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## Commentary

# The orphan nuclear receptor TLX: an emerging master regulator of cross-talk between microglia and neural precursor cells

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Neuroinflammation and neurogenesis have both been the subject of intensive investigation over the past 20 years. The sheer complexity of their regulation and their ubiquity in various states of health and disease have sometimes obscured the progress that has been made in unraveling their mechanisms and regulation.

A recent study by Kozareva et al. (*Neuronal Signaling* (2019) 3), provides evidence that the orphan nuclear receptor TLX is central to communication between microglia and neural precursor cells and could help us understand how inflammation, mediated by microglia, influences the development of new neurons in the adult hippocampus.

Here, we put recent studies on TLX into the context of what is known about adult neurogenesis and microglial activation in the brain, along with the many hints that these processes must be inter-related.

## Commentary

The orphan nuclear receptor TLX, first identified in retinal photoreceptors 20 years ago [1,2], has been studied mostly for its role in regulating the ongoing creation of new neurons in the adult hippocampus [3–5]. This adult neurogenesis occurs in at least several mammalian species, including humans [6–11] and has been implicated in learning, memory, stress regulation and maintaining emotional resilience [6,7,12–14]. There has been considerable interest in harnessing neurogenesis to treat disorders ranging from depression to Alzheimer's [6,8,10,12,15] but much remains to be learned about how the process is regulated and why it sometimes fails. In a recent paper in *Neuronal Signaling*, Kozareva et al. [16] made a significant contribution to our understanding of neurogenesis by demonstrating a new role for TLX in mediating communication between the neural stem cells and neighboring microglia.

The birth, migration, differentiation and functional integration of the newborn neurons into the adult hippocampal circuitry is influenced by various factors: exercise and intellectual/social stimulation promote neurogenesis, whereas stress, loneliness, and inflammation suppress it [6,7,13,17–19]. Also diet, specific nutrients and sleep (deprivation) modify neurogenesis, often in an age-specific manner [20–24]. Certain microRNAs and transcription factors can influence specific stages of the neurogenic process and modulate the proliferation of neural stem cells or their subsequent survival [25–30]. While one microRNA can regulate many different target genes, each microRNA can in turn be regulated by various other genes or regulatory factors.

When regulation is this complex and interdependent, there are often 'master' or 'upstream' factors that exert a higher level of control. This appears to be the function of the orphan nuclear receptor TLX (Nr2e1), whose role in hippocampal neurogenesis has been increasingly appreciated over the past decade

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[3–5,31,32]. TLX is expressed in both neurogenic niches (the subventricular zone of the ventricular walls and the subgranular zone of the dentate gyrus), specifically in the neuronal precursor cells (NPCs), which it maintains in a proliferative state by preventing them from undergoing ectopic differentiation. Consistent with this functional role, TLX knockout mice display impaired neurogenic responses, diminished hippocampal volume, impaired long-term potentiation in the dentate gyrus and deficits in hippocampal memory and related behaviors [3–5,32,35].

Interestingly, TLX has also been linked to neuro-inflammatory changes and to microglia, the brain's immune cells [36–39]. Microglia contribute to synaptic pruning and phagocytic clearance of subsets of the adult-born cells [40,41]. They show specific morphological changes with age [42–44] and the neuro-inflammatory mediators they produce during this process and in related diseases impair hippocampal function and suppress neurogenesis [18,19,41,45,46]. Specifically, the pro-inflammatory cytokine interleukin-1 $\beta$  (IL-1 $\beta$ ), which is induced in microglia after peripheral inflammation [47,48], suppresses both hippocampal NPC proliferation and TLX expression [49–53]. IL-1 $\beta$  also induces a range of transcriptional changes that are regulated by TLX [51], but in the absence of TLX, microglia become activated and induce hippocampal inflammation [50,53,54].

