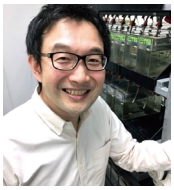
Understanding the fundamental principles of aging and cancer for development of the preemptive medicine



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Abstract

For preventing age-related decline and extending healthy life expectancy, preemptive medicine interfering the initial processes of aging and age-related diseases would be effective. To develop such medical approach, the processes priming aging and age-related diseases should be clarified. Our laboratory is tackling to make clear them using characteristic model animals and state-of-the-art technologies. Recently, we discovered that animal tissues possess an anti-cancer mechanism which sense and eliminate precancerous cells in an immune cell-independent manner and dysregulation of this mechanism primes tumorigenesis, using zebrafish imaging analyses. In addition, we also succeeded in development of a platform for high-resolution screening and mechanistic elucidation of aging regulators using an ultra-short-lived killifish *Nothobranchius furzeri* (*N. furzeri*), which has the shortest lifespan among laboratory animals and exhibits aging phenotypes similar to those of humans.

Background & Results

Cancer is one of the major age-related diseases. Most cancers are thought to arise through oncogenic cell generation followed by additional mutations. How a new oncogenic cell primes tumorigenesis by acquiring additional mutations remains unclear. To make clear them, we developed a new experimental system for exploring the mechanisms of primary tumorigenesis using zebrafish, a model animal suitable for live imaging (Fig 1). Our zebrafish imaging analyses revealed that a newly emerged precancerous cell with the Ras^{G12V} mutation becomes senescent and is eliminated from the epithelia, which is prevented by adding a TP53 gain-of-function mutation ($TP53^{R175H}$) into Ras^{G12V} cells. Surviving Ras^{G12V}-$TP53^{R175H}$ double-mutant cells senesced and secreted inflammatory molecules that convert neighboring normal cells into either senescent or proliferative cells, generating a heterogeneous primary tumor. Interestingly, although precancerous cells were efficiently eliminated, tissue damage including inflammation and senescence prevented the elimination of precancerous cells and stimulated the primary tumorigenesis. Thus, we revealed the novel mechanisms controlling the initial step of tumorigenesis (Fig 2; Nature Commun 2019; 2022).

We are also tackling to clarify the fundamental mechanisms of systemic aging using an ultra-short-lived killifish *N. furzeri* as a model. We successfully set up a large-scale breeding facility for *N. furzeri* and establish rapid reverse genetics methods for creating knockout and knock-in reporter *N. furzeri* (Sci Rep 2022). Utilizing these methods, we have identified several new factors that control systemic aging (in preparation).

Significance of the research and Future perspective

Conventional aging studies using mouse models require a considerable amount of time owing to the slow pace of mouse aging. In addition, mouse is not suitable for live imaging analysis. Therefore, these tend to focus on analyzing the factors related to known theories of aging and cancer. By utilizing characteristic animals including *N. furzeri* and zebrafish, we aim to accelerate the clarification of fundamental mechanisms controlling the initial step of aging and cancer. Based on our discoveries, we would like to develop preemptive medicine preventing aging and cancer to extend human health span.

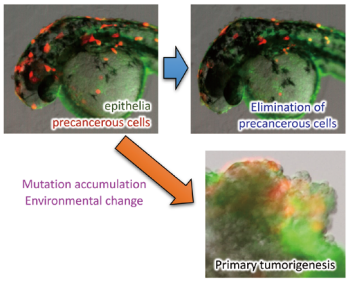

Fig 1) Zebrafish imaging system for investigating the mechanismsunderlying primary tumorigenesis

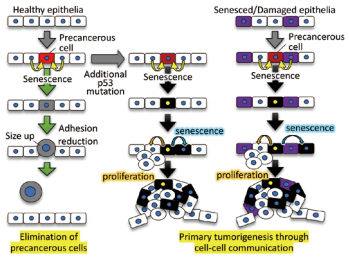

Fig 2) Cell-Cell communication-driven mechanisms of primary tumorigenesis

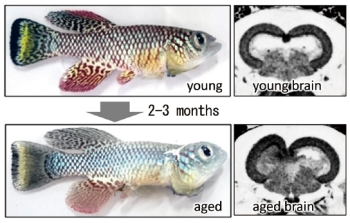

Fig 3) Killifish becomes senescent within several months

Patent	
Treatise	Haraoka, Yukinari et al. Zebrafish imaging reveals TP53 mutation switching oncogene-induced senescence from suppressor to driver in primary tumorigenesis. Nature Commun. 2022, 13(1), 1417. doi: 10.1038/s41467-022-29061-6 Oginuma, Masayuki et al. Rapid reverse genetics systems for Nothobranchius furzeri, a suitable model organism to study vertebrate aging. Sci Rep. 2022, 12(1), 11628. doi: 10.1038/s41598-022-15972-3 Akieda, Yuki et al. Cell competition corrects noisy Wnt morphogen gradients to achieve robust patterning in the zebrafish embryo. Nature Commun. 2019, 10(1), 4710. doi: 10.1038/s41467-019-12609-4
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Keyword	cancer, systemic aging, preemptive medicine, mechanisms which control the initial step of aging and cancer.