Revista Española de Geriatría y Gerontología 60 (2025) 101607

Revista Española de Geriatría y Gerontología

www.elsevier.es/regg

REVIEW ARTICLE

Regenerative characteristics of the immortal jellyfish, *Turritopsis dohrnii*, and their potential implications for human aging

Valentina Velasco-Muñoz [a], Mateo Uribe-Gaviria [a], Santiago Andrés Suárez-Gómez [a], Antonio Villamizar-Romero [a], Andrés Ricaurte-Fajardo [b,c,*], Isabel Cristina Vásquez-Vélez [d], Carlos A. Cano-Gutiérrez [e]

[a] *School of Medicine, Pontificia Universidad Javeriana, Bogotá, Colombia*
[b] *Department of Radiology, Weill Cornell Medical College of Cornell University, New York, NY, USA*
[c] *Department of Neurology, Pontificia Universidad Javeriana, Bogotá, Colombia*
[d] *Department of Physiological Sciences, Pontificia Universidad Javeriana, Bogotá, Colombia*
[e] *Department of Geriatrics, Aging Institute, Pontificia Universidad Javeriana, Bogotá, Colombia*

ARTICLE INFO

Article history:
Received 26 April 2024
Accepted 22 October 2024

Keywords:
Turritopsis dohrnii
Transdifferentiation
Regeneration
Aging

ABSTRACT

The jellyfish *Turritopsis dohrnii* (*T. Nutricala*) is a cnidarian of the Oceaniidae family that lives in the Mediterranean Sea. It is known as the immortal jellyfish since, through a process of cell development called transdifferentiation, it manages to return to a polyp state. The role of regeneration processes and their impact on aging have been studied in recent years for their potential applications in the development of more efficient pharmacology to address disorders related to aging. Reviewing the terms related to transdifferentiation in jellyfish and understanding the underlying mechanisms can help comprehend diverse processes such as aging, regeneration, and the molecular bases of diseases like cancer. This paper's purpose is to provide a description of the regenerative characteristics of the jellyfish *T. dohrnii*, investigate how its regenerative processes allow it to rejuvenate, and determine if these tissue restoration processes are also found in humans.

© 2024 SEGG. Published by Elsevier España, S.L.U. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

Características regenerativas de la medusa inmortal, *Turritopsis dohrnii*, y sus posibles implicaciones para el envejecimiento humano

Palabras clave:
Turritopsis dohrnii
Transdiferenciación
Regeneración
Envejecimiento

RESUMEN

La medusa *Turritopsis dohrnii* (*T. nutricula*) es un cnidario de la familia Oceaniidae que vive en el Mar Mediterráneo. Es conocida como la medusa inmortal ya que, a través de un proceso de desarrollo celular llamado transdiferenciación, logra regresar a un estado de pólipo. El papel de los procesos de regeneración y su impacto en el envejecimiento han sido estudiados en los últimos años por sus posibles aplicaciones en el desarrollo de una farmacología más eficiente para abordar trastornos relacionados con el envejecimiento. Revisar los términos relacionados con la transdiferenciación en las medusas y comprender los mecanismos subyacentes puede ayudar a comprender diversos procesos como el envejecimiento, la regeneración y las bases moleculares de enfermedades como el cáncer. El propósito de este documento es proporcionar una descripción de las características regenerativas de la medusa *Turritopsis dohrnii*, investigar cómo sus procesos de regeneración le permiten rejuvenecer y determinar si estos procesos de restauración de tejidos también se encuentran en los seres humanos.

© 2024 SEGG. Publicado por Elsevier España, S.L.U. Se reservan todos los derechos, incluidos los de minería de texto y datos, entrenamiento de IA y tecnologías similares.