To delineate pathways of communication between TLX and microglia, Kozareva et al. [16] assessed microRNA expression patterns of known up- or downstream signaling molecules of TLX in the hippocampus of mice lacking CX3CR1, a microglially expressed receptor for the chemokine CX3CL1 (fractalkine) that is released by adult neurons [55,56]. The authors show that in these knockout mice, expression of TLX and its downstream, but not upstream, targets, were selectively reduced. Instead, there is an up-regulation of the TLX repressor MIR-378 and increases in levels of the target genes bone morphogenic protein 4 (BMP4) and PTEN. However, no change in other miRNAs, such as miR-9, miR-137, miR-let7d or miR-let7b, which suppress TLX both *in vitro* and *in vivo*, were observed. Therefore, the reduction in TLX in CX3CR1-KO mice must be independent of both the TLX-miR-let7b regulatory loop and the TLX-miR-9 feedback pathway. This is consistent with the concept that an absence of CX3CR1 could down-regulate TLX via a self-repression mechanism [35,57–60] and positions TLX as a potential target or co-regulator of the CX3CR1/CX3CL1 pathway. The concomitant reduction in hippocampal neurogenesis observed in CX3CR1 knockout mice may thus result from activation of TLX-suppressing signaling pathways that inhibit activation of quiescent NSCs and maintain them in a non-proliferative state through PTEN signaling. By identifying these factors, Kozareva et al. [16] extend the work of Ó'Léime et al. [50] to provide the pathways linking microglia activation and IL-1 $\beta$  increases to reductions in TLX and neurogenesis [42,51,52,60].

TLX overexpression increases neuronal precursor cell proliferation, hippocampal neurogenesis and enhances learning and memory [61]. Similar gain of function approaches could shed light on gliogenesis, and whether this also involves CX3CL1/CX3CR1-dependent mechanisms. Whereas Kozareva et al. [16] has studied whole hippocampal homogenates, a more specific analysis of the NSCs isolated from the dentate gyrus would be very informative. Similarly, future studies of the other neurogenic regions of the brain, such as the subventricular zone, will determine whether the microglia behave differently in this region. Given that TLX is involved in the transcriptional repression of BMP4, which is involved in astrogenesis, it would be of considerable interest to examine whether the reduction in hippocampal neurogenesis in CX3CR1 knockout mice is coupled to changes in hippocampal astrogenesis. Astrocytes can produce IL-1 $\beta$  in the central nervous system and thus may act as the 'middle man' in the cascade that suppresses neurogenesis as a result of CX3CR1 and/or TLX deficiency.

It will also be interesting to characterize the role of TLX in neurogenesis–microglia communication under conditions that are known to modulate neurogenesis and/or inflammation, such as chronic stress, aging, inflammation or disease [6,7,10,11,18,19,40]. The same applies for a possible role for TLX in the rapid clearance of apoptotic newborn cells, which is mediated by microglia [41], and it will be interesting to assess this under conditions of immune suppression, TLX targeting or knockdown, blocked or depleted microglia activity, or other environmental or pharmacological manipulations [17,44,62,63].

Studies further investigating the relationship between TLX and CX3CL1/CX3CR1 signaling will provide valuable information to understand the implications and functional roles of this master regulator. Mediators of neuro-inflammation are involved in brain diseases ranging from depression to Alzheimer's, and a better understanding of the roles of TLX will provide important insights into the basic mechanisms of hippocampal plasticity and neurogenic–microglial cross-talk. Much remains to be learned in order to develop preventive or anti-inflammatory therapies for the hippocampal changes in these disorders, but studies like this are making clear progress toward this goal.

## Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

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## Author Contribution

P.J.L. wrote the first draft of the manuscript to which all the co-authors contributed with their input.

## Abbreviations

BMP4, bone morphogenic protein 4; IL-1 $\beta$ , interleukin 1 $\beta$ ; NPC, neuronal precursor cell.

