

Traumatic Brain Injury May Increase the Risk for Frontotemporal Dementia through Reduced Progranulin

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Key Words

Frontotemporal dementia · Progranulin · Traumatic brain injury · Microglia · Elastase

Abstract

Frontotemporal lobar degeneration with TAR-DNA-binding protein inclusions (FTLD-TDP) is the most common pathological subtype of frontotemporal dementia (FTD). Mutations leading to a loss of function in the progranulin gene (*PGRN*) are the most common known cause of FTLD-TDP. In agreement with the proposed loss of function disease mechanism, several groups have reported decreased plasma levels of PGRN in patients carrying *PGRN* mutations compared to individuals without *PGRN* mutations. We propose that traumatic brain injury (TBI), an environmental factor, may also increase the risk of FTD by altering PGRN metabolism. TBI may lead to an increase in the central nervous system levels of microglial elastases, which proteolyze PGRN into proinflammatory products called granulins causing a reduction in PGRN levels. Hence, inhibiting microglial activation may have an important implication for the prevention of FTD in patients with TBI.

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Frontotemporal dementia (FTD) is the second most common form of dementia in individuals under the age of 65 years. Frontotemporal lobar degeneration (FTLD)

with neuronal inclusions of the TAR-DNA-binding protein 43 (TDP-43) is the most common pathological subtype of FTD (FTLD-TDP). Mutations leading to a loss of function in the progranulin gene (*PGRN*) are the most common known cause of FTLD-TDP [1].

PGRN codes for the protein PGRN. In agreement with the proposed loss of function disease mechanism, several groups have reported decreased plasma levels of PGRN in patients carrying *PGRN* mutations compared to individuals without *PGRN* mutations [1, 2]. Finch et al. [1] further observed that there may be a discrepancy in the PGRN mRNA levels and plasma PGRN levels in *PGRN* mutation carriers, the latter being further reduced. This finding suggests that apart from haploinsufficiency of PGRN, these individuals may also have an abnormal PGRN metabolism whereby the processing of PGRN is altered.

Traumatic brain injury (TBI) remains the only established environmental risk factor of FTD. A retrospective case-control analysis showed that patients with FTD are 3.3 times more likely to have experienced a head trauma as compared to normal age-matched controls [3]. Based on recent findings, we hypothesize that TBI may increase the risk of FTD by modulating PGRN processing and expression.

PGRN is a pleiotropic protein that has wide-ranging functions both in the periphery and the central nervous system (CNS). In the periphery, PGRN is expressed in epithelial and hemopoietic cells and is implicated in multiple inflammatory processes, i.e. tissue repair, wound

healing and tumorigenesis [4]. The expression and functions of PGRN in the CNS are more complicated. In the embryonic brain, PGRN is abundant and is involved in sexual differentiation of the brain [5]. In the adult brain, PGRN expression is limited to microglia and certain neuronal populations: pyramidal neurons in the neocortex and hippocampus and Purkinje cells in the cerebellum. PGRN has been suggested to function in neuronal repair and growth in the adult brain and spinal cord [6].

The function of PGRN is regulated by an interaction between elastases and secretory leukocyte protease inhibitor in the periphery. Elastases secreted by neutrophils cleave PGRN into smaller peptides called granulins (GRNs). PGRN and GRNs have opposing properties: PGRN is anti-inflammatory, whereas GRNs are proinflammatory. Elastase cleavage of PGRN is inhibited by secretory leukocyte protease inhibitor secreted by macrophages and neutrophils [4]. There is currently limited information about the regulation of PGRN during inflammatory processes in the CNS. However, given the non-neuronal origin of microglia, a mechanism similar to the periphery is likely to exist. It has been hypothesized that release of elastases by microglia during CNS injury or inflammation may cleave PGRN into proinflammatory GRNs. This cleavage may be inhibited by secretory leukocyte protease inhibitor released by astrocytes [6].

