C11 Astrocytes in neurodegenerative disease processes

C11.A
GLIAL SIGNALING, TNF-α AND DOPAMINERGIC NEURODEGENERATION

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The pathogenic mechanisms underlying Parkinson's disease (PD) remain enigmatic. To identify early molecular events associated with PD, we profiled genomic and proteomic changes in the MPTP mouse model of PD. Specifically, we focused on the role of TNF-α, IL-1B and IL-6, since enhanced expression of these proinflammatory cytokines has been found in association with glial cells of patients with PD. MPTP caused a time-dependent increase in the mRNA expression of these cytokines in striatum, but not in hippocampus, and their expression preceded striatal dopaminergic degeneration (loss of dopamine and tyrosine hydroxylase), activation of JAK/STAT3 pathway and astrogliosis (upregulation of GFAP). Deficiency of the IL-6 gene did not alter striatal nerve terminal loss, but attenuated astrogliosis. However, in transgenic mice lacking TNF receptors (TNFR-DKO), loss of striatal dopaminergic markers, phosphorylation of STAT3, upregulation of GFAP and astrocyte hypertrophy were nearly abolished. Interestingly, the lack of TNF receptors exacerbated hippocampal neuronal damage (increased Fluoro Jade-B staining and loss of MAP-2 immunoreactivity) after MPTP. These findings implicate a region-specific role for TNF-α in the brain: a promoter of neurodegeneration in striatum and a protector against neurodegeneration in hippocampus. From a Parkinson's disease perspective, these findings are suggestive of a primary role for TNF-α in the pathogenesis of this disorder. As deficiency of TNF receptors attenuated phosphorylation of JAK-STAT3 and upregulation of GFAP, the findings implicate these signaling pathways in upregulation of GFAP. Since the activation of these pathways are early events in MPTP neurotoxicity, they may serve as potential therapeutic targets for modulation of neuronal loss and/or glial response following dopaminergic neurodegeneration.

C11.B
SIGNAL TRANSDUCTION IN THE ASTROGLIAL REACTION TO ISCHEMIC INJURY

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Ischemia/reperfusion injury of CNS results in astrogliosis, a cellular response characterized by increases in GFAP production and cellular hypertrophy. The family of interleukin-6 (IL-6) cytokines promotes the reactive transformation of astrocytes. Janus kinase signal transducer and activator of transcription (JAK–STAT) is an important downstream signal pathway of gp130, shared signal-transducing receptor of IL-6 family. Here, signalling modules linked to induction of reactive gliosis in *in vivo* ischemic model has been studied. There is coordinated and long-lasting upregulation of gp130 and STAT3 activation in reactive astrocytes of the post-ischemic hippocampus, suggesting that they may be involved in the astrocytic response to an ischemic insult. Nearly coinciding with the time course of gp130 expression and STAT3 activation, the suppressors of cytokine signaling3 and STAT3-interacting protein regulating cytokine-activated JAK/STAT signalling are increased in reactive astrocytes, indicating that they may be involved in the regulation of STAT signalling in the astrocytic response to an ischemic insult. Upregulation of gp130 and STAT3 in reactive astrocytes following ischemic preconditioning, indicating that this signal pathway is also involved in the astroglial reaction to ischemic preconditioning. In addition, increased phosphorylation of phosphatase and tensin homolog deleted on chromosome 10 (PTEN) and Akt in reactive astrocytes of the post-ischemic hippocampus, suggests that the PTEN may be also involved in the astroglial reaction as an upstream regulator for Akt.

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C11.C
ETHANOL-INDUCED INFLAMMATORY MEDIATORS IN BRAIN AND IN ASTROCYTES

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Glial swelling and astrogliosis are triggered in the nervous system by inflammation and trauma, and may lead astrocytes to produce cytokines, inducible nitric oxide synthase (iNOS) and cyclooxygenase 2 (COX-2), which are proinflammatory and can cause damage. Since acute and chronic ethanol treatments can result in brain damage and neurodegeneration, we tested the hypothesis that activation of glial cells by ethanol would induce stimulation of signalling pathways and inflammatory mediators in brain, and would cause neurotoxicity. Treatment of cultured astrocytes with 50 mM ethanol causes up-regulation of NO production and of iNOS and COX-2 expression, measured as mRNA and as protein, with peaks at 30 min and after 24 h of ethanol treatment, and occurring concomitantly with the activation of NFkappaB, supporting the involvement of this transcription factor in iNOS and COX-2 induction. Furthermore, chronic ethanol intake by rats or chronic ethanol exposure of cultured astrocytes up-regulates iNOS, COX-2 and IL-1β in the rat cerebral cortex and in the cultured astrocytes and these effects concomitantly occur with the stimulation of IRAK and MAP kinases ERK1/2, p-38 and JNK, and with the downstream activation of the oxidant-sensitive transcription factors NF-kappaB and AP-1. These effects are associated with an increase in caspase-3 and in apoptosis. These results indicate that ethanol stimulates glial cells, up-regulating the production and the expression of inflammatory mediators in the brain, and activating signalling pathways and transcription factors involved in inflammatory damage and cell death.

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C11.D
METAL ACCUMULATION BY ASTROCYTES: RELATIONSHIP TO DISEASE

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Astrocytes are sites of deposition for toxic metals, such as lead (Pb), manganese (Mn), and copper (Cu), a role that may be related the neurodegenerative disease etiologies. Three new studies from our lab-