## References

- 1 Kobayashi, M., Takezawa, S., Hara, K., Yu, R.T., Umesono, Y., Agata, K. et al. (1999) Identification of a photoreceptor cell-specific nuclear receptor. *Proc. Natl. Acad. Sci. U.S.A.* **96**, 4814–4819, <https://doi.org/10.1073/pnas.96.9.4814>
- 2 Benod, C., Villagomez, R. and Webb, P. (2016) TLX: an elusive receptor. *J. Steroid Biochem. Mol. Biol.* **157**, 41–47, <https://doi.org/10.1016/j.jsbmb.2015.11.001>
- 3 Sobhan, P.K. and Funa, K. (2017) TLX—its emerging role for neurogenesis in health and disease. *Mol. Neurobiol.* **54**, 272–280, <https://doi.org/10.1007/s12035-015-9608-1>
- 4 Zhang, C.L., Zou, Y., He, W., Gage, F.H. and Evans, R.M. (2008) A role for adult TLX-positive neural stem cells in learning and behaviour. *Nature* **451**, 1004–1007, <https://doi.org/10.1038/nature06562>
- 5 Murai, K., Qu, Q., Sun, G., Ye, P., Li, W., Asuelime, G. et al. (2014) Nuclear receptor TLX stimulates hippocampal neurogenesis and enhances learning and memory in a transgenic mouse model. *Proc. Natl. Acad. Sci. U.S.A.* **111**, 9115–9120, <https://doi.org/10.1073/pnas.1406779111>
- 6 Toda, T., Parylak, S.L., Linker, S.B. and Gage, F.H. (2019) The role of adult hippocampal neurogenesis in brain health and disease. *Mol. Psychiatry* **24**, 67–87, <https://doi.org/10.1038/s41380-018-0036-2>
- 7 Lucassen, P.J., Oomen, C.A., Naninck, E.F.G., Fitzsimons, C.P., van Dam, A.M., Czeh, B. et al. (2015) Regulation of adult neurogenesis and plasticity by (early) stress, glucocorticoids and inflammation. *Cold Spring Harb. Perspect. Biol.* **7**, a021303, <https://doi.org/10.1101/cshperspect.a021303>
- 8 Kempermann, G., Gage, F.H., Aigner, L., Song, H., Curtis, M.A., Thuret, S. et al. (2018) Human adult neurogenesis: evidence and remaining questions. *Cell Stem Cell* **23**, 25–30, <https://doi.org/10.1016/j.stem.2018.04.004>
- 9 Lucassen, P.J., Toni, N., Kempermann, G., Frisen, J., Gage, F.H. and Swaab, D.F. (2019) Limits to human neurogenesis - really? *Mol. Psych.*, <https://doi.org/10.1038/s41380-018-0337-5>
- 10 Moreno-Jiménez, E.P., Flor-García, M., Terreros-Roncal, J., Rábano, A., Cafini, F., Pallas-Bazarrá, N. et al. (2019) Adult hippocampal neurogenesis is abundant in neurologically healthy subjects and drops sharply in patients with Alzheimer's disease. *Nat. Med.*, <https://doi.org/10.1038/s41591-019-0375-9>
- 11 Boldrini, M., Fulmore, C.A., Tartt, A.N., Simeon, L.R., Pavlova, I., Poposka, V. et al. (2018) Human hippocampal neurogenesis persists throughout aging. *Cell Stem Cell* **22**, 589–599, <https://doi.org/10.1016/j.stem.2018.03.015>
- 12 Boldrini, M., Galfalvy, H., Dwork, A.J., Rosoklija, G.B., Trencsevska-Ivanovska, I., Pavlovski, G. et al. (2019) Resilience is associated with larger dentate gyrus, while suicide decedents with major depressive disorder have fewer granule neurons. *Biol. Psych.*, <https://doi.org/10.1016/j.biopsych.2018.12.022>
