A HOLISTIC APPROACH TO HEALTH IN JAPAN

RESEARCH INTO PHYSICAL AND MENTAL HEALTH at different life stages is helping to improve quality of life.

One in ten people in Japan are over the age of 80, while three in ten are over 65, making it the country with the most aged population in the world. This means healthy longevity and preserving wellness throughout later life is a topic of crucial importance in Japan.

Kanazawa University in Ishikawa is at the forefront of groundbreaking initiatives on physical and mental health in old age, but also earlier in life too. Scientists at the university are addressing challenges associated with health across different life stages through research on combating cancer recurrence, reversing cellular ageing, and improving children's wellbeing.

CURBING RECURRENCE

Advances in diagnostic techniques and molecular targeted drugs have helped make many cases of cancer curable. However, the number of deaths from breast cancers — the most diagnosed cancer among women worldwide — is continuing to rise, says Noriko Gotoh, a cancer biologist at Kanazawa University's Cancer Research Institute. This is partially due to recurrence of aggressive triple-negative breast cancers, which account for 15% of breast cancer cases.

"Unlike other cancers, it's not unusual for breast cancers to recur after a decade or even two," Gotoh says. "Living in fear of recurrence for such long periods is upsetting and detrimental to survivors' quality of life."

One problem had been that the subtype of stem cells responsible for the recurrence of triple-negative breast cancer had never been isolated, and their characteristics were wrapped in mystery. That was until 2023, when Gotoh and her collaborators identified them for the first time — a breakthrough for understanding drug-tolerant cells that persist after initial treatment.

Gotoh's team found that these cells, which they named ancestor-like cancer stem cells, have a high expression of the membrane protein FXYD3, which maintains the plasma membrane pump activity, exchanging sodium and potassium ions in and out of cells[1].

They also discovered that cardiac glycosides, which inhibit sodium–potassium exchange pump activity and are used to treat heart failure, made ancestor-like cancer stem cells susceptible to anticancer drugs in mice.

"As cardiac glycosides have been in use for a long time, we have extensive knowledge about their side effects, which means we could bring new treatments for patients relatively quickly," says Gotoh. "It would be a game changer for reducing the chances of recurrence if we can find an effective combination of cardiac glycosides and anticancer drugs."

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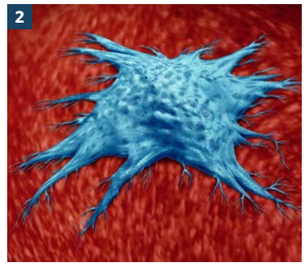

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▲ **1. Early diagnosis of autism will help neurodiverse children receive the individualized support they need.**
2. Senescent cells play a critical role in many diseases. Yoshikazu Johmura and his team are exploring ways to rejuvenate them.
3. Takashi Wada, president of Kanazawa University.

REJUVENATING AGED CELLS

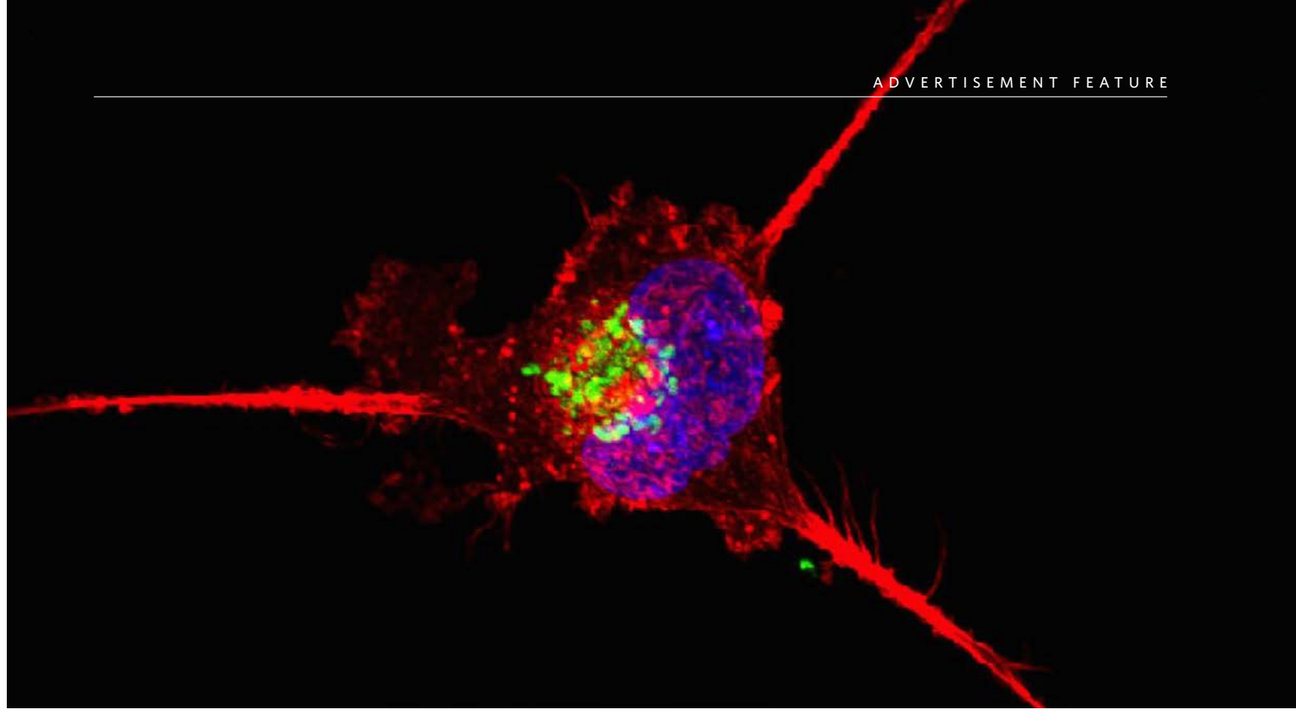
The risk of getting cancer increases with age. One reason for that is because aged cells, known as senescent cells, play a critical role in causing and worsening age-related diseases, including cancers. Yoshikazu Johmura, a professor at Kanazawa's Cancer Research Institute, is spearheading senotherapy, an emerging field aiming to prevent and treat the ageing of cells.

