NAIST® Research Highlights

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Genetics

Stress response gene underlies loss of vision

A key gene protects retina cells from oxidative stress, but also causes them to age prematurely

Age-related macular degeneration is the leading cause of severe, irreversible vision loss in people over 55. Its basis remains poorly understood, and no effective treatment exists. Recent research at NAIST has shown how a stress response gene plays a role, linking the genetic and environmental factors behind this debilitating disease.

In 2006, two research groups discovered a link between the *HtrA1* gene and age-related macular degeneration. Since then, increasing evidence has demonstrated that high *HtrA1* levels in the retinal pigment layer play a central role in the disease – but the gene's function in this tissue has remained a mystery. The retina is exposed to high levels of physiological stress in the form of oxidative damage, prompting Masashi Kawaichi's team at NAIST to investigate whether *HtrA1* activity modifies the retina's stress-response.

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NAIST researchers are studying the link between the *HtrA1* gene and stress response of the retina.

> **"We believe that the same senescence process is a major part of the physiological function of HtrA1 in ossification and its pathological function in arthritis, both of osteoarthritis and rheumatoid arthritis."**

The team used cultures of embryonic mouse cells and human retinal cells to test how *HtrA1* responds to oxidants such as hydrogen peroxide. Their experiments showed that cells under oxidative stress activate *HtrA1* expression; this protects them from dying due to the stress, but also causes them to senesce earlier[1]. The researchers believe that increased senescence resulting from persistent exposure to oxidative stress eventually causes retinal damage in the form of macular degeneration.

HtrA1 is also expressed in a variety of other tissues, such as cartilage, ligaments and tendons, and has been linked with diseases from pre-eclampsia to arthritis. Oxidative stress is known to play a role in causing arthritis, raising the possibility that similar mechanisms may underlie the two conditions. "We believe that the same senescence process is a major part of the physiological function of *HtrA1* in ossification and its pathological function in arthritis, both of osteoarthritis and rheumatoid arthritis," says Kawaichi.

Unfortunately, the diversity of *HtrA1*'s roles also presents a challenge to efforts to transform these findings into improved treatments. "Some researchers believe that *HtrA1* is a tumour suppressor gene. A decrease in *HtrA1* expression levels is frequently associated with malignant transformation or metastasis of ovary cancers, gastric cancers, melanoma, and so forth," explains Kawaichi.

"General administration of potent inhibitors of *HtrA1* could have side effects, particularly in the long term. If we could have an effective inhibitor which could be used for ocular instillation or topical injection into joints, we hope those would provide promising remedies to these prevalent diseases," Kawaichi adds.

Reference

1. Supanji, Shimomachi, M., Hasan, M. Z., Kawaichi, M. & Oka, C. *HtrA1* is induced by oxidative stress and enhances cell senescence through p38 MAPK pathway. *Experimental Eye Research* **112,** 79-92 (2013).

More information about the group's research can be found at the Gene Function in Animals Laboratory webpage:
http://bsw3.naist.jp/eng/courses/courses206.html