Scopus

Documents

Chleilat, E.[a] , Skatulla, L.[a] , Rahhal, B.[a b] , Hussein, M.T.[a c] , Feuerstein, M.[a] , Krieglstein, K.[a] , Roussa, E.[a]

TGF-β Signaling Regulates Development of Midbrain Dopaminergic and Hindbrain Serotonergic Neuron Subgroups
(2018) *Neuroscience*, 381, pp. 124-137.

DOI: 10.1016/j.neuroscience.2018.04.019

[a] Institute of Anatomy and Cell Biology, Department of Molecular Embryology, Faculty of Medicine, University of Freiburg, Freiburg, Germany
[b] School of Medicine and Health Sciences, An-Najah National University, Nablus, Palestine
[c] Department of Anatomy and Histology, Faculty of Vet. Medicine, Assiut University, Assiut, Egypt

Abstract
Molecular and functional diversity within midbrain dopaminergic (mDA) and hindbrain serotonergic (5-HT) neurons has emerged as a relevant feature that could underlie selective vulnerability of neurons in clinical disorders. We have investigated the role of transforming growth factor beta (TGF-β) during development of mDA and 5-HT subgroups. We have generated TβRIIflox/flox::En1cre/+ mice where type II TGF-β receptor is conditionally deleted from engrailed 1-expressing cells and have investigated the hindbrain serotonergic system of these mice together with Tgf-β2−/− mice. The results show a significant decrease in the number of 5-HT neurons in TGF-β2-deficient mice at embryonic day (E) 12 and a selective significant decrease in the hindbrain paramedian raphe 5-HT neurons at E18, compared to wild type. Moreover, conditional deletion of TGF-β signaling from midbrain and rhombomere 1 leads to inactive TGF-β signaling in cre-expressing cells, impaired development of mouse mDA neuron subgroups and of dorsal raphe 5-HT neuron subgroups in a temporal manner. These results highlight a selective growth factor dependency of individual rostral hindbrain serotonergic subpopulations, emphasize the impact of TGF-β signaling during development of mDA and 5-HT subgroups, and suggest TGF-βs as potent candidates to establish diversity within the hindbrain serotonergic system. Thus, the data contribute to a better understanding of development and degeneration of mDA neurons and 5-HT-associated clinical disorders. © 2018 IBRO

Author Keywords
5-HT; cell fate; growth factor; neurogenesis; raphe nuclei

Funding details
Deutsche Forschungsgemeinschaft
Deutsche Forschungsgemeinschaft

References

- Alonso, A., Merchan, P., Sandoval, J.E., Sanchez-Arrones, L., Garcia-Cazorla, A., Artuch, R., Ferran, J.L., Puelles, L.
Development of the serotonergic cells in murine raphe nuclei and their relations to rhombomeric domains
(2013) *Brain Struct Funct*, 218, pp. 1229-1277.

- Anderegg, A., Poulin, J.F., Awatramani, R.
Molecular heterogeneity of midbrain dopaminergic neurons – moving toward single cell resolution
(2015) *FEBS Lett*, 589, pp. 3714-3726.

- Blaess, S., Bodea, G.O., Kabanova, A., Chanet, S., Mugniery, E., Derouiche, A., Stephen, D., Joyner, A.L.
Temporal-spatial changes in Sonic hedgehog expression and signaling reveal different potentials of ventral mesencephalic progenitors to populate distinct ventral midbrain nuclei
(2011) *Neural Dev*, 6, p. 29.

- Brust, R.D., Corcoran, A.E., Richerson, G.B., Nattie, E., Dymecki, S.M.
Functional and developmental identification of a molecular subtype of brain serotonergic neuron specialized to regulate breathing dynamics
(2014) *Cell Rep*, 9, pp. 2152-2165.

- Cai, J., Schleidt, S., Pelta-Heller, J., Hutchings, D., Cannarsa, G., Iacovitti, L.
BMP and TGF-β pathway mediators are critical upstream regulators of Wnt signaling during midbrain dopamine differentiation in human pluripotent stem cells
(2013) *Dev Biol*, 376, pp. 62-73.

- Chytil, A., Magnuson, M.A., Wright, C.V., Moses, H.L.
Conditional inactivation of the TGF-beta type II receptor using Cre:Lox
(2002) *Genesis*, 32, pp. 73-75.

- Dias, J.M., Alekseenko, Z., Applequist, J.M., Ericson, J.
TGFβ signalling regulates temporal neurogenesis and potency of neural stem cells in the CNS
(2014) *Neuron*, 84, pp. 927-939.

- Ernsberger, U., Patzke, H., Tissier-Seta, J.P., Reh, T., Goridis, C., Rohrer, H.
The expression of tyrosine hydroxylase and the transcription factors cPhox-2 and Cash-1: evidence for distinct inductive steps in the differentiation of chick sympathetic precursor cells
(1995) *Mech Dev*, 52, pp. 125-136.