Some senescent cells are unable to replicate and some secrete molecules that trigger inflammation and damage DNA. Johmura's team has been focusing on ways to remove senescent cells by inducing cell death, particularly by disrupting their metabolic processes and making them more susceptible to the body's innate immune response.

Johmura found that different cell types within a given tissue become senescent, each undergoing significant functional changes unique to their cell type, which then influence their contribution to disease[2]. For example, liver Kupffer cells, which protect the organ from infections, begin releasing more molecules associated with inflammation as they transform into senescent cells.

On the other hand, liver sinusoidal endothelial cells, which serve as a barrier between the blood and other liver cells, begin functioning in ways similar to immune cells. "Understanding the diversity of senescent cells will become increasingly important for developing treatments that target senescent cells," says Johmura.

Furthermore, Johmura discovered that senescent cells also exist in non-dividing cell types such as nerve cells. "Removing senescent cells could irreparably damage tissues with non-dividing cells," says Johmura. "Therefore, rejuvenating cells, or better still, preventing cell ageing, could become a hot topic of research." These discoveries will ultimately lead to the development of drugs that help with age-associated diseases.



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▲ **A triple-negative breast cancer cell undergoing cell death. Noriko Gotoh's team at Kanazawa University's Cancer Research Institute has identified the subtype of stem cells that cause the recurrence of triple-negative breast cancer cells.**

NEURODIVERSITY

But it is not enough to merely improve physical health in old age, mental health, across various life stages, matters too. As part of the Japanese government's Moonshot Program — which is tackling social and other issues through innovative research — Mitsuru Kikuchi, a psychiatrist in the Graduate School of Medical Sciences and his collaborators hope to visualize children's neurodiversity with 'magnetoencephalography', which measures magnetic fields arising from electrical currents in the brain.

> **"REJUVENATING CELLS, OR BETTER STILL, PREVENTING CELL AGEING, COULD BECOME A HOT TOPIC OF RESEARCH."**

For this initiative, the team is attempting to evaluate autism spectrum disorder. Their findings so far suggest that children with social communication difficulties, who do not fully meet the criteria for autism, still show brain network patterns at certain brain-wave frequencies that have similarities to the brain network patterns seen in children with autism[3].

The researchers are also studying the brain patterns of neurodiverse children as they interact with their caregivers. Kanazawa University is the only location in Japan with a magnetoencephalography system capable of simultaneously recording brain activity in both children and adults, allowing them to observe how interactions affect brain activity.

As the mechanisms of autism still remain unclear, Kikuchi warns against using brain recordings as definitive indicators of autism. "Such data, however, add a new perspective to current survey-based diagnoses, helping increase diagnosis accuracy," he explains. "Timely diagnosis is essential before children enter primary school to prevent them from becoming socially isolated, especially as learning environments in Japan emphasize conformity." Early diagnosis allows for the creation of individualized learning support plans, making school a more comfortable environment for people with autism.

Kikuchi and his team have partnered with local schools to assess the effects of music therapy and to investigate situations in which school children feel relaxed or stressed, through monitoring biological indicators such as hormone levels and heart rate. Through the combination of these initiatives, the researchers hope to help cultivate an environment for neurodiverse people to tap into their strengths.

All three projects are examples of ways that Kanazawa University is seeking to promote the welfare of society. "We will contribute to health science in the future society by advancing research on these topics," says university president Takashi Wada. ■

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