Involvement of exosomes in inflammatory dopaminergic neurodegeneration.

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Parkinson's disease is one of the neurodegenerative disorders, caused by progressive degeneration of dopamine (DA) neurons in substantia nigra. Microglial activation by IFNγ/LPS treatment triggers selective loss of DA neurons in midbrain slice cultures. Exosomes are regarded as a novel factor that mediates cell-to-cell interactions. In the present study, we investigated the involvement of exosomes in DA neurodegeneration triggered by microglial activation in rat midbrain slice culture. IFNγ/LPS treatment prominently elevated exosome release from midbrain slice cultures. GW4869, a neutral sphingomyelinase 2 inhibitor, decreased exosome release and prevented IFNγ/LPS-triggered DA degeneration without the inhibition of microglial activation. To directly elucidate the involvement of activated microglial-derived exosome in DA neurodegeneration, we isolated exosomes from culture media of IFNγ/LPS-treated slices and treated them to other slice cultures. Although exosomes from control slices did not affect the survival of DA neurons, exosomes from IFNγ/LPS-treated slices significantly decreased DA neurons. Microglial activation was not triggered by exosomes from IFNγ/LPS-treated slices. These findings suggest that exosomes from activated microglia directly react to neurons and mediate DA neurodegeneration.

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