- Farkas, L.M., Dünker, N., Roussa, E., Unsicker, K., Krieglstein, K.
Transforming growth factor-beta(s) are essential for the development of midbrain dopaminergic neurons in vitro and in vivo
(2003) *J Neurosci*, 23, pp. 5178-5186.

- Galter, D., Unsicker, K.
Regulation of the transmitter phenotype of rostral and caudal groups of cultured serotonergic raphe neurons
(1999) *Neuroscience*, 88, pp. 549-559.

- Galter, D., Unsicker, K.
Brain-derived neurotrophic factor and trk-B are essential for cAMP-mediated induction of the serotonergic neuronal phenotype
(2000) *J Neurosci Res*, 61, pp. 295-301.

- Galter, D., Böttner, M., Unsicker, K.
Developmental regulation of the serotonergic transmitter phenotype in rostral and caudal raphe nucleus by transforming growth factor betas
(1999) *J Neurosci Res*, 56, pp. 531-538.

- Hale, M.W., Shekhar, A., Lowry, C.A.
Stress-related serotonergic systems: implications for symptomatology of anxiety and affective disorders
(2012) *Cell Mol Neurobiol*, 32, pp. 695-708.

- Haugas, M., Tikker, L., Achim, K., Salminen, M., Partanen, J.
Gata2 and Gata3 regulate the differentiation of serotonergic and glutamatergic neuron subtypes of the dorsal raphe
(2016) *Development*, 143, pp. 4495-4508.

- Hendricks, T., Francis, N., Fyodorov, D., Deneris, E.S.
The ETS domain factor of Pet-1 is an early and precise marker of central serotonin neurons and interacts with a conserved element in serotonergic genes
(1999) *J Neurosci*, 19, pp. 10348-10356.

- Jensen, P., Farago, A.F., Awartamani, R.B., Scott, M.M., Deneris, E.S., Dymecki, S.M.
Redefining the serotonergic system by genetic lineage
(2008) *Nat Neurosci*, 11, pp. 417-419.

- Kimmel, R.A., Turnbull, D.H., Blanquet, V., Wurst, W., Loomis, C.A., Joyner, A.L.
Two lineage boundaries coordinate vertebrate apical ectodermal ridge formation
(2000) *Genes Dev*, 14, pp. 1377-1389.

- Kouwenhoven, W.M., Veenvliet, J.V., van Hooft, J.A., van der Heide, L.P., Smidt, M.P.
Engrailed 1 shapes the dopaminergic and serotonergic landscape through proper isthmic organizer maintenance and function
(2016) *Biol Open*, 5, pp. 279-288.

- Lopes, D.A., Lemes, J.A., Melo-Thomas, L., Schor, H., de Andrade, J.S., Machado, C.M., Horta-Junior, J.A.C., Viana, M.B.
Unpredictable chronic mild stress exerts anxiogenic-like effects and activates neurons in the dorsal and caudal region in the lateral wings of the dorsal raphe nucleus
(2016) *Behav Brain Res*, 297, pp. 180-186.

- McDevitt, R.A., Hiroi, R., Mackenzie, S.M., Robin, N.C., Cohn, A., Kim, J.J., Neumaier, J.F.
Serotonin 1B autoreceptors originating in the caudal dorsal raphe nucleus reduce expression of fear and depression-like behaviour
(2011) *Biol Psychiatry*, 69, pp. 780-787.

- Morales, M., Margolis, E.B.
Ventral tegmental area: cellular heterogeneity, connectivity and behaviour
(2017) *Nat Neurosci*, 18, pp. 73-85.

- Niederkofler, V., Asher, T.E., Dymecki, S.M.
Functional interplay between dopaminergic and serotonergic neuronal systems during development and adulthood
(2015) *ACS Chem Neurosci*, 6, pp. 1055-1070.

- Niederkofler, V., Asher, T.E., Okaty, B.W., Rood, B.D., Narayan, A., Hwa, L.S., Beck, S.G., Dymecki, S.M.
Identification of serotonergic neuronal modules that affect aggressive behavior
(2016) *Cell Rep*, 17, pp. 1934-1949.

- Okaty, B.W., Freren, M.E., Rood, B.D., Brust, R.D., Hennessy, M.L., deBairos, D., Kim, J.C., Dymecki, S.M.
Multi-scale molecular deconstruction of the serotonin neuron system
(2015) *Neuron*, 88, pp. 774-791.

- Poulin, J.F., Drouin-Ouellet, J., Kim, K.Y., Cicchetti, F., Awatramani, R.B.
Defining midbrain dopaminergic neuron diversity by single-cell gene expression profiling
(2014) *Cell Rep*, 9, pp. 930-943.

- Ramalingam, R., Larmonier, C.B., Thurston, R.D., Midura-Kiela, M.T., Zheng, S.G., Ghishan, F.K., Kiela, P.R.

