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.

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. 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