REVIEW ARTICLE

INVESTIGACIÓN en DISCAPACIDAD

Vol. 8, No. 3
September-December 2022
pp 124-131
doi: 10.35366/107513

Zebrafish: modeling senescence in the context of disease and regeneration

Pez cebra: modelado de senescencia en el contexto de la enfermedad y la regeneración

Samantha Carrillo-Rosas,* Alfonso D Ríos-Pérez,* Cecilia Zampedri*

Keywords:
senescence,
disease modeling,
zebrafish, cancer,
neurodegeneration,
heart regeneration.

Palabras clave:
*senescencia,
modelado de enfermedades,
pez cebra, cáncer,
neurodegeneración,
regeneración cardiaca.*

Abstract

Cellular senescence is a natural biological process characterized by a permanent and irreversible state of cellular arrest, mitochondrial alteration, and secretion of senescence-associated phenotype (SASP) components. Several factors can induce senescence, including but not limited to DNA damage, oxidative stress, and neuroinflammation, these factors have also been linked to several disorders such as Alzheimer's, Parkinson's, cancer, among others. The increased presence of senescent cells among different diseases suggests the importance of senescence in the pathophysiology of a great number of disorders, thus the need for different models that could help deepen our understanding of the molecular mechanisms of senescence, identify possible targets for therapeutic interventions, and arising challenges. In addition to in vitro models, most senescent research has come from classical model species, i.e., mouse (Mus musculus) and rat (Rattus norvegicus). However, senescence is highly conserved; different studies have shown that senescent cells seem to accumulate in all vertebrate organisms and that several associated genes show similar expression patterns, opening the door to new vertebrate models. The zebrafish has become a strong emerging model for different diseases, such as cancer, inflammation, neurodegeneration, among others; it shares multiple advantages with classical models, such as well-established genome editing tools and a fully sequenced genome. Additionally, zebrafish exhibit multiple advantages, including high fecundity for robust statistical analysis, external fertilization, and optical transparency that enables powerful imaging capabilities and makes it a versatile model for experimental manipulation and structural visualization. Here we present the zebrafish as a model that can contribute significantly to our understanding of the processes involved in senescence and age-related diseases.

Resumen

La senescencia celular es un proceso biológico natural caracterizado por un estado permanente e irreversible de arresto celular, alteraciones mitocondriales y secreción de componentes del fenotipo asociado a la senescencia (SASP). Varios factores pueden inducir la senescencia, incluidos el daño al ADN, estrés oxidante y neuroinflamación; estos factores también se han relacionado con varios trastornos como el Alzheimer, el Parkinson, el cáncer, entre otros. La mayor presencia de células senescentes entre diferentes enfermedades sugiere la importancia de la senescencia en la fisiopatología de un gran número de trastornos, por lo tanto, la necesidad de diferentes modelos que podrían ayudar a profundizar nuestra comprensión de los mecanismos moleculares de la senescencia, identificar posibles objetivos para intervenciones terapéuticas y los desafíos que surgen. Además de los modelos in vitro, la mayoría de las investigaciones senescentes provienen de especies modelo clásicas, es decir, ratón (Mus musculus) y rata (Rattus norvegicus). Sin embargo, la senescencia está muy conservada;

* Multidisciplinary Zebrafish Laboratory, Department of Bioengineering. School of Engineering and Sciences, Tecnológico de Monterrey. Mexico City Campus. Mexico City, Mexico.

Ejemplar de uso personal

How to cite: Carrillo-Rosas S, Ríos-Pérez AD, Zampedri C. Zebrafish: modeling senescence in the context of disease and regeneration. Invest Discapacidad. 2022; 8 (3): 124-131. https://dx.doi.org/10.35366/107513

www.medigraphic.com/rid

Correspondence:
Cecilia Zampedri, MD
E-mail: cecilia.zampedri@tec.mx

Received: May 24, 2022
Accepted: July 05, 2022

diferentes estudios han demostrado que las células senescentes parecen acumularse en todos los organismos vertebrados y que varios genes asociados muestran patrones de expresión similares, abriendo la puerta a nuevos modelos vertebrados. El pez cebra se ha convertido en un fuerte modelo emergente para distintas enfermedades, como el cáncer, la inflamación, la neurodegeneración, entre otras; comparte múltiples ventajas con los modelos clásicos, como herramientas de edición de genomas bien establecidas y un genoma completamente secuenciado. Además, el pez cebra exhibe múltiples ventajas, incluida una alta fecundidad para un análisis estadístico sólido, fertilización externa y transparencia óptica que permite potentes capacidades de imagen y lo convierte en un modelo versátil para la manipulación neuroexperimental y la visualización estructural. Aquí presentamos el pez cebra como un modelo que puede contribuir significativamente a nuestra comprensión de los procesos involucrados en la senescencia y las enfermedades relacionadas con la edad.