Dendritic cell-specific disruption of TGF-β receptor II leads to altered regulatory T cell phenotype and spontaneous multiorgan autoimmunity
(2012) *J Immunol*, 189, pp. 3878-3893.

- Rodriguez-Pallares, J., Guerra, M.J., Labandeira-Garcia, J.L.
Elimination of serotonergic cells induces a marked increase in generation of dopaminergic neurons from mesencephalic precursors
(2003) *Eur J Neurosci*, 18, pp. 2166-2174.

- Roussa, E., Farkas, L.M., Krieglstein, K.
TGF-β promotes survival on midbrain dopaminergic neurons in cooperation with SHH and FGF8
(2004) *Neurobiol Dis*, 16, pp. 300-310.

- Roussa, E., Wiehle, M., Dünker, N., Becker-Catins, S., Oehlke, O., Krieglstein, K.
Transforming growth factor beta is required for differentiation of mouse mesencephalic progenitors into dopaminergic neurons in vitro and in vivo: ectopic induction in dorsal mesencephalon
(2006) *Stem Cells*, 24, pp. 2120-2129.

- Roussa, E., Oehlke, O., Rahhal, B., Heermann, S., Heidrich, S., Wiehle, M., Krieglstein, K.
Transforming growth factor beta cooperates with persephin for dopaminergic phenotype induction
(2008) *Stem Cells*, 7, pp. 1683-1694.

- Rudge, J.S., Eaton, M.J., Mather, P., Lindsay, R.M., Whittemore, S.R.
CNTF induces raphe neuronal precursors to switch from a serotonergic to a cholinergic phenotype in vitro
(1996) *Mol Cell Neurosci*, 7, pp. 204-221.

- Rumajogee, P., Madeira, A., Verge, D., Hamon, M., Miquel, M.C.
Up-regulation of the neuronal serotoninergic phenotype in vitro: BDNF and cAMP share Trk-B-dependent mechanisms
(2002) *J Neurochem*, 83, pp. 1525-1528.

- Sanford, L.P., Ormsby, I., Gittenberger-de Groot, A.C., Sariola, H., Friedman, R., Boivin, G.P., Cardell, E.L., Doetschman, T.
TGFbeta2 knockout mice have multiple developmental defects that are non-overlapping with other TGFbeta knockout phenotypes
(1997) *Development*, 124, pp. 2659-2670.

- Schrödl-Häußel, M., Theparambil, S.M., Deitmer, J.W., Roussa, E.
Regulation of functional expression of the electrogenic sodium bicarbonate cotransporter 1, NBCe1 (SLC4A4), in mouse astrocytes
(2015) *Glia*, 63, pp. 1226-1239.

- Sueyoshi, T., Yamamoto, K., Akiyama, H.
Conditional deletion of Tgfbr2 in hypertrophic chondrocytes delays terminal chondrocyte differentiation
(2012) *Matrix Biol*, 31, pp. 352-359.

- Teissier, A., Chemiakine, A., Inbar, B., Bagchi, S., Ray, R.S., Palmiter, R.D., Dymecki, S.M., Ansorge, M.S.
Activity of raphe serotonergic neurons controls emotional behaviors
(2015) *Cell Rep*, 13, pp. 1965-1976.

- Veenvliet, J.V., Smidt, M.P.
Molecular mechanisms of dopaminergic subset specification: fundamental aspects and clinical perspectives
(2014) *Cell Mol. Life Sci*, 71, pp. 4703-4727.

- Veenvliet, J.V., Alves dos Santos, M.T., Kouwenhoven, W.M., von Oerthel, L., Lim, J.L., van der Linden, A.J., Koerkamp, M.J., Smidt, M.P.
Specification of dopaminergic subsets involves interplay of En1 and Pitx3
(2013) *Development*, 140, pp. 3373-3384.

- Wu, H.H., Levitt, P.
Prenatal expression of MET receptor tyrosine kinase in the fetal mouse dorsal raphe nuclei and the visceral motor/sensory brainstem
(2013) *Dev Neurosci*, 35, pp. 1-16.

- Wurst, W., Prakash, N.
Wnt1-regulated genetic networks in midbrain dopaminergic neuron development
(2014) *J Mol Cell Biol*, 6, pp. 34-41.

- Wylie, C.J., Hendricks, T.J., Zhang, B., Wang, L., Lu, P., Leahy, P., Fox, S., Deneris, E.S.
Distinct transcriptomes define rostral and caudal serotonin neurons
(2010) *J Neurosci*, 30, pp. 670-684.

- Ye, W., Shimamura, K., Rubenstein, J.L., Hynes, M.A., Rosenthal, A.
FGF8 and Shh signals create inductive centers for dopaminergic and serotonergic neurons in the anterior neural plate
(1998) *Cell*, 93, pp. 755-766.

Publisher: Elsevier Ltd

ISSN: 03064522
CODEN: NRSCD