* Corresponding author.
E-mail addresses: ajr4002@med.cornell.edu, andres.ricaurte@javeriana.edu.co (A. Ricaurte-Fajardo).

https://doi.org/10.1016/j.regg.2024.101607
0211-139X/© 2024 SEGG. Published by Elsevier España, S.L.U. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

Introduction

Aging is a physiological process that every living being will have to go through. It is characterized by a progressive deterioration of physiological integrity, leading to impaired functional ability and ultimately increased susceptibility to diseases and death.[1] A series of molecular processes take place in a chronic and detrimental way that might affect the functionality and morphology of the different tissues, associated with genetic and ambiental factors.[1] Some of these tissue remodeling processes are also found during embryogenesis such as cellular senescence, which is a permanent state of cell cycle arrest that occurs in proliferating cells subjected to different stresses.[1] Cellular senescence is one of the main causative processes of aging and it has been associated with aging-related disorders.[1,2] In embryogenesis it allows a proper development of the embryo and tissue repair if needed.[2] In diseases such as cancer, senescence works as a potent barrier to prevent tumorigenesis.[2] Cellular remodeling is natural and predictable; the processes linked to it, protects them but also damages them according to the context.[2] But in an aging influenced by chronic diseases such as cardiovascular disease, diabetes, neurological degeneration and cancer, these pathologies could accelerate the curse of an individual deterioration compromising their functionality.[2,3]

In general, aging increases the risk of several diseases. Understanding the mechanisms behind these pathologies has led an unprecedented progress in aging research, particularly the discovery that the rate of aging is at least partly controlled by evolutionarily conserved genetic pathways and biological processes.[3] Biological research found some animals that had developed the ability to reverse their biological processes in aging into their embryologic function,[4] tricking nature in an immortality loophole where there was supposed to be a chronic and progressive deterioration that culminated in their respective death.[4] Nature has its own way of maintaining balance, if biologically these animals can deceive it, they will not have the same luck with their predators, unlike the human, who has developed tools to protect himself throughout history.[4] This becomes a balanced system that leaves researchers with multiple questions.[4]

Among these animals, stands out the jellyfish *Turritopsis dohrnii* (*T. Nutricala*).[4] A cnidarian of the Oceaniidae family that lives in the Mediterranean Sea.[4] It is known as the immortal jellyfish, since through a process of cell development of transdifferentiation, the direct conversion of one differentiated cell fate into another identity, it manages to return to a polyp state.[5,6]

This paper aims to investigate the regenerative processes of the jellyfish *T. dohrnii* and explore the potential implications of these processes for human tissue restoration. By understanding how the jellyfish rejuvenates through transdifferentiation, we seek insights that may contribute to the broader field of neuroscience and our comprehension of aging-related disorders.

Methods

A narrative review was conducted using MeSH terms "Jellyfish", "*Turritopsis dohrnii*", "Aging" in databases such as PubMed, Elsevier, Google Scholar, using inclusion criteria "Aging process". In PubMed 29 articles were found, from which 2 were selected reading abstract by abstract to discern relevance. In Elsevier base data Scopus 10 papers were found and 8 were selected as well. Google Scholar had the biggest base data with 189 articles found, from which only 11 papers were selected. The sum of all articles found was 226 although we selected only 21 from them using inclusion and exclusion criteria (Fig. 1).

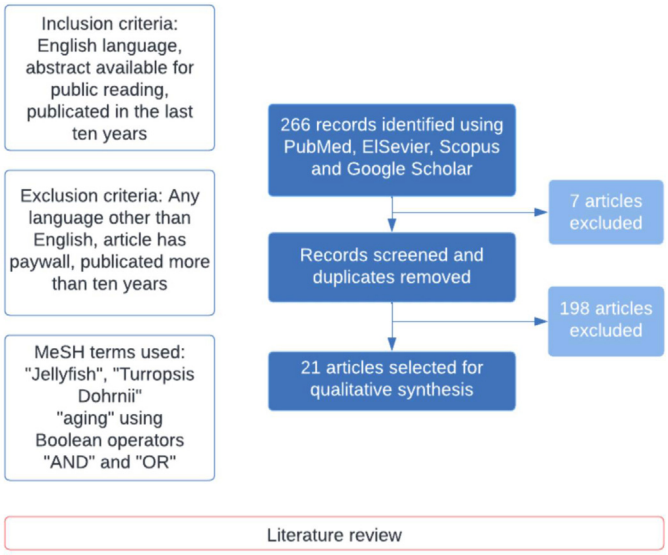


Fig. 1. Flow diagram for the methodology of the review.