INTRODUCTION

The process of senescence was first described by Hayflick L, et al. (1961), when they reported that human fibroblasts cultured *in vitro* reached a state after a determined number of passages where the cells remained viable but lacked the capacity to divide any further.

Senescence has been described as a permanent cell-cycle arrest in response to oncogene induced DNA damage. In consequence, a senescent cell loss its proliferative potential and provokes a permanent arrest.[1-3]

Additionally, multiple age-related conditions such as atherosclerosis, glaucoma, cataracts and type 2 diabetes present an increased number of senescent cells.[4,5]

This process is highly conserved among vertebrates; different studies have shown that senescent cells seem to accumulate in all vertebrate organisms and that several associated genes show similar expression patterns in different tissues, including zebrafish.[6]

Zebrafish is a popular model for vertebrate development and genetic studies.[7] Since the introduction of the zebrafish as a model in 1974 by George Streisinger,[8] zebrafish has become the second most used vertebrate in research and an invaluable model for translational research.[9] The reason for this popularity is the many advantages that this model has. The zebrafish genome is well curated by multiple databases, allowing the identification of zebrafish orthologs for most human genes. Approximately 72% of human genes have at least one ortholog in the zebrafish genome, with 84% of known human disease-causing genes having a zebrafish counterpart.[10] Combined with numerous techniques that have been successfully adapted to this model has enable relatively straightforward reverse genetic manipulation of genes of interest generating a great number of models for diseases of interest.[11,12] Additionally, the zebrafish has high fecundity, rapid and external development, a small size and an optical clearance of the embryo. Altogether makes the zebrafish an excellent complementary model to the mouse.

SENESCENCE AND CANCER MICROENVIRONMENT

Different reports have demonstrated that accumulated senescent cells in our body are related to the progression of many types of cancer.[13-16] We know that cellular senescence is necessary to prevent cell proliferation in an uncontrolled manner leading to cancer development through irreversible cell cycle arrest. However, accumulated senescent cells secrete a variety of proteins, such as inflammatory cytokines, chemokines, growth factors, and matrix metalloproteinases. This phenomenon is called the senescence-associated secretory phenotype (SASP). Several SASP factors can reinforce the senescence program in an autocrine manner, influence the tissue microenvironment in a paracrine manner,[17,18] and provoke immune surveillance of senescent cells, leading to the elimination of senescent cells by NK cells or macrophages recruited through SASP induction.[19] Conversely, senescent cells in the tumor microenvironment (TME) showing the SASP help to promote tumor proliferation and metastasis in various types of cancer.[20]

Cancer therapy, either ionizing radiation or chemotherapy, induces cellular senescence, the so-called therapy-induced senescence (TIS). Whether TIS is a pro or anti-tumorigenic process is currently an open question. TIS can be induced in immortal and transformed cancer cells by selected anticancer compounds or radiation, and accumulated data indicate that TIS may produce reduced toxicity-related side effects and increased tumor-specific immune

www.medigraphic.org.mx

activity. But we also know that the senescent cells are metabolically active and secrete a collection of growth factors, cytokines, proteases, and matrix-remodeling proteins collectively defined as SASP. Through SASP, senescent cells modify their microenvironment and engage in a dynamic dialog with neighbor cells. Senescence of neoplastic cells, at least temporarily, reduces tumor expansion, but SASP of senescent cancer cells as well as SASP of senescent stromal cells in the tumor microenvironment may promote the growth of more aggressive cancer subclones.[21] Cellular senescence in stromal cells is one of the reasons for therapeutic resistance in advanced cancer; therefore, it is an interesting phenomenon to address for finding effective cancer treatment strategies.[22] Current research suggests that therapy-induced senescence (TIS) represents a novel functional target that may improve cancer therapy.

The comprehensive study of cancer using model organisms is one of the most interesting strategies in the search for better therapies and therapeutic targets. The zebrafish has become one of the favorite organisms since several of the genetic and molecular techniques developed in recent times can be applied to model whole diseases or discrete disease-related processes using this organism.

Zebrafish xenotransplantation represents a step forward in modeling the complexity of cancer tumors, and the involvement of a particular gene in each of the events that accompany cancer, as cells are implanted into a living organism in which many types of dynamic interactions can occur. In zebrafish, with all functional organs, tumors can engage in both local and systemic cell-cell interactions, shaping tumor progression. These interactions occur between tumor and host and vice versa, with long-distance communication, allowing recapitulation of cancer features such as cell migration, invasion, metastasis, angiogenesis, and immune evasion that are not possible to observe *in vitro*. Zebrafish cell xenotransplantation studies have the advantage of maintaining the effects of the microenvironment in cell communication and cancer progression, even when there are inter species differences.[23] When cancer cells are implanted, many different zebrafish cells are recruited to the tumor site following tumor instructions.[24,25] Zebrafish xenotransplantation of cancer cells enabled the discovery of a new mechanism of metastatic niche formation, and the roles of macrophages in this process were described.[24] These latest findings suggest that the zebrafish xenotransplantation model will facilitate the study of processes occurring around several cellular components of the tumor microenvironment such as stromal cells, endothelial cells, and mesenchymal stem cells that impact cancer progression, such as the induction of the secretory phenotype associated with cellular senescence during cancer.

