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Fractalkine signaling and Tau hyper-phosphorylation are associated with autophagic alterations in lentiviral Tau and $A\beta_{1-42}$ gene transfer models

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ABSTRACT

Tau hyper-phosphorylation (p-Tau) and neuro-inflammation are hallmarks of neurodegeneration. Previous findings suggest that microglial activation via CX3CL1 promotes p-Tau. We examined inflammation and autophagic p-Tau clearance in lentiviral Tau and mutant P301L expressing rats and used lentiviral $A\beta_{1-42}$ to induce p-Tau. Lentiviral Tau or P301L expression significantly increased caspase-3 activity and TNF-α, but CX3CL1 was significantly higher in animals expressing Tau compared to P301L. Lentiviral $A\beta_{1-42}$ induced p-Tau 4 weeks post-injection, and increased caspase-3 activation (8-fold) and TNF-α levels. Increased levels of ADAM-10/17 were also detected with p-Tau. IL-6 levels were increased but CX3CL1 did not change in the absence of p-Tau (2 weeks); however, p-Tau reversed these effects, which were associated with increased microglial activity. We observed changes in autophagic markers, including accumulation of autophagic vacuoles (AVs) and p-Tau accumulation in autophagosomes but not lysosomes, suggesting alteration of autophagy. Taken together, microglial activation may promote p-Tau independent of total Tau levels via CX3CL1 signaling, which seems to depend on interaction with inflammatory markers, mainly IL-6. The simultaneous change in autophagy and CX3CL1 signaling suggests communication between microglia and neurons, raising the possibility that accumulation of intraneuronal amyloid, due to lack of autophagic clearance, may lead microglia activation to promote p-Tau as a tag for phagocytic degradation.

Introduction

Tauopathies are pathologically characterized by accumulation of insoluble aggregates of hyper-phosphorylated Tau (p-Tau) in neurons and glia (Hasegawa et al., 1998; Hutton et al., 1998; Jiang et al., 2003; Poorkaj et al., 1998). Extracellular β-amyloid (Aβ) plaques and intracellular p-Tau-containing neurofibrillary tangles (NFTs) are characteristics of Alzheimer's disease (AD) (Grundke-Iqbal et al., 1986; Hardy and Allsop, 1991; Hardy and Higgins, 1992). NFTs correlate highly with the degree of dementia in AD (Braak and Braak, 1991). Other Tauopathies include progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and frontotemporal dementia with Parkinsonism linked to chromosome 17 (FTDP-17) (Bird et al., 1999; Gasparini et al., 2007). Increased Tau is also detected in Parkinson's disease (PD) brain, mainly striatum (Tobin et al., 2008). Tau binds to and stabilizes microtubules in a process regulated by phosphorylation (Lindwall and Cole, 1984). Some findings report that Tau modification affects the flux of autophagy due to destabilization of microtubules and impairment of organelle movement (Dawson et al., 2001, 2010; Gomez-Isla et al., 1997; Harada et al., 1994; Jimenez-Mateos et al., 2006), while others suggest that Tau aggregates are removed by autophagy (Dolan and Johnson, 2010; Wang et al., 2010).

In AD, Aβ and/or Tau are inflammatory stimuli that may provoke microglial activation (Ransohoff and Perry, 2009; Rogers et al., 1996). However, it is unclear whether microglial activation has beneficial or detrimental effects in the brain (Cameron and Landreth, 2010; Frank-Cannon et al., 2009; Wyss-Coray and Mucke, 2002). Fractalkine (CX3CL1) is a chemokine (Bazan et al., 1997; Harrison et al., 1998), which may regulate inflammation via neuron-microglia communication. Neurons secrete CX3CL1 (Harrison et al., 1998), which exists in both membrane-bound and soluble forms (Hatori et al., 2002). Increased levels of serum CX3CL1 are reported in patients with multiple sclerosis (Kastenbauer et al., 2003; Tong et al., 2000), traumatic brain injury (Rancan et al., 2004) and human immunodeficiency virus (HIV) with CNS complications (Sporer et al., 2003). Reduced levels of CX3CL1 receptors (CX3CR1) are also linked to age-related macular degeneration in humans (Combadiere et al., 2007).

Recent developments reveal a crucial role for the autophagy pathway and proteins involved in regulating the immune response to balance the beneficial and detrimental effects of immunity and inflammation (Lee et al., 2012; Levine et al., 2011; Saitoh and Akira, 2010). We developed several gene transfer animal models via lentiviral

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delivery of human wild type Tau and P301L, which is a Tau mutation in exon 10 at codon 301, resulting in a Pro to Leu substitution, and is associated with FTDP-17 (Mirra et al., 1999). We also used lentiviral $A\beta_{1-42}$ to induce accumulation of intracellular proteins and autophagy (Khandelwal et al., 2012; Lonskaya et al., 2013). We observed p-Tau accumulation, autophagic alterations and cell death in lentiviral gene