- 13 Voss, M.W., Soto, C., Yoo, S., Sodoma, M., Vivar, C. and van Praag, H. (2019) Exercise and hippocampal memory systems. *Trends Cogn. Sci.* **23**, 318–333, <https://doi.org/10.1016/j.tics.2019.01.006>
- 14 Hill, A.S., Sahay, A. and Hen, R. (2015) Increasing adult hippocampal neurogenesis is sufficient to reduce anxiety and depression-like behaviors. *Neuropsychopharmacology* **40**, 2368–2378, <https://doi.org/10.1038/npp.2015.85>
- 15 Santarelli, L., Saxe, M., Gross, C. et al. (2003) Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science* **301**, 805–809, <https://doi.org/10.1126/science.1083328>
- 16 Kozareva, D.A., Moloney, G.M., Hoban, A.E., Rossini, V., Nally, K., Cryan, J.F. et al. (2019) A role for the orphan nuclear receptor TLX in the interaction between neural precursor cells and microglia. *Neuronal Signaling* **3**, <https://doi.org/10.1042/NS20180177>
- 17 Borsini, A., Alboni, S., Horowitz, M.A., Tojo, L.M., Cannazza, G., Su, K.P. et al. (2017) Rescue of IL-1 $\beta$ -induced reduction of human neurogenesis by omega-3 fatty acids and antidepressants. *Brain Behav. Immun.* **65**, 230–238, <https://doi.org/10.1016/j.bbi.2017.05.006>
- 18 Valero, J., Bernardino, L., Cardoso, F., Silva, A.P., Fontes-Ribeiro, C., Ambrósio, A.F. et al. (2017) Impact of neuroinflammation on hippocampal neurogenesis: relevance to aging and Alzheimer's disease. *J. Alzheimers Dis.* **60**, S160–S168, <https://doi.org/10.3233/JAD-170239>
- 19 Monje, M.L., Toda, H. and Palmer, T.D. (2003) Inflammatory blockade restores adult hippocampal neurogenesis. *Science* **302**, 1760–1765, <https://doi.org/10.1126/science.1088417>
- 20 Ogrodnik, M., Zhu, Y., Langhi, L.G.P., Tchkonja, T., Krüger, P., Fielder, E. et al. (2019) Obesity-induced cellular senescence drives anxiety and impairs neurogenesis. *Cell Metab.* **29**, 1061–1077, <https://doi.org/10.1016/j.cmet.2018.12.008>
- 21 Ferreira, A., Castro, J.P., Andrade, J.P., Dulce Madeira, M. and Cardoso, A. (2018) Cafeteria-diet effects on cognitive functions, anxiety, fear response and neurogenesis in the juvenile rat. *Neurobiol. Learn Mem.* **155**, 197–207, <https://doi.org/10.1016/j.nlm.2018.07.014>
- 22 Navarro-Sanchis, C., Brock, O., Winsky-Sommerer, R. and Thuret, S. (2017) Modulation of adult hippocampal neurogenesis by sleep: impact on mental health. *Front. Neural Circuits* **11**, 74, <https://doi.org/10.3389/fncir.2017.00074>
- 23 Murata, Y., Oka, A., Iseki, A., Mori, M., Ohe, K., Mine, K. et al. (2018) Prolonged sleep deprivation decreases cell proliferation and immature newborn neurons in both dorsal and ventral hippocampus of male rats. *Neurosci. Res.* **131**, 45–51, <https://doi.org/10.1016/j.neures.2017.08.008>