Finally, drug sensitivity profiling of cancer cells using the zebrafish xenotransplantation model allows the assessment of pharmacokinetics, pharmacodynamics, toxicity and senescence-inducing activity in a whole living organism, and in a short time. *In vivo* testing has great advantages over *in vitro* assays. E.g., to produce *in vivo* phenotypes, compounds must be absorbed, reach targets, circumvent elimination, and cannot be too toxic, otherwise the animal will not survive. The complexity of *in vitro* models is given by the experience of the investigator, whereas in *in vivo* models, the complexity is built according to the dynamic instructions and signals of the tumor itself. Zebrafish xenotransplantation also allows *in vivo* evaluation at the single cell level of the cell autonomous and non-cell autonomous effects of a drug on the different hallmarks of cancer.[26]

NERVOUS SYSTEM AND SENESCENCE

Different types of cells present in the Central and Peripheral Nervous Systems, exhibit tendencies towards senescence. In the central nervous system (CNS), neurons,[27-29] microglia,[30-32] astrocytes,[33,34] ependymal cells,[35,36] and oligodendrocytes[37,38] can become senescent. Additionally, despite its peripheral location, the retina i.e., the neural portion of the eye, is part of the CNS and its components such as photoreceptors, and retinal ganglion cell exhibit senescence as well.[39,40] Furthermore, in the peripheral nervous system (PNS) satellite and Schwann cells can also become senescent.[41,42]

Interestingly, many of these senescent cells have been observed in the context of neurodegenerative disorders.[43,44] However, the causes for neuronal senescence in physiological or pathological conditions remain unclear since different factors may contribute to a cell experiencing a particular state of senescence for each pathological condition and each cell type. Therefore, a deep and detailed understanding of the different processes involved in neuronal senescence represents a critical step to understand our nervous system and to propose optimal therapeutic targets.

www.medigraphic.org.mx

Neurodegenerative disorders and senescence. Cellular senescence is characterized by multiple phenotypes including cell cycle arrest, SASP, mitochondrial dysfunction, telomeric and non-telomeric DNA damage, epigenetic modification, and morphological changes. These phenotypes present different alterations in the context of disease compared to normal aging that led to an earlier onset and aggravation of the disease.

For example, in Alzheimer's disease (AD), there is an increased release of proinflammatory cytokines and other SASP that enhances the pathology of amyloid and tau aggregates.[45] In Parkinson's disease (PD), as in other neurodegenerative disorders, neural inflammation plays a central role is believed to be result of an activated microglia and astrocytes leading to a dopaminergic loss. Additionally, analysis of expression in post-mortem PD samples have shown an increase of SASP markers.[46] In multiple sclerosis (MS) mouse models as well as patient samples have shown an increase of senescent cells with activated SASP.[47] Showing that senescent cells play an important role in the pathogenesis of different neurodegenerative disorders and thus the need of more research in different context.

Zebrafish neurodegenerative models. Different anatomical structures, cellular morphology and function, organization, and molecular pathways present in the human CNS have found a true homolog in the zebrafish, making it a powerful model for neurological research.[48,49] The study of embryonic, larval, and adult zebrafish has increased our understanding of brain development, function, and dysfunction.[50-52] Furthermore, zebrafish has become a complementary model for evaluating the toxicity of different molecules and drug candidates in a high-throughput manner, making it a good model for screening new drugs to find effective therapies for multiple neurodegenerative disorders.[53]

The zebrafish CNS is divided into the fore-, mid-, and hindbrain. The forebrain is the most anterior part of the brain and contains the telencephalon, diencephalon and hypothalamus, these structures have been studied in the context of age-associated disorders and senescence.[54-56] The midbrain includes different regions like the optic tectum and midbrain tegmentum key for visual processing and movement coordination, respectively.[57,58] The hindbrain is the posterior part of the brain and houses the cerebellum an important region that integrates sensory inputs and has a key role in different motor programs.[59] Due to the important role of the cerebellum, it has been widely studied in the context of aging, disease, and senescence.[60,61]

In addition to the neuroanatomical shared structures, the zebrafish CNS harbors many of the nervous system cells of interest including neurons, astrocytes, ependymal cells, oligodendrocytes, and Purkinje cells. Furthermore, zebrafish share important neuroanatomical structures such as the blood-brain barrier that is functionally similar to humans. Finally, the zebrafish has become a good model for the study of complex behaviors. All together has made the zebrafish a valuable model for brain development, function and dysfunction .

