inducen la supervivencia de motoneuronas espinales mediante la activación de la fosfatidilinositol 3 quinasa.
Tipo de participación: Póster
Congreso: Sociedad Española de Neurociencia: VIII Congreso Nacional
Lugar: Murcia **Fecha:** 1999

Autores: Encinas M, Iglesias M, Wang H, Liu Y, Comella JX.

Título: Estudio del proceso de diferenciación neuronal de una línea de neuroblastoma humano.

Tipo de participación: Póster

Congreso: Sociedad Española de Neurociencia: VIII Congreso Nacional

Lugar: Murcia

Fecha: 1999

Autores: Comella JX, Dolcet X, Soler RM, Encinas M, Egea J, Bayascas JR,

Título: Receptors of the GDNF family of neurotrophic factors signal cell survival through PI 3-K pathway in motoneurons

Tipo de participación: Póster

Congreso: Society for Neurosciences, 29th Annual Meeting

Lugar: Miami Beach, Fla (USA)

Fecha: 1999

Autores: Dolcet X, Soler RM, Encinas M, Egea J, Bayascas JR, Comella JX

Título: PI 3-kinase mediates survival effects of the GDNF family members on cultured chick motoneurons.

Tipo de participación: Póster

Congreso: EU Biotech Sectorial Meeting

Lugar: Santa Tecla (Italy)

Fecha: 2000

Autores: Gallego, C., Encinas, M., Wang, H., Liu, Y., Comella, J.X.,

Aldea, M.

Título: Apoptosis induced by neurotrophin deprivation in a human neuronal model is associated with unscheduled S-phase entry.

Tipo de participación: Póster

Congreso: Keystone Symposium on Cancer, Cell Cycle and Therapeutics

Lugar: Steamboat Springs, CO. USA

Fecha: 2000

Autores: Encinas, M., Iglesias, M., Liu, Y., Wang, H., Muhaisen, A., Ceña, V., Gallego, C., Comella, J.X.,

Título: Protocol de diferenciació de cèl·lules de neuroblastoma SH-SY5Y per donar lloc a cèl·lules neuronals diferenciades i depenents de factor tròfic

Tipo de participación: Comunicación oral

Congreso: III Simposi de Neurobiologia Experimental

Lugar: Barcelona

Fecha:2000

PUBLICACIONES

Encinas M.; Iglesias M.; Llecha N.; Comella J.X. (1999) Extracellular-regulated kinases and phosphatidylinositol 3-kinase are involved in brain-derived neurotrophic factor-mediated survival and neuritogenesis of the neuroblastoma cell line SH-SY5Y. *J. Neurochem.* 73:1409-1421.

Soler R.M.*; Dolcet X.*; Encinas M.; Egea J.; Bayascas J.R.; Comella J.X. (1999) Receptors of the glial cell line-derived neurotrophic factor family of neurotrophic factors signal cell survival through the phosphatidylinositol 3-kinase pathway in spinal cord motoneurons. *J. Neurosci.* 19: 9160-9169. (*Ambos autores deben ser considerados primeros autores).

Encinas M.; Iglesias M.; Liu Y.; Wang H.; Muhaisen A.; Ceña V.; Gallego C.; Comella J.X. (2000) Sequential treatment of SH-SY5Y cells with retinoic acid and brain-derived neurotrophic factor gives rise to fully differentiated, neurotrophic factor-dependent, human neuron-like cells. *J Neurochem.* 75:991-1003.

Encinas M.*; Tansey M.G.*; Tsui-Pierchala B.A.; Comella J.X.; Milbrandt J.; Johnson E.M., Jr. c-Src is required for GFL-mediated neuronal survival through a PI-3-K-dependent pathway. *J Neurosci.* (en prensa). (*Ambos autores deben ser considerados primeros autores).

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