

Neuroscience Research: Glial Cells

Publications by NanoString Customers

[Impact of TREM2 risk variants on brain region-specific immune activation and plaque microenvironment in Alzheimer's disease patient brain samples](#)

Prokop S et al. Acta Neuropathol. 2019;138(4):613-630

University of Pennsylvania School of Medicine, University of Florida, NanoString Technologies, Inc.

TREM2 (triggering receptor expressed on myeloid cells 2) is one of the immune-related genetic risk variants for Alzheimer's disease (AD). In this study, microglia from human AD samples were comprehensively analyzed at different stages of disease based on TREM2 risk variants. The plaque microenvironment in AD brains was analyzed with the GeoMx® Digital Spatial Profiler (DSP), and immune response patterns were profiled using the nCounter® Human Neuropathology and Neuroinflammation gene expression panels. This comprehensive analysis revealed that microglia were activated as AD neuropathological changes progressed as well as concurrent beta-amyloid/tau pathogenesis. Carriers of TREM2 risk variants showed a reduction in plaque-associated microglia and an increase in dystrophic neurites and pathological tau. Furthermore, DSP analysis in the plaque microenvironment revealed regional-dependent variations in immune response patterns. Gene expression analyses indicated profound differences in inflammation, neuronal, and synaptic integrity pathways as well as astrocyte-associated pathways between the brain regions. In summary, TREM2 risk variants strongly impact brain region-specific immune activation and the plaque microenvironment in human AD brains.

[Absence of TGFβ signaling in retinal microglia induces retinal degeneration and exacerbates choroidal neovascularization](#)

Ma W et al. Elife. 2019;8:e42049.

National Eye Institute, National Institutes of Health.

TGFβ signaling has a critical role in maintaining retinal neurons and blood vessels and is implicated in the neurodegeneration and microglial activation seen in age-related macular degeneration (AMD). This study investigated the role of TGFβ signaling in microglial physiology in the mouse retina as well as the regulation of inflammatory, neurodegenerative, and neovascular processes in AMD. The effects of TGFβ signaling on gene expression were profiled using the nCounter Mouse Immunology Panel. Loss of the TGFβ receptor TGFBR2 in microglia induced a pathological microglial gene expression profile characterized by microglial activation, Müller cell gliosis, and neuronal apoptosis in the surrounding retina. In addition, TGFBR2-deficient microglia decreased their ability to sense environmental signals reflecting abnormal synaptic transmission, and increased pathological choroidal neovascularization, a hallmark of advanced exudative AMD. These data indicate that aberrant regulation of TGFβ signaling in retinal microglia can drive chronic neuroinflammation, which contributes to AMD-related neurodegeneration and pathological choroidal neovascularization.

[Transcriptional regulation of homeostatic and disease-associated-microglial genes by IRF1, LXR \$\beta\$, and CEBP \$\alpha\$](#)

Gao T et al. *Glia*. 2019;67(10):1958-1975.

Emory University, Xiangya Hospital at Central South University, University of Georgia.

In neurodegeneration, homeostatic microglia transform to disease-associated-microglia (DAM) profiles with distinct pro-inflammatory and anti-inflammatory sub-profiles. In this study, in-vitro siRNA analysis in primary microglia was performed to identify the roles of transcriptional factors (TFs) in regulating microglial activation. Expression profiling of microglia using the nCounter Neuroinflammation Panel revealed distinct gene clusters with regulatory patterns of each TF. The three TFs IRF1, LXR β , and CEBP α positively regulated core DAM genes (ApoE, Axl, Clec7a, Tyrobp, & Trem2), homeostatic and pro-inflammatory DAM genes. By contrast, treatment with LPS and IFN γ increased pro-inflammatory DAM expression but reduced homeostatic and anti-inflammatory DAM expression via an ERK1/2 signaling pathway. Silencing of IRF1 and LXR β suppressed microglial phagocytic activity, as IRF1 silencing strongly decreased pro-inflammatory cytokines in response to LPS. In summary, the microglial TFs CEBP α , IRF1, and LXR β are regulators of homeostatic, pro-inflammatory, and anti-inflammatory DAM states, indicating their critical roles in Alzheimer's and other neurodegenerative diseases.

[Capicua regulates neural stem cell proliferation and lineage specification through control of Ets factors](#)

Ahmad ST et al. *Nat Commun*. 2019;10(1):2000.

University of Calgary, University of Toronto, California Institute of Technology, Zymeworks, King Abdullah International Medical Centre, University of California, San Francisco, BC Genome Sciences Centre.