SENESCENCE AND REGENERATION

Heart regeneration. According to the World Health Organization (WHO), cardiovascular diseases (CVDs) are the leading cause of death globally, estimating 17.9 million people died from CVDs in 2019 (cardiovascular diseases [CVDs], n.d.).

Notwithstanding of the treatment advances, the use of animal modeling to unveil the biology of the CVDs is essential.[62]

Adult mammals have around 1% of cardiomyocyte proliferation during wound repair trough cell migration per year.[63] Usually, humans as other mammals generate fibrotic scar tissue after cardiac damage, as the surrounding cardiomyocytes undergo hypertrophy in order to increase muscle density. As long as zebrafish can regenerate till the 20% of the heart after amputation in a period of 60 days, presenting a normal histology and heartbeat rate. This regeneration process is mediated through cardiomyocytes infiltration to the formed clot yet there are some studies that suggest little participation of differentiation.[64]

The cardiomyocyte migration during gastrulation can be modulated by sdf1-expressing cells, guiding the CXCR4A-expressing endodermal cells to the dorsal side of the embryo.[65] Thus, blocking of CXCR4 function causes heart regeneration impairment following ventricular resection.[66]

Despite MAPKs/ERK-p38 axis being related to cardiogenesis during heart development,[67] since the differentiation during heart regeneration has been minimally observed, other signaling pathways have been suggested. The epicardial cells that undergoes the initial stages of regeneration re-express wt1b, which expression is downregulated at the subsequent migration into the myocardium, after heart cryo-wounding,[68] wt1b-null mutant zebrafish presented delayed fin growth upon

www.medigraphic.org.mx

caudal fin amputation, and reduced cardiomyocyte proliferation following cardiac injury.[69] Recently it was seen a downregulated in expression in wt1a and wt1b at the transition from proepicardial to pericardial cells that contributes to heart development suggesting that the ectopic expression of this genes can lead to transdifferentiation into epicardial-like cells.[70]

It has been reported that WNT (b-catenin dependent) pathway is activated after myocardial infarction during granulation tissue formation in response.[71] Short-term WNT inhibition through GNF-6231 administration lead to interstitial cells proliferation, cardiomyocyte reduced apoptosis, reduced infarct size and a reduction in collagenous scar in mice.[72]

While adult zebrafish hearts response to cryoinjury activated the Wnt/β-catenin signaling in cardiomyocytes at the wound border, with subsequent scar reabsorption, contractarian to some previous reports.[73] Additionally, several transient cell states with fibroblast characteristics were observed following heart injury in zebrafish, Wnt/β-catenin signaling inhibition led to a significant delay in heart regeneration of the endocardial fibroblast response.[74] So, the related signaling pathways become of great interest in heart regeneration in animal models.

Senescence and heart regeneration. Zebrafish acquire an aged phenotype after 3.5 years old, including the appearance of senescence-associated beta-galactosidase activity in the skin and the accumulation of oxidized proteins in the muscle.[75] Croy Wounding old zebrafish hearts result in macrophages accumulation, cell behavioral changes and a significantly collagen enriched wound in old fish at seven days post injury, with over expression of 'inflammation'-like process and a regenerative response impairment in the old zebrafish heart.[76]

CONCLUSION

Senescence is a natural and necessary process in all organisms. However, the desire to delay and prevent the mechanisms of aging has led us to approach the study of cellular senescence and its relationship with health-disease processes and to search for increasingly more suitable models. Zebrafish has become an excellent model for multiple diseases including cancer, heart and neurodegenerative diseases, metabolic disorders, inflammation, and infection amongst others. These disorders have reported an increase in the number of senescent cells, so the use of the zebrafish model represents an opportunity for research of senescence in the context of different diseases.

Senescence is commonly associated with aging and tumor suppression; however, it is present in other physiological processes such as development, where it has shown to play a major role in the development program of different organisms. Zebrafish has established itself as an excellent

