● LETTER TO THE EDITOR

Naringin as a beneficial natural product against degeneration of the nigrostriatal dopaminergic projection in the adult brain

The progressive degeneration of nigral dopaminergic (DA) neurons and the biochemical reduction of striatal dopamine levels are associated with major clinical symptoms, including tremor at rest, rigidity of the limbs, slowness and paucity of voluntary movement (bradykinesia), and postural instability (a tendency to fall even in the absence of weakness or cerebellar balance disturbance) (Kim et al., 2011, 2012). These phenotypes are frequently seen in patients with Parkinson's disease (PD). We still do not fully understand the etiology of PD, which is reflected by the fact that there is no current therapy to block the neurodegeneration associated with the disease. However, accumulating evidence suggests that microglial activation (Leem et al., 2014; Nam et al., 2014; Shin et al., 2015) and insufficient support from neurotrophic factors may be crucial for the initiation and progression of PD (Kim et al., 2011, 2012; Nam et al., 2015). Microglial activation results in the production of potentially neurotoxic molecules, including inducible nitric oxide synthase (iNOS) and proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β) (Kim et al., 2010; Nam et al., 2014; Shin et al., 2015; Jang et al., 2017). Insufficient support from growth factors leads to a decrease in the activity of mammalian target of rapamycin complex 1 (mTORC1) in DA neurons (Kim et al., 2011, 2012; Jeon et al., 2015; Nam et al., 2015).

Microglia are the resident immune cells of the central nervous system (CNS) and the major cause of CNS neurotoxic inflammation in response to a variety of stimuli, including infection, trauma, and toxins (Kim et al., 2010; Shin et al., 2015). Microglia are stimulated by various activators, and undergo phagocytic morphological changes, which are characterized by an enlarged cell body and short processes (Kim et al., 2010; Shin et al., 2015). They then produce neurotoxic inflammatory cytokines such as IL-1β, TNF-α, and IL-6 (Kim et al., 2010; Jung et al., 2014; Nam et al., 2014; Jeong et al., 2015; Shin et al., 2015; Leem et al., 2016; Jang et al., 2017). In addition, activated microglia can produce reactive oxygen species (ROS) such as O_2^- and O_2^--derived oxidants, and excessive ROS production is implicated in the death of DA neurons in the adult brain (Choi et al., 2005; Kim et al., 2010; Chung et al., 2011).

mTOR kinase, which plays central roles in the integration of cell growth in response to various environmental conditions, exists in two complexes, mTOR complex 1 (mTORC1) and mTORC2 (Kim et al., 2012; Kim, 2014; Jeon et al., 2015). mTORC1 is an important mediator of protein kinase B (Akt). mTORC2 can activate Akt, which in turn can act on mTORC1. Activation of the Akt/mTOR signaling pathway enhances the activity of intracellular cell survival pathways, under a variety of conditions, including trophic factor withdrawal, ischemic shock, and oxidative stress (Cheng et al., 2011; Kim et al., 2011, 2012; Nam et al., 2015; Jeon et al., 2015). Moreover, recent reports showed that the activation of neuronal mTORC1 (a key biomolecule for neurotrophic support) by either the delivery of a specific gene or the direct administration of trophic factors, could induce protective effects against neurodegeneration in animal models of PD (Siegel and Chauhan, 2000; Allen et al., 2013; Nam et al., 2015).

As described above, a large body of experimental evidence suggests that the control of microglial activation and the induction of mTORC1 in DA neurons may be important to prevent the degeneration of DA neurons in PD. However, there is no report of a successful clinical trial with chemical compounds inhibiting microglial activation for anti-neurodegeneration in PD, and the treatment with neurotrophic factors to activate mTORC1 has a critical problem because they do not cross the blood-brain barrier, which is the membrane protecting the brain from exogenous pathogen/toxic agents through the structural and functional complex, thus direct application of neurotrophic factors to the brain is needed (Kim et al., 2012; Kim, 2014; Nam et al., 2015). Thus, we need to develop other therapeutics, which are capable to control microglial activation and induce activation of mTORC1 in DA neurons, easily reaching to the brain for PD treatment.