There is evidence to suggest that the CNS levels of elastase increase after spinal cord trauma and stroke [7, 8]. An increase in elastase levels is also likely after TBI as it leads to activation of microglia, which in turn secrete multiple cytokines including elastase [9]. This raises the

possibility that TBI may cause an increase in elastases, which would result in a reduction in the levels of PGRN and an increase in the proinflammatory GRNs. Hence, TBI can potentially induce a 'PGRN insufficiency' state leading to a greater susceptibility to FTD. We also hypothesize that this effect will be pronounced many folds in individuals carrying a *PGRN* mutation, who already suffer from PGRN haploinsufficiency.

TBI is a known environmental risk factor for Alzheimer's disease, Parkinson's disease and other neurodegenerative conditions, some of which do not involve a *PGRN* mutation [10]. The role of TBI in the pathogenesis of FTD is also likely to be multifactorial and the lowered levels of PGRN might just be one element. However, this pathway may be important from a therapeutic point of view. Recently, Chung et al. [11] described an important pathway of microglial activation in the CNS. They showed that microglial activation secondary to TBI can be significantly reduced by administration of metallothionein. In the future, individuals with TBI might be given metallothionein and other potent inhibitors of microglia in order to reduce the production of elastases. This would prevent abnormal metabolism of PGRN and avoid the reductions in PGRN that may increase the susceptibility to FTD after TBI.

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References

- 1 Finch N, Baker M, Crook R, Swanson K, Kuntz K, Surtees R, Bisceglia G, Rovelet-Lecrux A, Boeve B, Petersen RC, Dickson DW, Younkin SG, Deramecourt V, Crook J, Graff-Radford NR, Rademakers R: Plasma progranulin levels predict progranulin mutation status in frontotemporal dementia patients and asymptomatic family members. *Brain* 2009;132:583–591.
- 2 Ghidoni R, Benussi L, Glionna M, Franzoni M, Binetti G: Low plasma progranulin levels predict progranulin mutations in frontotemporal lobar degeneration. *Neurology* 2008;71:1235–1239.
- 3 Rosso SM, Landweer EJ, Houterman M, Donker Kaat L, van Duijn CM, van Swieten JC: Medical and environmental risk factors for sporadic frontotemporal dementia: a retrospective case-control study. *J Neurol Neurosurg Psychiatry* 2003;74:1574–1576.
- 4 Ahmed Z, Mackenzie IR, Hutton ML, Dickson DW: Progranulin in frontotemporal lobar degeneration and neuroinflammation. *J Neuroinflammation* 2007;4:7.
- 5 Suzuki M, Yoshida S, Nishihara M, Takahashi M: Identification of a sex steroid-inducible gene in the neonatal rat hypothalamus. *Neurosci Lett* 1998;242:127–130.
- 6 Eriksen JL, Mackenzie IR: Progranulin: normal function and role in neurodegeneration. *J Neurochem* 2008;104:287–297.
- 7 Taoka Y, Okajima K: Spinal cord injury in the rat. *Prog Neurobiol* 1998;56:341–358.
- 8 Shimakura A, Kamanaka Y, Ikeda Y, Kondo K, Suzuki Y, Umemura K: Neutrophil elastase inhibition reduces cerebral ischemic damage in the middle cerebral artery occlusion. *Brain Res* 2000;858:55–60.
- 9 Israelsson C, Wang Y, Kylberg A, Pick CG, Hoffer B, Ebendal T: Closed head injury in a mouse model results in molecular changes indicating inflammatory responses. *J Neurotrauma* 2009, Epub ahead of print.
- 10 Kiraly M, Kiraly SJ: Traumatic brain injury and delayed sequelae: a review – traumatic brain injury and mild traumatic brain injury (concussion) are precursors to later-onset brain disorders, including early-onset dementia. *Sci World J* 2007;7:1768–1776.
- 11 Chung RS, Leung YK, Butler CW, Chen Y, Eaton ED, Pankhurst MW, West AK, Guillemin GJ: Metallothionein treatment attenuates microglial activation and expression of neurotoxic quinolinic acid following traumatic brain injury. *Neurotox Res* 2009;15:381–389.