How can the jellyfish T. dohrnii *be immortal?*

The jellyfish *T. dohrnii* (*T. Nutricala*) has a life cycle that starts with a polyp. Afterwards, the polyp differentiates to generate a medusa like most jellyfish species, but the crucial difference responds to senescence, damage, or environmental changes.[6] When encountered with these obstacles, the specimen can morph into a cyst which has the capability to regress the organism to a state denominated reversed polyp.[6] Afterwards, this polyp can undergo cellular and molecular changes to produce a jellyfish again. Hence, technically speaking when this species is faced with adversity it has the capability to regress its life cycle and start over.[6] This life cycle colloquially gave the *T. dohrnii* the name of the "immortal jellyfish". This process is denominated as transdifferentiation, not to be confused with dedifferentiation (Fig. 2).[6] While in dedifferentiation the mature cell can reverse its state to a progenitor of its own cellular lineage, in transdifferentiation the cell can reverse itself to a progenitor which can adapt to any cellular lineage for the species.[1]

The key to this procedure lies on the molecular modifications activated when the cyst phase is activated.[7] Genetic and epigenetic mechanisms are involved to over or under express genes in this state.[7] Comparing gene expression in the different Medusa, Cyst and Polyp stages demonstrated an over-expression in genes involving DNA synthesis, integration, repair, nucleic acid metabolism and telomere maintenance. Under expressed genes were mostly cellular communication and signaling pathway genes.[7] Wnt and Notch pathways, which play a role in embryonic development, cell spatial distribution and organogenesis, are silenced while the jellyfish is in the Cyst stage.[7] Furthermore, while DNA synthesis and related mechanisms genes were overexpressed, cell division and mitotic related genes were under expressed, which can be interpreted as taking care of DNA as a priority over cellular division (Fig. 3).[7] Also, stimulus response and other cellular differentiation genes were under expressed in the Cyst stage.[7]

Concrete examples include the overexpression of POLD1 and POLA2 which encode different DNA polymerases, TOP3B for DNA topoisomerase, GEN 1 for endonuclease, BRCA 1 for tumor suppressing, among others.[8,9] This can be interpreted as a prioritization of DNA replication, repair, and regulation enhancement mechanisms.[8,9] Genes such as MrsA, Ubiquitin related factors, TXN, glutathione reductase, among others, protect DNA from external oxidative stress, respond to DNA damage and increase repair capabilities.[8,9] Telomere maintenance is also correlated