- 24 Kreutzmann, J.C., Havekes, R., Abel, T. and Meerlo, P. (2015) Sleep deprivation and hippocampal vulnerability: changes in neuronal plasticity, neurogenesis and cognitive function. *Neuroscience* **309**, 173–190, <https://doi.org/10.1016/j.neuroscience.2015.04.053>
- 25 Schouten, M., Fratantoni, S.A., Hubens, C.J., Piersma, S.R., Pham, T.V., Bielefeld, P. et al. (2015) MicroRNA-124 and -137 cooperativity controls caspase-3 activity through BCL2L13 in hippocampal neural stem cells. *Sci. Rep.* **5**, 12448, <https://doi.org/10.1038/srep12448>
- 26 Stappert, L., Klaus, F. and Brüstle, O. (2018) MicroRNAs engage in complex circuits regulating adult neurogenesis. *Front. Neurosci.* **12**, 707, <https://doi.org/10.3389/fnins.2018.00707>
- 27 Bielefeld, P., Schouten, M., Lucassen, P.J. and Fitzsimons, C.P. (2017) Transcription factor oscillations in neural stem cells: Implications for accurate control of gene expression. *Neurogenesis* **4**, e1262934, <https://doi.org/10.1080/23262133.2016.1262934>
- 28 Bielefeld, P., Mooney, C., Henshall, D.C. and Fitzsimons, C.P. (2017) MiRNA-mediated regulation of adult hippocampal neurogenesis; implications for epilepsy. *Brain Plast.* **3**, 43–59, <https://doi.org/10.3233/BPL-160036>
- 29 Schouten, M., Buijink, M.R., Lucassen, P.J. and Fitzsimons, C.P. (2012) New neurons in aging brains: molecular control by small non-coding RNAs. *Front. Neurosci.* **6**, 25, <https://doi.org/10.3389/fnins.2012.00025>
- 30 Semerci, F., Choi, W.T., Bajic, A., Thakkar, A., Encinas, J.M., Depreux, F. et al. (2017) Lunatic fringe-mediated Notch signaling regulates adult hippocampal neural stem cell maintenance. *Elife* **6**, <https://doi.org/10.7554/eLife.24660>
- 31 Sun, G., Cui, Q. and Shi, Y. (2017) Nuclear receptor TLX in development and diseases. *Curr. Top. Dev. Biol.* **125**, 257–273, <https://doi.org/10.1016/bs.ctdb.2016.12.003>
- 32 Li, W., Sun, G., Yang, S., Qu, Q., Nakashima, K. and Shi, Y. (2008) Nuclear receptor TLX regulates cell cycle progression in neural stem cells of the developing brain. *Mol. Endocrinol.* **22**, 56–64, <https://doi.org/10.1210/me.2007-0290>
- 33 Kozareva, D.A., O'Leary, O.F., Cryan, J.F. and Nolan, Y.M. (2018) Deletion of TLX and social isolation impairs exercise-induced neurogenesis in the adolescent hippocampus. *Hippocampus* **28**, 3–11, <https://doi.org/10.1002/hipo.22805>
- 34 O'Leary, J.D., O'Leary, O.F., Cryan, J.F. and Nolan, Y.M. (2018) Regulation of behaviour by the nuclear receptor TLX. *Genes Brain Behav.* **17**, e12357, <https://doi.org/10.1111/gbb.12357>
- 35 Kozareva, D.A., Foley, T., Moloney, G.M., Cryan, J.F. and Nolan, Y.M. (2019b) TLX knockdown in the dorsal dentate gyrus of juvenile rats differentially affects adolescent and adult behaviour. *Behav. Brain Res.* **360**, 36–50, <https://doi.org/10.1016/j.bbr.2018.11.034>
- 36 Galatro, T.F., Holtman, I.R., Lerario, A.M., Vainchtein, I.D., Brouwer, N., Sola, P.R. et al. (2017) Transcriptomic analysis of purified human cortical microglia reveals age-associated changes. *Nat. Neurosci.* **20**, 1162–1171, <https://doi.org/10.1038/nn.4597>
- 37 Dubbelaar, M.L., Kracht, L., Eggen, B.J.L. and Boddeke, E.W.G.M. (2018) The kaleidoscope of microglial phenotypes. *Front. Immunol.* **9**, 1753, <https://doi.org/10.3389/fimmu.2018.01753>
- 38 Doorn, K.J., Brevé, J.J.P., O'Toole, T., Huitinga, I., Boddeke, H.J.W., Drukarch, B. et al. (2015) Brain region specific gene expression profiles in freshly isolated rat microglia. *Front. Cell. Neurosci.* **9**, 84, <https://doi.org/10.3389/fncel.2015.00084>