Using natural compounds such as phytochemicals to inhibit microglial activation and induce mTORC1 activation in adult neurons may be useful for the development of a novel protective agent for the nigrostriatal DA system in the adult brain. Moreover, phytochemicals are usually considered to be harmless to health. They are also less toxic and have fewer side effects than synthetic drugs. Among many kinds of phytochemicals, naringin is a well-known flavanone glycoside found in grapefruits and citrus fruits (Singh et al., 2003; Choi et al., 2010; Golechha et al., 2011; Rong et al., 2012; Xianchu et al., 2016). It has the ability to exert a variety of biological and pharmacological effects, including anti-inflammatory, anti-oxidant, and lipid-lowering activities (Kim et al., 2009; Choi et al., 2010; Golechha et al., 2011; Rong et al., 2012; Leem et al., 2014; Xianchu et al., 2016). Naringin has recently been considered as a potential protective agent against neurodegenerative diseases, due to its anti-oxidant and neuroprotective activities (Choi et al., 2010; Golechha et al., 2011; Leem et al., 2014; Kim et al., 2016). The anti-oxidant effects by naringin administration modulate the oxidative stress and inflammatory responses in the adult brain, and its neuroprotective effects are also controlled by the induction of neurotrophic factors and the activation of anti-apoptotic pathways (Rong et al., 2012; Leem et al., 2014; Kim et al., 2016). However, it was largely unknown whether naringin can have neuroprotective effects against degeneration of the nigrostriatal DA projection in the adult brain, which is associated with PD.

Our recent observations of the effects of naringin in animal models of PD showed that its treatment could protect the whole nigrostriatal DA projection from neurotoxicity in the adult brain (Leem et al., 2014; Kim et al., 2016). Treatment with naringin could activate mTORC1 in adult DA neurons *in vivo* (Leem et al., 2014; Kim et al., 2016), and its administration gave DA neurons the ability to produce glial cell line-derived neurotrophic factor (GDNF) which acts against degeneration of DA neurons (Leem et al., 2014; Kim et al., 2016), suggesting that it might be a beneficial natural compound for the activation of neurotrophic signaling pathways. It also attenuated microglial activation in a neurotoxin-treated animal model of PD, which consequentially produced anti-inflammatory effects such as a reduction in neurotoxic cytokines (Leem et al., 2014; Kim et al., 2016). Although treatment with naringin was not sufficient to restore the lesioned nigrostriatal DA projection in a mouse model of PD (Kim et al., 2016), these observations suggest that naringin maybe possess the ability to further prevent against neurodegeneration in PD (Leem et al., 2014; Kim et al., 2016). Currently, there is a lack of evidence of any neuroprotective role of naringin in clinical trials, and our knowledge of the

mechanisms of naringin-mediated effects in the nigrostriatal DA system is insufficient. Therefore, further studies are needed to evaluate naringin-induced effects on the adult brain in detail and to investigate whether naringin can prevent against neurodegeneration in humans. In addition, it may be worthwhile to test consistently whether other phytochemicals, which are known to have similar physiological activities to naringin (Jung et al., 2014; Jeong et al., 2015), can modulate microglial activation and insufficient neurotrophic supports in the adult brain because appropriate usage of these natural compounds may be a useful strategy to protect and maintain the nigrostriatal DA system in the adult brain.

This study was supported by grants from the Korea Healthcare Technology R&D Project, Ministry of Health & Welfare (HI15C1928) and the National Research Foundation of Korea (NRF-2017R1A2B4002675).

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***Accepted:** 2017-08-01*

***doi:** 10.4103/1673-5374.213694*
***How to cite this article:** Kim SR (2017) Naringin as a beneficial natural product against degeneration of the nigrostriatal dopaminergic projection in the adult brain. Neural Regen Res 12(8):1375-1376.*
***Plagiarism check:** Checked twice by iThenticate.*
***Peer review:** Externally peer reviewed.*

***Open peer reviewer:** Daniel M. Johnstone, University of Sydney, Australia.*

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Copyedited by Li CH, Song LP, Zhao M