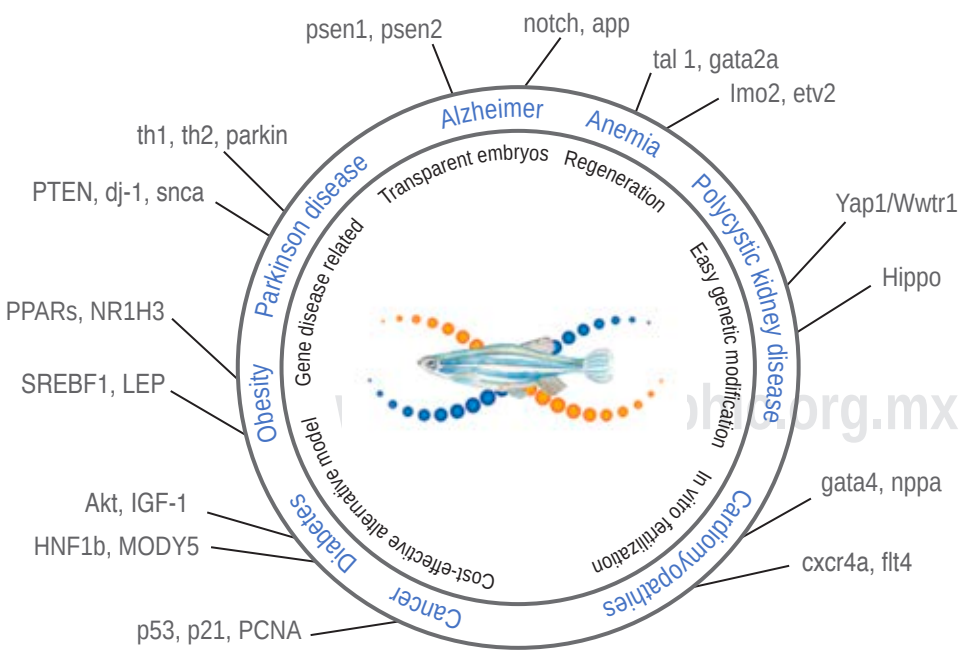

Figure 1:

Zebrafish disease modeling can be performed with genetic engineering using some key pathways, thanks to the existence of human ortholog genes.

model for developmental studies, making it an alternative model for senescence in the context of embryonic development.

Over time zebrafish have become a reliable model for several diseases *(Figure 1)*. In the context of senescence and age-related disorders, zebrafish exhibit age-related decline in cognitive functions, an increase in senescent cells, and other hallmarks. However, it remains to elucidate to what extent the age-related mechanisms and consequences present in a short-lived model such as zebrafish are transferable to long-lived species such as humans. But undoubtedly, the characteristics and advantages as a model organism make the zebrafish a great complement to the classic rodent models and will allow a better understanding of the highly dynamic and multiple-step process of senescence in different contexts.

References

1. Hayflick L, Moorhead PS. The serial cultivation of human diploid cell strains. Exp Cell Res. 1961; 25: 585-621.
2. Hernandez-Segura A, Nehme J, Demaria M. Hallmarks of cellular senescence. Trends Cell Biol. 2018; 28 (6): 436-453.
3. He S, Sharpless NE. Senescence in health and disease. Cell. 2017; 169 (6): 1000-1011.
4. Caprioli J. Glaucoma: a disease of early cellular senescence. Invest Ophthalmol Vis Sci. 2013; 54 (14): ORSF60-ORSF67.
5. Narasimhan A, Flores RR, Robbins PD, Niedernhofer LJ. Role of cellular senescence in type II diabetes. Endocrinology. 2021; 162 (10): bqab136.
6. Barth E, Srivastava A, Stojiljkovic M, Frahm C, Axer H, Witte OW et al. Conserved aging-related signatures of senescence and inflammation in different tissues and species. Aging (Albany NY). 2019; 11 (19): 8556-8572.
7. Ota S, Kawahara A. Zebrafish: a model vertebrate suitable for the analysis of human genetic disorders. Congenit Anom (Kyoto). 2014; 54 (1): 8-11.
8. Varga M. The doctor of delayed publications: the remarkable life of George Streisinger (1927-1984). Zebrafish. 2018; 15 (3): 314-319.
9. Patton EE, Zon LI, Langenau DM. Zebrafish disease models in drug discovery: from preclinical modelling to clinical trials. Nat Rev Drug Discov. 2021; 20 (8): 611-628.
10. Howe K, Clark MD, Torroja CF, Torrance J, Berthelot C, Muffato M et al. The zebrafish reference genome sequence and its relationship to the human genome. Nature. 2013; 496 (7446): 498-503.