- 39 Valero, J., Eiriz, M.F., Santos, T., Neiva, I., Ferreira, R. and Malva, J.O. (2012) Microglia: the bodyguard and the hunter of the adult neurogenic niche. In *Advances in Stem Cell Research Stem Cell Biology and Regenerative Medicine* (Baharvand, H. and Aghdami, N., eds), pp. 245–279, Humana Press, New York, N.Y.
- 40 Sierra, A., Beccari, S., Diaz-Aparicio, I., Encinas, J.M., Comeau, S. and Tremblay, M.È (2014) Surveillance, phagocytosis, and inflammation: how never-resting microglia influence adult hippocampal neurogenesis. *Neural Plast.* 610343
- 41 Sierra, A., Encinas, J.M., Deudero, J.J., Chancey, J.H., Enikolopov, G., Overstreet-Wadiche, L.S. et al. (2010) Microglia shape adult hippocampal neurogenesis through apoptosis-coupled phagocytosis. *Cell Stem Cell* **7**, 483–495, <https://doi.org/10.1016/j.stem.2010.08.014>
- 42 Wynne, A.M., Henry, C.J., Huang, Y., Cleland, A. and Godbout, J.P. (2010) Protracted downregulation of CX3CR1 on microglia of aged mice after lipopolysaccharide challenge. *Brain Behav. Immun.* **24**, 1190–1201, <https://doi.org/10.1016/j.bbi.2010.05.011>
- 43 Van Olst, L., Bielefeld, P., Fitzsimons, C.P., de Vries, H.E. and Schouten, M. (2018) Glucocorticoid-mediated modulation of morphological changes associated with aging in microglia. *Aging Cell* e12790, <https://doi.org/10.1111/accel.12790>
- 44 Bhavsar, P.K., Sukkar, M.B., Khorasani, N., Lee, K.Y. and Chung, K.F. (2008) Glucocorticoid suppression of CX3CL1 (fractalkine) by reduced gene promoter recruitment of NF- $\kappa$ B. *FASEB J.* **22**, 1807–1816, <https://doi.org/10.1096/fj.07-094235>
- 45 Schaafsma, W., Basterra, L.B., Jacobs, S., Brouwer, N., Meerlo, P., Schaafsma, A. et al. (2017) Maternal inflammation induces immune activation of fetal microglia and leads to disrupted microglia immune responses, behavior, and learning performance in adulthood. *Neurobiol. Dis.* **106**, 291–300, <https://doi.org/10.1016/j.nbd.2017.07.017>
- 46 Valero, J., Paris, I. and Sierra, A. (2016) Lifestyle shapes the dialogue between environment, microglia, and adult neurogenesis. *ACS Chem. Neurosci.* **7**, 442–453, <https://doi.org/10.1021/acscemneuro.6b00009>
- 47 Van Dam, A.M., Brouns, M., Louisse, S. and Berkenbosch, F. (1992) Appearance of interleukin-1 in macrophages and in ramified microglia in the brain of endotoxin-treated rats: a pathway for the induction of non-specific symptoms of sickness? *Brain Res.* **588**, 291–296, [https://doi.org/10.1016/0006-8993\(92\)91588-6](https://doi.org/10.1016/0006-8993(92)91588-6)
- 48 Van Dam, A.M., Bauer, J., Tilders, F.J. and Berkenbosch, F. (1995) Endotoxin-induced appearance of immunoreactive interleukin-1 beta in ramified microglia in rat brain: a light and electron microscopic study. *Neuroscience* **65**, 815–826, [https://doi.org/10.1016/0306-4522\(94\)00549-K](https://doi.org/10.1016/0306-4522(94)00549-K)
- 49 Zunszain, P.A., Anacker, C., Cattaneo, A., Choudhury, S., Musaeelyan, K., Myint, A.M. et al. (2012) Interleukin-1 $\beta$ : a new regulator of the kynurenine pathway affecting human hippocampal neurogenesis. *Neuropsychopharmacology* **37**, 939–949, <https://doi.org/10.1038/npp.2011.277>
- 50 Ó'Leime, C.S., Kozareva, D.A., Hoban, A.E., Long-Smith, C.M., Cryan, J.F. and Nolan, Y.M. (2018a) TLX is an intrinsic regulator of the negative effects of IL-1 $\beta$  on proliferating hippocampal neural progenitor cells. *FASEB J.* **32**, 613–624, <https://doi.org/10.1096/fj.201700495R>
- 51 Ó'Leime, C.S., Hoban, A.E., Hueston, C.M., Stilling, R., Moloney, G., Cryan, J.F. et al. (2018b) The orphan nuclear receptor TLX regulates hippocampal transcriptome changes induced by IL-1 $\beta$ . *Brain Behav. Immun.* **70**, 268–279, <https://doi.org/10.1016/j.bbi.2018.03.006>