Mutations in the transcriptional repressor Capicua (CIC) are associated with cancers, including the brain cancer oligodendroglioma. This study was designed to determine the effects of Cic expression on regulation of neuronal-glial lineage specification in the mammalian forebrain. Expression of neurodevelopmental and brain cancer-associated genes was measured on the nCounter system using a Custom CodeSet. Expression of nuclear Cic was high in astrocytes and neurons while its expression was low in stem cells and oligodendroglial lineage cells. In a conditional Cic-knockout mouse model, forebrain-specific Cic deletion enhanced proliferation and self-renewal of neural stem cells. Furthermore, loss of Cic led neural stem cells towards glial lineage selection, expanding oligodendrocyte precursor cells (OPCs). These proliferation and lineage effects of Cic-knockout were dependent on de-repression of Ets transcription factors. In patient-derived oligodendroglioma cells, CIC re-expression lowered lineage bias, proliferation, and tumorigenicity. These results suggest that loss of Cic contributes to oligodendroglioma by promoting glial lineage selection with expansion of OPCs via de-repressed Ets.

NLRP3 inflammasome activation drives tau pathology

Ising C et al. Nature. 2019;575(7784):669-673.

University Hospital of Bonn, German Center for Neurodegenerative Diseases, IFM Therapeutics GmbH, University of Texas Medical Branch, University of Lille, University of Massachusetts Medical School.

Amyloid- β accumulation in plaques, neuroinflammation, and aggregation of hyperphosphorylated tau are closely involved in the development and progression of Alzheimer's disease. Amyloid- β activates the NLRP3 inflammasome in microglia, leading to increased caspase-1 activity and downstream IL-1 β release. This study investigated the influence of the NLRP3 inflammasome on tau pathogenesis by profiling RNAs from mouse brain homogenates using the nCounter Mouse Neuroinflammation Panel. Gene expression analysis revealed age-related differences between wild-type and Tau22 mice, and a dynamic gene regulation network, such as induction of the NLRP3 inflammasome pathway via upregulation of Casp1 and Il1b. Loss of NLRP3 inflammasome function protected mice from tau hyper-phosphorylation and aggregation and prevented cognitive decline. As amyloid- β fibrils activated the NLRP3 inflammasome, intracerebral injection of fibrillar amyloid- β homogenates induced tau pathogenesis. Overall, the NLRP3 inflammasome mediates amyloid- β -induced tau pathogenesis, supporting the involvement of the amyloid- β /microglial activation/neurofibrillary tangle cascade in Alzheimer's disease.

Microglia-derived microvesicles affect microglia phenotype in glioma

Grimaldi A et al. Front Cell Neurosci. 2019;13:41.

Istituto Italiano di Tecnologia at Sapienza, Sapienza University of Rome, University of Roma Tre, IRCCS Neuromed.

Extracellular-released vesicles (EVs), e.g., microvesicles (MVs) and exosomes, provide a means for intercellular communication by directly transferring proteins, lipids, and nucleic acids from one cell to another. In the nervous system, EVs promote neuron-glia cell cross-talk in order to preserve brain homeostasis but can be associated with CNS disease when their transmission becomes dysfunctional. This study investigated whether microglia-derived EVs could transfer a protective signal to dysfunctional microglia. When MVs isolated from LPS/IFN γ -stimulated inflammatory microglia were injected into the brain of glioma-bearing mice, the anti-inflammatory phenotype of tumor-associated myeloid cells was decreased, and tumor size and neurotoxicity were significantly reduced. Total RNA isolated from microglia-derived MVs was profiled for expression of 243 inflammation-related genes using the nCounter system. Analysis revealed that the LPS/IFN γ -MV cargo, which contained upregulated transcripts of inflammatory genes, transferred the information to the brain of glioma-bearing mice, resulting in modification of the microglial gene expression profile towards a protective phenotype. Thus, the MV cargo can transfer a protective signal to recipient cells to reduce neuronal death and glioma invasion, leading to the recovery of brain homeostasis.

Time-dependent changes in microglia transcriptional networks following traumatic brain injury

Izzy S et al. Front Cell Neurosci. 2019;13:307.

Brigham and Women's Hospital, Harvard Medical School, Massachusetts General Hospital, Fudan University, Broad Institute of Harvard and Massachusetts Institute of Technology, Tufts University.