11. Hruscha A, Krawitz P, Rechenberg A, Heinrich V, Hecht J, Haass C et al. Efficient CRISPR/Cas9 genome editing with low off-target effects in zebrafish. Development. 2013; 140 (24): 4982-4987.
12. Huang P, Zhu Z, Lin S, Zhang B. Reverse genetic approaches in zebrafish. J Genet Genomics. 2012; 39 (9): 421-433.
13. Childs BG, Baker DJ, Wijshake T, Conover CA, Campisi J, van Deursen JM. Senescent intimal foam cells are deleterious at all stages of atherosclerosis. Science. 2016; 354 (6311): 472-477.
14. Gorgoulis V, Adams PD, Alimonti A, Bennett DC, Bischof O, Bishop C et al. Cellular senescence: defining a path forward. Cell. 2019; 179 (4): 813-827.
15. Minamino T, Orimo M, Shimizu I, Kunieda T, Yokoyama M, Ito T et al. A crucial role for adipose tissue p53 in the regulation of insulin resistance. Nat Med. 2009; 15 (9): 1082-1087.
16. Niccoli T, Partridge L. Ageing as a risk factor for disease. Curr Biol. 2012; 22 (17): R741-R752.
17. Lujambio A, Akkari L, Simon J, Grace D, Tschaharganeh DF, Bolden JE et al. Non-cell-autonomous tumor suppression by p53. Cell. 2013; 153 (2): 449-460.
18. Acosta JC, O'Loghlen A, Banito A, Guijarro MV, Augert A, Raguz S et al. Chemokine signaling via the CXCR2 receptor reinforces senescence. Cell. 2008; 133 (6): 1006-1018.
19. Krizhanovsky V, Yon M, Dickins RA, Hearn S, Simon J, Miething C et al. Senescence of activated stellate cells limits liver fibrosis. Cell. 2008; 134 (4): 657-667.
20. Faget DV, Ren Q, Stewart SA. Unmasking senescence: context-dependent effects of SASP in cancer. Nat Rev Cancer. 2019; 19 (8): 439-453.
21. Mongiardi MP, Pellegrini M, Pallini R, Levi A, Falchetti ML. Cancer response to therapy-induced senescence: a matter of dose and timing. Cancers (Basel). 2021; 13 (3): 484.
22. Yasuda T, Baba H, Ishimoto T. Cellular senescence in the tumor microenvironment and context-specific cancer treatment strategies. FEBS J. 2021.
23. Zampedri C, Martinez-Flores WA, Melendez-Zajgla J. The use of zebrafish xenotransplant assays to analyze the role of lncRNAs in breast cancer. Front Oncol. 2021; 11: 687594.
24. Britto DD, Wyroba B, Chen W, Lockwood RA, Tran KB, Shepherd PR et al. Macrophages enhance Vegfa-driven angiogenesis in an embryonic zebrafish tumour xenograft model. Dis Model Mech. 2018; 11 (12): dmm035998.
25. Hanna SJ, McCoy-Simandle K, Leung E, Genna A, Condeelis J, Cox D. Tunneling nanotubes, a novel mode of tumor cell-macrophage communication in tumor cell invasion. J Cell Sci. 2019; 132 (3): jcs223321.
26. Varanda AB, Martins-Lograd A, Ferreira MG, Fior R. Zebrafish xenografts unveil sensitivity to Olaparib beyond BRCA status. Cancers (Basel). 2020; 12 (7): 1769.