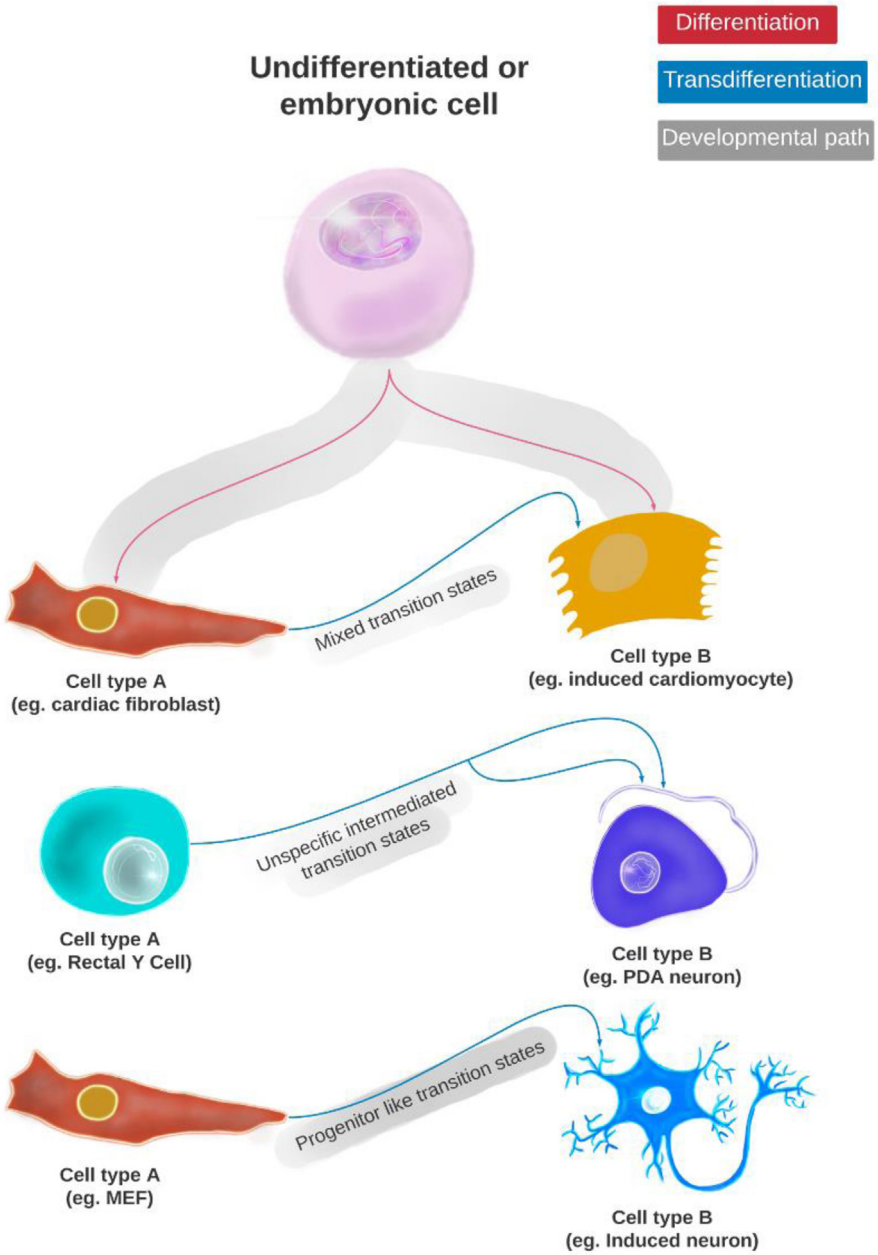


Fig. 2. Converting cells can deviate from the path of development. Cell undergoing transdifferentiation can pass through mixed, unspecific intermediate or progenitor-like transition states. MEF: mouse embryonic fibroblasts; PDA neuron: motor neuron termed PDA.[6]

with longevity. *T. dohrnii* has more copies of the GAR1 gene, enhancing the telomerase complex.[8,9] Also, POT1 gene variants are found. POT1 attaches to telomeres, inhibiting the action of the telomerase.[8,9] This variant of POT1 has less affinity for telomeres, augmenting the capability of the telomerase.[8,9] GLI3 is a gene duplicated in the species which helps stem cell function via aiding Sonic Hedgehog signaling.[8,9] Finally, genes regulating cell plasticity and apoptosis are also activated.[8,9] PSEN1 and BMP7 regulate apoptosis and TUBG1, CLASP1, SPAST, among others, help with microtubule regulation, aiding cellular plasticity. Epigenetic changes are also present.[8,9] For example, PCR2 enables methylation to maintain pluripotency in stem cells. Pascual-Torner M et al.[8] made the comparative genomics to analyze the genetic and epigenetic behavior for the aforementioned genes.[8,9]

