Plenary session speech

Neuroimmune Dysfunction and Neurodegeneration

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Date: 9/3 (Sat.) 13:40~14:25
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Abstract

Neuroimmune dysfunction is a cardinal feature of neurodegenerative diseases. But how immune dysregulation in the brain contributes to neurodegeneration remains unclear. My research focuses on dominant mutations in the human Progranulin (GRN) gene – a leading cause of frontotemporal dementia (FTD). Patients with GRN mutations have much lower progranulin (PGRN) protein levels in the cerebrospinal fluid (CSF) and serum, suggesting that haploinsufficiency in PGRN could be a major cause of disease. To model the impacts of PGRN deficiency, we show that mice with a complete loss of PGRN (Grn-/-) and those that carry humanized GRNR493X mutation exhibit age-dependent microgliosis that preferentially affects the thalamocortical circuit, where it promotes excessive synaptic pruning, neuronal degeneration, and TDP-43 proteinopathy in the thalamocortical circuits. My lecture will discuss our recent strategies to further uncover how PGRN deficiency contributes to neurodegeneration. Our approaches include blocking both complement pathways and proinflammatory cytokines to mitigate neuroinflammation caused by PGRN deficiency. In addition, we use proteomic and lipidomic approaches to uncover the essential role of Progranulin in intracellular vesicle trafficking and how these defects impede lysosome-mediated lipid degradation and secretion, leading to lipid-mediated toxicity during the late phase of neurodegeneration in the Grn-/- mouse model. Finally, to determine the contributions of the glial pathology to human disease, we perform single cell transcriptomic analyses in the thalamocortical circuits in Grn-/- mice and in FTD patients with GRN mutations. This approach provides a comprehensive understanding of the impacts of glial pathology to neurodegeneration in mice and human.

Selected recent publications:

1. Martens LH, Zhang J, et al. Progranulin deficiency promotes neuroinflammation and neuron loss following toxin-induced injury. J Clin Invest. 2012 Nov 1;122(11):3955-9.
2. Lui H, Zhang J, et al. Progranulin Deficiency Promotes Circuit-Specific Synaptic Pruning by Microglia via Complement Activation. Cell. 2016 May 5;165(4):921-35.
3. Kao AW, McKay A, Singh PP, Brunet A, Huang EJ. Progranulin, lysosomal regulation and neurodegenerative disease. Nature Rev Neurosci. 2017 Jun;18(6):325-333.
4. Nguyen AD, Nguyen TA, Zhang J, et al.. Murine knockin model for progranulin-deficient frontotemporal dementia with nonsense-mediated mRNA decay. Proc Natl Acad Sci U S A. 2018 Mar 20;115(12):E2849-E2858.
5. Zhang J, Velmeshev D, Hashimoto K, Huang HY, et al. Neurotoxic microglia promote TDP-43 proteinopathy in progranulin deficiency. Nature. 2020 Dec;588(7838):459-465.

Plenary session speech

What are brain circuit therapeutics and how do we map and modulate them with Deep TMS

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Psychiatry Department, Brigham and Women's Hospital
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Abstract

Topics:

Overview and history of brain circuit mapping and modulation.

Finding the right TMS target.

Common brain circuit modulation with TMS, DBS, and Brain Lesions.

What's on the horizon?

Selected recent publications:

1.Siddiqi, S. H., Schaper, F. L., Horn, A., Hsu, J., Padmanabhan, J. L., Brodtmann, A., & Fox, M. D. (2021). Brain stimulation and brain lesions converge on common causal circuits in neuropsychiatric disease. Nature human behaviour, 5(12), 1707-1716.

2.Siddiqi, S. H., Weigand, A., Pascual-Leone, A., & Fox, M. D. (2021). Identification of personalized transcranial magnetic stimulation targets based on subgenual cingulate connectivity: an independent replication. Biological psychiatry, 90(10), e55-e56.

3. Cash, R. F., Weigand, A., Zalesky, A., Siddiqi, S. H., Downar, J., Fitzgerald, P. B., & Fox, M. D. (2021). Using brain imaging to improve spatial targeting of transcranial magnetic stimulation for depression. Biological psychiatry, 90(10), 689-700.

4.Siddiqi, S., Taylor, S., Cooke, D., George, M., Pascual-Leone, A., & Fox, M. (2019). Distinct symptom-specific treatment targets for antidepressant neuromodulation. Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation, 12(2), 537.

5. Padmanabhan, J. L., Cooke, D., Joutsa, J., Siddiqi, S. H., Ferguson, M., Darby, R. R., & Fox, M. D. (2019). A human depression circuit derived from focal brain lesions. Biological psychiatry, 86(10), 749-758.

Plenary session speech

Peripheral sodium channels and human pain – recent progress in analgesic therapies.

John N Wood and The Molecular Nociception Group

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Date: 9/3 (Sat.) 13:40~14:25

Abstract

Human genetics have provided us with useful insights into novel validated analgesic drug targets, but the harvest has been poor. SCN9A encoding voltage-gated sodium channel Nav1.7 is required for pain in mice and humans, but small molecule antagonists have not proved useful. We have found that this is due to a key role in neurotransmitter release for this channel within the spinal cord. Opioid signalling within sensory neurons is massively enhanced in the absence of Nav1.7 and this blocks nociceptive transmission. Gene therapy targeting Nav1.7 in the periphery thus has many attractions over centrally acting antagonists that are likely to have side effects, given the broad expression of Nav1.7 with the central nervous system and its known role in the hypothalamus (PMID: 27315482).