www.medigraphic.org.mx

27. Jurk D, Wang C, Miwa S, Maddick M, Korolchuk V, Tsolou A et al. Postmitotic neurons develop a p21-dependent senescence-like phenotype driven by a DNA damage response. Aging Cell. 2012; 11 (6): 996-1004.
28. Dehkordi SK, Walker J, Sah E, Bennett E, Atrian F, Frost B et al. Profiling senescent cells in human brains reveals neurons with CDKN2D/p19 and tau neuropathology. Nat Aging. 2021; 1 (12): 1107-1116.
29. Zhang C, Zhu Q, Hua T. Aging of cerebellar Purkinje cells. Cell Tissue Res. 2010; 341 (3): 341-347.
30. Hu Y, Fryatt GL, Ghorbani M, Obst J, Menassa DA, Martin-Estebane M et al. Replicative senescence dictates the emergence of disease-associated microglia and contributes to Abeta pathology. Cell Rep. 2021; 35 (10): 109228.
31. Shahidehpour RK, Higdon RE, Crawford NG, Neltner JH, Ighodaro ET, Patel E et al. Dystrophic microglia are associated with neurodegenerative disease and not healthy aging in the human brain. Neurobiol Aging. 2021; 99: 19-27.
32. Hu Y, Huang Y, Xing S, Chen C, Shen D, Chen J. Abeta promotes CD38 expression in senescent microglia in Alzheimer's disease. Biol Res. 2022; 55 (1): 10.
33. Ungerleider K, Beck J, Lissa D, Turnquist C, Horikawa I, Harris BT et al. Astrocyte senescence and SASP in neurodegeneration: tau joins the loop. Cell Cycle. 2021; 20 (8): 752-764.
34. Limbad C, Oron TR, Alimirah F, Davalos AR, Tracy TE, Gan L et al. Astrocyte senescence promotes glutamate toxicity in cortical neurons. PLoS One. 2020; 15 (1): e0227887.
35. Capilla-Gonzalez V, Cebrian-Silla A, Guerrero-Cazares H, Garcia-Verdugo JM, Quinones-Hinojosa A. Age-related changes in astrocytic and ependymal cells of the subventricular zone. Glia. 2014; 62 (5): 790-803.
36. Harkins D, Cooper HM, Piper M. The role of lipids in ependymal development and the modulation of adult neural stem cell function during aging and disease. Semin Cell Dev Biol. 2021; 112: 61-68.
37. Rivellini C, Porrello E, Dina G, Mrakic-Sposta S, Vezzoli A, Bacigaluppi M et al. JAB1 deletion in oligodendrocytes causes senescence-induced inflammation and neurodegeneration in mice. J Clin Invest. 2022; 132 (3): e145071.
38. Tanaka J, Okuma Y, Tomobe K, Nomura Y. The age-related degeneration of oligodendrocytes in the hippocampus of the senescence-accelerated mouse (SAM) P8: a quantitative immunohistochemical study. Biol Pharm Bull. 2005; 28 (4): 615-618.
39. Zhang J, Gao F, Ma Y, Xue T, Shen Y. Identification of early-onset photoreceptor degeneration in transgenic mouse models of Alzheimer's disease. iScience. 2021; 24 (11): 103327.
40. Rocha LR, Nguyen Huu VA, Palomino La Torre C, Xu Q, Jabari M, Krawczyk M et al. Early removal of senescent cells protects retinal ganglion cells loss in experimental ocular hypertension. Aging Cell. 2020; 19 (2): e13089.
41. Kohlmeyer JL, Kaemmer CA, Umesalma S, Gourronc FA, Klingelhutz AJ, Quelle DE. RABL6A regulates Schwann cell senescence in an RB1-dependent manner. Int J Mol Sci. 2021; 22 (10): 5367.
42. Parker MH. The altered fate of aging satellite cells is determined by signaling and epigenetic changes. Front Genet. 2015; 6: 59.
43. Sreekumar PG, Hinton DR, Kannan R. The emerging role of senescence in ocular disease. Oxid Med Cell Longev. 2020; 2020: 2583601.
44. Rouillard ME, Hu J, Sutter PA, Kim HW, Huang JK, Crocker SJ. The cellular senescence factor extracellular HMGB1 directly inhibits oligodendrocyte progenitor cell differentiation and impairs CNS remyelination. Front Cell Neurosci. 2022; 16: 833186.
45. Olivieri F, Prattichizzo F, Grillari J, Balistreri CR. Cellular senescence and inflammaging in age-related diseases. Mediators Inflamm. 2018; 2018: 9076485.
46. Mogi M, Harada M, Kondo T, Riederer P, Inagaki H, Minami M et al. Interleukin-1 beta, interleukin-6, epidermal growth factor and transforming growth factor-alpha are elevated in the brain from parkinsonian patients. Neurosci Lett. 1994; 180 (2): 147-150.
47. Nicaise AM, Wagstaff LJ, Willis CM, Paisie C, Chandok H, Robson P et al. Cellular senescence in progenitor cells contributes to diminished remyelination potential in progressive multiple sclerosis. Proc Natl Acad Sci U S A. 2019; 116 (18): 9030-9039.
48. Schmidt R, Strahle U, Scholpp S. Neurogenesis in zebrafish - from embryo to adult. Neural Dev. 2013; 8: 3.
49. Panula P, Chen YC, Priyadarshini M, Kudo H, Semenova S, Sundvik M et al. The comparative neuroanatomy and neurochemistry of zebrafish CNS systems of relevance to human neuropsychiatric diseases. Neurobiol Dis. 2010; 40 (1): 46-57.
50. Guo S. Using zebrafish to assess the impact of drugs on neural development and function. Expert Opin Drug Discov. 2009; 4 (7): 715-726.
51. Panula P, Sallinen V, Sundvik M, Kolehmainen J, Torkko V, Tiittula A et al. Modulatory neurotransmitter systems and behavior: towards zebrafish models of neurodegenerative diseases. Zebrafish. 2006; 3 (2): 235-247.
52. Blader P, Strahle U. Zebrafish developmental genetics and central nervous system development. Hum Mol Genet. 2000; 9 (6): 945-951.
53. Cassar S, Adatto I, Freeman JL, Gamse JT, Iturria I, Lawrence C et al. Use of zebrafish in drug discovery toxicology. Chem Res Toxicol. 2020; 33 (1): 95-118.
54. Kim K, Choe HK. Role of hypothalamus in aging and its underlying cellular mechanisms. Mech Ageing Dev. 2019; 177: 74-79.
55. Zhang Y, Kim MS, Jia B, Yan J, Zuniga-Hertz JP, Han C et al. Hypothalamic stem cells control ageing speed