In traumatic brain injury (TBI), the neuroinflammatory response and persistent activation of microglia play critical roles in neurotoxicity as well as neuroprotection. In this study, controlled cortical impact (CCI), a mouse model of focal cerebral contusion, was used to investigate the cellular and molecular mechanisms that drive the outcome of TBI. Time-dependent, injury-associated changes in microglial gene expression were profiled using the nCounter Mouse Inflammation Panel. In the early stages of post-CCI, changes in microglial gene expression were associated with a reduced ability to sense tissue damage, perform housekeeping, and maintain homeostasis, characterized by the upregulation of chemotaxis and cytokine signaling. In this model, recovery and transition to a pro-inflammatory state started at 14 days post-injury, along with a biphasic pattern of IFN- γ , IL-4, and IL-10 gene expression and variations in pro-inflammatory and anti-inflammatory gene expression profiles. Overall, these transcriptomic data promote an understanding of the roles of microglial and the identification of immunological pathways that affect the pathogenesis of TBI at the molecular level.

[Region-specific glial homeostatic signature in prion diseases is replaced by a uniform neuroinflammation signature, common for brain regions and prion strains with different cell tropism](#)

Makarava N et al. Common for Brain Regions and Prion Strains With Different Cell Tropism. *Neurobiol Dis.* 2020;137:104783.

University of Maryland School of Medicine.

This study investigated changes in the region-specific homeostatic signature of glia with the progression of prion disease and reactive phenotypes distinctive to different prion strains. Gene expression in the thalamus, cortex, hypothalamus, and hippocampus of prion-infected mice was assessed at the subclinical, early clinical, and advanced stages of the disease using the nCounter Mouse Neuroinflammation Panel. At the subclinical stage, region-specific homeostatic signatures were preserved. As clinical signs appeared, region-specific homeostatic signatures in glia were partially lost and replaced by a region-independent neuroinflammation signature. Clustering analysis demonstrated that the astrocyte function pathway was altered by responding to prion infection prior to the activated microglia or neuron and neurotransmission pathways. Moreover, this work established a prion disease-associated neuroinflammation gene-expression signature, which is independent of the brain region or prion cell tropism. Importantly, this prion disease-associated neuroinflammation signature only partially overlapped with the microglia-degenerative phenotype identified in other neurodegenerative diseases.

[Driving neuronal differentiation through reversal of an ERK1/2-miR-124-SOX9 axis abrogates glioblastoma aggressiveness](#)

Sabelström H et al. *Cell Rep.* 2019;28(8):2064-2079.e11.

UC San Francisco, Lund University, Pfizer, City of Hope.

It has been shown that constitutive activation of the RAS-ERK1/2 pathway in embryonic cortical progenitors and in neurogenic astrocytes induces malignant gliomas in mouse models. To understand the role of the ERK1/2 axis further, this study explored the impact of constitutive ERK1/2 activation on a stem-like state in glioblastoma. Inhibition of ERK1/2 activation restored neurogenesis during astrocytoma formation, inducing neuronal differentiation in tumorspheres. miRNA expression profiling using the nCounter Mouse miRNA Expression Assay confirmed that constitutive ERK1/2 activation globally regulated miRNA expression in glioblastomas. Interestingly, after inhibition of ERK1/2 activation, expression of miR-124 and depletion of its target gene SOX9 were required for neuronal differentiation of glioblastoma tumorspheres. Furthermore, overexpression of miR-124 blocked SOX9 expression, which in turn, promoted a stem-like-to-neuronal transition leading to decreased tumorigenicity and increased radiation sensitivity. In summary, inhibition of the ERK1/2-miR-124-SOX9 axis mediates neuronal differentiation, abrogates tumor progression, and promotes radiosensitivity in glioblastoma.

[Human and mouse single-nucleus transcriptomics reveal TREM2-dependent and TREM2-independent cellular responses in Alzheimer's disease](#)

Zhou Y et al. Nat Med. 2020;26(1):131-142.

Washington University School of Medicine, St. Louis, Bluefin Biomedicine, NanoString Technologies, Inc., University of Brescia, ITMO University, Niigata University, Rush University Medical Center, and others.