Nav1.8 is another appealing analgesic target, but has been linked to Brugada syndrome with sudden death caused by cardiac dysfunction. Recent studies (PMID: 33910361) have now shown that a C-terminal fragment of Nav1.8 only produced in the heart potentiates cardiac sodium channel Nav1.5 function. This information allows cardiac side effects to be avoided with either carefully designed small molecules or gene therapy. A quarter of a century after the cloning of Nav1.8, antagonists have proved to be excellent analgesics in Phase 2 trials of acute pain, providing more relief than opioids.

Basic mechanistic studies highlightthe importance of basic science in translational advances.

Acknowledgements
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Selected recent publications:

1. Donald Iain MacDonald, Shafaq Sikandar, Jan Weiss, Martina Pyrski, Ana P. Luiz, Queensta Millet, Edward C. Emery, Flavia Mancini Gian D. Iannetti, Sascha R.A. Alles, Manuel Arcangeletti, Jing Zhao, James J Cox, Robert M. Brownstone, Frank Zufall, and John N. Wood The mechanism of analgesia in NaV1.7 null mutants Neuron. 2021 May 5;109(9):1497-151
2. Alles SRA, Nascimento F, Luján R, Luiz AP, Millet Q, Bangash MA, Santana-Varela S, Zhou X, Cox JJ, Okorokov AL, Beato M, Zhao J, Wood JN.Sensory neuron-derived NaV1.7 contributes to dorsal horn neuron excitability. Sci Adv. 2020 Feb 19;6(8): PMID: 32128393
3. Donald Iain MacDonald, Ana P. Luiz, Queensta Millet, Edward C. Emery and John N. Wood Silent cold-sensing neurons drive cold allodynia in neuropathic pain states Brain 2021 Jul 28;144(6):1711-1726.
4. Luiz AP, MacDonald DI, Santana-Varela S, Millet Q, Sikandar S, Wood JN, Emery EC. Cold sensing by Nav1.8-positive and Nav1.8-negative sensory neurons. Proc Natl Acad Sci U S A. 2019 Feb 26;116(9):3811-3816
5. Raouf R, Lolignier S, Sexton JE, Millet Q, Santana-Varela S, Biller A, Fuller AM, Pereira V, Choudhary JS, Collins MO, Moss SE, Lewis R, Tordo J, Henckaerts E, Linden M, Wood JN. Inhibition of somatosensory mechanotransduction by annexin A6. Sci Signal. 2018 Jun 19;11(535).

Plenary session speech

Neural regeneration through cell fate reprogramming in vivo

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Abstract

Neural injury or neurodegeneration frequently leads to irreversible loss of neurons; however, the adult mammalian central nervous system (CNS) has largely lost the ability to produce new neurons. A key question in the regeneration field is how to generatenew neurons for functional reconstruction in the adult CNS. Our lab has taken an in vivo reprogramming approach, which is to engineer the fate of resident glial cells to let them become neurogenic. In this talk, I will focus on two types of glial cells, astrocytes and NG2 glia. Our results show that resident astrocytes or NG2 glia can be in vivo reprogrammed to produce new neurons in the adult mouse brain or spinal cord. Importantly, these glia-generated new neurons can become mature, make synaptic connections, and may contribute to functional recovery in a mouse model of spinal cord injury. Further development in this reprogramming approach may lead to a regeneration-based therapeutic strategy for many of the neurological diseases.

Selected recent publications:

1. Zhang Y, Li B, Cananzi S, Han C, Wang W, Zou Y, Fu Y, Hon G, Zhang CL. A single factor elicits multilineage reprogramming of astrocytes in the adult mouse striatum. Proc Natl Acad Sci U S A. 2022 Mar 15;119(11):e2107339119. doi: 10.1073/pnas.2107339119. PMID: 35254903.
2. Wang LL, Serrano C, Zhong X, Ma S, Zou Y, Zhang CL. Revisiting astrocyte to neuron conversion with lineage tracing in vivo. Cell. 2021 Oct 14;184(21):5465-5481.e16. doi: 10.1016/j.cell.2021.09.005. PMID: 34582787.
3. Yu Y, Shen T, Zhong X, Wang LL, Tai W, Zou Y, Qin J, Zhang Z, Zhang CL. NEK6 is an injury-responsive kinase cooperating with STAT3 in regulation of reactive astrogliosis. Glia. 2021 Oct 13. doi: 10.1002/glia.24104. PMID: 34643969
4. Tai W, Wu W, Wang LL, Ni H, Chen C, Yang J, Zang T, Zou Y, Xu XM, Zhang CL. In vivo reprogramming of NG2 glia enables adult neurogenesis and functional recovery following spinal cord injury. Cell Stem Cell. 2021 May 6;28(5):923-937.e4. doi: 10.1016/j.stem.2021.02.009. PMID: 33675690.
5. Ding B, Tang Y, Ma S, Akter M, Liu ML, Zang T, Zhang CL. Disease modeling with human neurons reveals LMNB1 dysregulation underlying DYT1 dystonia. J Neurosci. 2021 Jan 15:JN-RM-2507-20. doi: 10.1523/JNEUROSCI.2507-20.2020. PMID: 33468570