www.medigraphic.com/rid

partly through exosomal miRNAs. Nature. 2017; 548 (7665): 52-57.
56. Zambusi A, Pelin Burhan O, Di Giaimo R, Schmid B, Ninkovic J. Granulins regulate aging kinetics in the adult zebrafish telencephalon. Cells. 2020; 9 (2): 350.
57. Suzuki DG, Perez-Fernandez J, Wibble T, Kardamakis AA, Grillner S. The role of the optic tectum for visually evoked orienting and evasive movements. Proc Natl Acad Sci U S A. 2019; 116 (30): 15272-15281.
58. Thiele TR, Donovan JC, Baier H. Descending control of swim posture by a midbrain nucleus in zebrafish. Neuron. 2014; 83 (3): 679-691.
59. Heap LA, Goh CC, Kassahn KS, Scott EK. Cerebellar output in zebrafish: an analysis of spatial patterns and topography in eurydendroid cell projections. Front Neural Circuits. 2013; 7: 53.
60. Liang KJ, Carlson ES. Resistance, vulnerability and resilience: A review of the cognitive cerebellum in aging and neurodegenerative diseases. Neurobiol Learn Mem. 2020; 170: 106981.
61. Bernard JA, Seidler RD. Moving forward: age effects on the cerebellum underlie cognitive and motor declines. Neurosci Biobehav Rev. 2014; 42: 193-207.
62. Houser SR, Margulies KB, Murphy AM, Spinale FG, Francis GS, Prabhu SD et al. Animal models of heart failure: a scientific statement from the American Heart Association. Circ Res. 2012; 111 (1): 131-150.
63. Senyo SE, Lee RT, Kuhn B. Cardiac regeneration based on mechanisms of cardiomyocyte proliferation and differentiation. Stem Cell Res. 2014; 13 (3 Pt B): 532-541.
64. Poss KD, Wilson LG, Keating MT. Heart regeneration in zebrafish. Science. 2002; 298 (5601): 2188-2190.
65. Mizoguchi T, Verkade H, Heath JK, Kuroiwa A, Kikuchi Y. Sdf1/Cxcr4 signaling controls the dorsal migration of endodermal cells during zebrafish gastrulation. Development. 2008; 135 (15): 2521-2529.
66. Itou J, Oishi I, Kawakami H, Glass TJ, Richter J, Johnson A et al. Migration of cardiomyocytes is essential for heart regeneration in zebrafish. Development. 2012; 139 (22): 4133-4142.
67. Jing Y, Ren Y, Witzel HR, Dobreva G. A BMP4-p38 MAPK signaling axis controls ISL1 protein stability and activity during cardiogenesis. Stem Cell Reports. 2021; 16 (8): 1894-1905.
68. Gonzalez-Rosa JM, Peralta M, Mercader N. Pan-epicardial lineage tracing reveals that epicardium derived cells give rise to myofibroblasts and perivascular cells during zebrafish heart regeneration. Dev Biol. 2012; 370 (2): 173-186.
69. Sanz-Morejon A, Garcia-Redondo AB, Reuter H, Marques IJ, Bates T, Galardi-Castilla M et al. Wilms tumor 1b expression defines a pro-regenerative macrophage subtype and is required for organ regeneration in the zebrafish. Cell Rep. 2019; 28 (5): 1296-1306.e6.
70. Marques IJ, Ernst A, Arora P, Vianin A, Hetke T, Sanz-Morejon A et al. Wt1 transcription factor impairs cardiomyocyte specification and drives a phenotypic switch from myocardium to epicardium. Development. 2022; 149 (6): dev200375.
71. Aisagbonhi O, Rai M, Ryzhov S, Atria N, Feoktistov I, Hatzopoulos AK. Experimental myocardial infarction triggers canonical Wnt signaling and endothelial-to-mesenchymal transition. Dis Model Mech. 2011; 4 (4): 469-483.
72. Bastakoty D, Saraswati S, Joshi P, Atkinson J, Feoktistov I, Liu J et al. Temporary, systemic inhibition of the WNT/beta-catenin pathway promotes regenerative cardiac repair following myocardial infarct. Cell Stem Cells Regen Med. 2016; 2 (2): 10.16966/2472-6990.111.
73. Bertozzi A, Wu CC, Hans S, Brand M, Weidinger G. Wnt/beta-catenin signaling acts cell-autonomously to promote cardiomyocyte regeneration in the zebrafish heart. Dev Biol. 2022; 481: 226-237.
74. Hu B, Lelek S, Spanjaard B, El-Sammak H, Simoes MG, Mintcheva J et al. Origin and function of activated fibroblast states during zebrafish heart regeneration. Nat Genet. 2022; 54 (8): 1227-1237.
75. Kishi S, Uchiyama J, Baughman AM, Goto T, Lin MC, Tsai SB. The zebrafish as a vertebrate model of functional aging and very gradual senescence. Exp Gerontol. 2003; 38 (7): 777-786.
76. Reuter H, Perner B, Wahl F, Rohde L, Koch P, Groth M et al. Aging activates the immune system and alters the regenerative capacity in the zebrafish heart. Cells. 2022; 11 (3): 345.

www.medigraphic.org.mx