TREM2 (triggering receptor expressed on myeloid cells 2) is a microglia receptor involved in activation of disease-associated microglia (DAM), and variants of TREM2 increase the risk of Alzheimer's disease (AD). This study profiled TREM2 gene expression and its effect on AD pathogenesis in human and mouse brain tissue samples using single-nucleus RNA sequencing and the nCounter Analysis System. Although the gene expression signature of human AD microglia was distinct from that of DAM in the 5XFAD-mouse model, transcriptional data confirmed the presence of Trem2-dependent DAM and a Serpina3n+C4b+ reactive oligodendrocyte population in mice. Astrocyte profiles indicated a loss of metabolic coordination with neurons in AD. Also, the signature of amyloid β -dependent reactive oligodendrocytes was associated with impaired axonal myelination and metabolic adaptation to neuronal degeneration. Furthermore, AD glial signatures and neuronal loss were verified in human brain specimens using the nCounter Neuropathology Panel. Notably, AD patients who carried a TREM2 variant, R62H or R47H, had a reduced microglia reactive signature. In summary, TREM2 impacts the physiological and metabolic functions of microglia in both human AD and a mouse model of A β accumulation.

[Microglial activation increases cocaine self-administration following adolescent nicotine exposure](#)

Linker KE et al. Nat Commun. 2020;11(1):306.

University of California, Irvine.

The adolescent brain is sensitive to nicotine; it causes persistent changes in neuronal signaling and interferes with brain maturation. This study explored: 1) the effects of nicotine on adolescent microglia, 2) the importance of microglia in nicotine-induced increases in cocaine reinforcement, and 3) the underlying role of neuronal D2 receptors and the neuronal ligand CX3CL1 in rats. Gene expression profiles collected using the nCounter Neuropathology Panel showed that nicotine-induced expression of anti-inflammatory transcripts in adults was different to that of adolescents. Nicotine affected behavior and microglial activation via a multistep signaling mechanism, involving neuronal D2 receptors and fractalkine signaling, or CX3CR1-CX3CL1. In addition, nicotine decreased presynaptic markers via D2 receptors, microglia, and CX3CL1 signaling. Notably, nicotine exposure promoted a reactive phenotype in adolescent microglia, and this microglial phenotype was necessary for an increase in adolescent cocaine self-administration. Taken together, these data show that adolescent microglia are susceptible to nicotine-mediated perturbations, and adolescent-nicotine exposure promotes an increase in cocaine reinforcement by microglial activation via D2 receptors and CX3CL1 signaling cascades.

[Targeted complement inhibition salvages stressed neurons and inhibits neuroinflammation after stroke in mice](#)

Alawieh A et al. Sci Transl Med. 2018;10(441):eaao6459.

Medical University of South Carolina, Ralph H. Johnson VA Medical Center.

After ischemic stroke, pathologic activation of the complement system promotes post-stroke pathogenesis, worsening long-term motor and cognitive neurological impairment. Complement is activated by IgM antibodies that recognize post-stroke neoepitopes expressed in the brain. In this study, the complement system was inhibited with the single-chain antibody B4Crry that recognizes a post-ischemic neoepitope. Systemic administration of B4Crry demonstrated that this antibody specifically targeted ischemic cells and inhibited pathologic complement and microglial activation, resulting in motor and cognitive recovery. Gene expression profiling of 561 immune-related genes using the nCounter Mouse Immunology Panel identified that this complement inhibition prevented the propagation of chronic neuroinflammation and neurodegeneration signaling. In adult and aged mice, the therapeutic window of B4Crry was at least 24 hours after stroke, compared to a window of only a few hours with traditional treatments. Notably, the epitope recognized by B4Crry was overexpressed in the post-ischemic brains of acute stroke patients, suggesting the translational potential of this approach.

[Postnatal human enteric neurospheres show a remarkable molecular complexity](#)

Schmitteckert S et al. Neurogastroenterol Motil. 2019;31(10):e13674.

Heidelberg University Hospital, University Children's Hospital Basel, Translational Centre Regenerative Therapies Wuerzburg, Heidelberg University.

The enteric nervous system is a network of neurons and glial cells that coordinate gastrointestinal functions, and its aberrations can cause enteric neuropathies. This study investigated the cellular composition of enteric neurospheres (e.g., neural crest-derived stem cells and enteric neuronal progenitor cells). Enteric neurospheres and corresponding archived specimens from donors were molecularly evaluated with nCounter gene expression profiling using a Custom CodeSet. The data revealed an extensive heterogeneous cellular composition. Among the multipotent stem cell, progenitor cell, neuronal, glial, muscle and epithelial cell markers, the pluripotency marker POU5F1 (OCT4) was expressed at relatively high levels in enteric neurospheres. Immunoreactivity for GPR49, CgA, VIL1 was observed in submucosal and myenteric plexus regions of donor specimens and enteric neurospheres, while OCT4-positive cells were detectable only in enteric neurospheres. Collectively, the assessment of molecular signatures can facilitate the standardized characterization of enteric neurospheres as well as the development of cell replacement therapies to improve enteric neuronal dysfunction.

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