- 52 Ryan, S.M., O’Keeffe, G.W., O’Connor, C., Keeshan, K. and Nolan, Y.M. (2013) Negative regulation of TLX by IL-1 $\beta$  correlates with an inhibition of adult hippocampal neural precursor cell proliferation. *Brain Behav. Immun.* **33**, 7–13, <https://doi.org/10.1016/j.bbi.2013.03.005>
- 53 Green, H.F. and Nolan, Y.M. (2012) Unlocking mechanisms in interleukin-1 $\beta$ -induced changes in hippocampal neurogenesis—a role for GSK-3 $\beta$  and TLX. *Transl. Psychiatry* **2**, e194, <https://doi.org/10.1038/tp.2012.117>
- 54 Kozareva, D.A., Hueston, C.M., Ó’Léime, C.S., Crotty, S., Dockery, P., Cryan, J.F. et al. (2017) Absence of the neurogenesis-dependent nuclear receptor TLX induces inflammation in the hippocampus. *J. Neuroimmunol.* **S0165-5728**, 30204–30207
- 55 Reshef, R., Kudryavitskaya, E., Shani-Narkiss, H., Isaacson, B., Rimmerman, N., Mizrahi, A. et al. (2017) The role of microglia and their CX3CR1 signaling in adult neurogenesis in the olfactory bulb. *Elife* **6**, pii: e30809, <https://doi.org/10.7554/eLife.30809>
- 56 Hellwig, S., Brioschi, S., Dieni, S., Frings, L., Masuch, A., Blank, T. et al. (2016) Altered microglia morphology and higher resilience to stress-induced depression-like behavior in CX3CR1-deficient mice. *Brain Behav. Immun.* **55**, 126–137, <https://doi.org/10.1016/j.bbi.2015.11.008>
- 57 Bolós, M., Perea, J.R., Terreros-Roncal, J., Pallas-Bazarra, N., Jurado-Arjona, J., Ávila, J. et al. (2018) Absence of microglial CX3CR1 impairs the synaptic integration of adult-born hippocampal granule neurons. *Brain Behav. Immun.* **68**, 76–89, <https://doi.org/10.1016/j.bbi.2017.10.002>
- 58 Murai, K., Sun, G., Ye, P., Tian, E., Yang, S., Cui, Q. et al. (2016) The TLX-miR-219 cascade regulates neural stem cell proliferation in neurodevelopment and schizophrenia iPSC model. *Nat. Commun.* **7**, 10965, <https://doi.org/10.1038/ncomms10965>
- 59 Sun, G., Ye, P., Murai, K., Lang, M.F., Li, S., Zhang, H. et al. (2011) MiR-137 forms a regulatory loop with nuclear receptor TLX and LSD1 in neural stem cells. *Nat. Commun.* **2**, 529, <https://doi.org/10.1038/ncomms1532>
- 60 Zhao, C., Sun, G., Li, S. and Shi, Y. (2009) A feedback regulatory loop involving microRNA-9 and nuclear receptor TLX in neural stem cell fate determination. *Nat. Struct. Mol. Biol.* **16**, 365–371, <https://doi.org/10.1038/nsmb.1576>
- 61 Murai, K., Qu, Q., Sun, G., Ye, P., Li, W., Asuelime, G. et al. (2014) Nuclear receptor TLX stimulates hippocampal neurogenesis and enhances learning and memory in a transgenic mouse model. *Proc Natl Acad Sci U S A.* **111**, <https://doi.org/10.1073/pnas.1406779111>
- 62 Borsini, A., Zunszain, P.A., Thuret, S. and Pariante, C.M. (2015) The role of inflammatory cytokines as key modulators of neurogenesis. *Trends Neurosci.* **38**, 145–157, <https://doi.org/10.1016/j.tins.2014.12.006>
- 63 Benod, C., Villagomez, R., Filgueira, C.S., Hwang, P.K., Leonard, P.G., Poncet-Montange, G. et al. (2014) The human orphan nuclear receptor tailless (TLX, NR2E1) is druggable. *PLoS ONE* **9**, e99440, <https://doi.org/10.1371/journal.pone.0099440>