Transdifferentiation in humans

How to induce transdifferentiation in humans in order to give a more efficient and safer therapeutic alternative in several diseases, for example using cytokines such as IL-17 and IFN-γ in inflammatory skin disorders to spinal cord injury has been studied for the past years.[10,11] Direct conversion to several cell types including cardiomyocytes, various types of neurons, and pancreatic β-cells, has been reported.[12] For example, the expression of Oct4, Klf4, Sox2, and cMyc induces pluripotency in somatic cells (iPSCs); but if Oct4 is replaced with the neuro-specific factor Brn4, it induces transdifferentiation of fibroblasts into induced neural stem cells (iNSCs).[13]

The main limitation is that transdifferentiation fosters the generation of oncogenic activity, but also increases cancer's metastatic

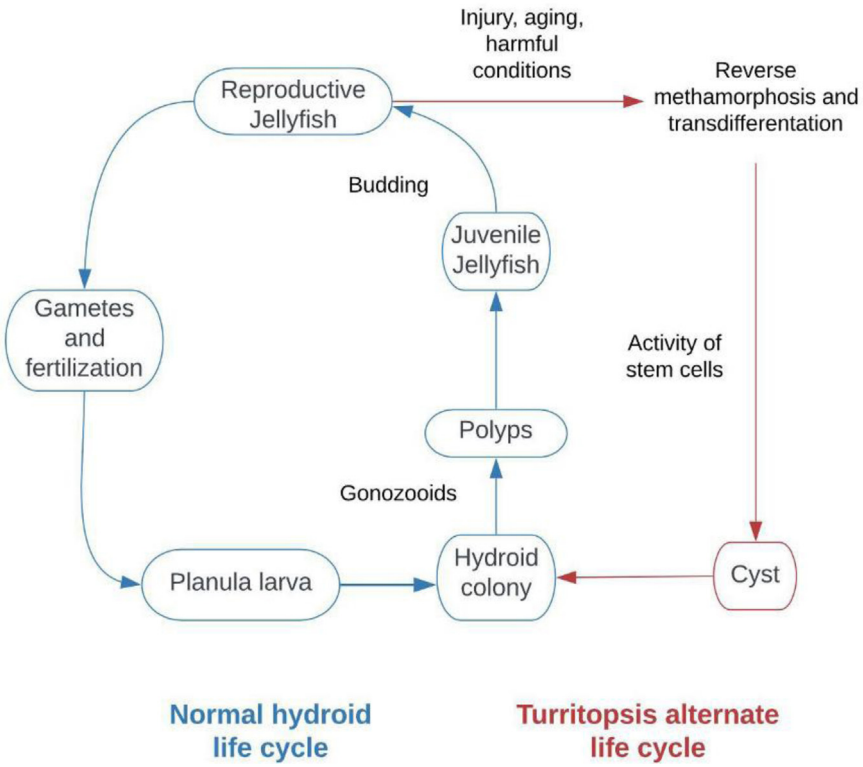


Fig. 3. The immortality program is launched to fight against harmful environmental conditions. The typical hydrozoan life cycle is indicated in blue (left), while the alternative life cycle of *Turritopsis dohrnii* is indicated in red (right).[1,7]

dissemination, and treatment resistance.[14] Cells translate force and modulate their behavior through mechanotransduction, oncogene activity, which increases the possibility of them losing their tensional homeostasis leading to carcinogenesis.[14] Among these, we found epithelial-mesenchymal transition (EMT) which is the transdifferentiation of epithelial cells into motile mesenchymal cells, initiated and controlled by signaling pathways that respond to extracellular cues like transforming growth factor-β (TGFβ).[15] This is also mediated by key transcription factors (such as SNAIL, zinc-finger E-box-binding (ZEB) and basic helix-loop-helix transcription factors) regulated at the transcriptional, translational, and post-translational levels.[15] Transdifferentiation has been seen in dissemination, increasing risk mortality.[16] Ovarian cancer has one of the lowest prognoses among carcinomas due to its high risk of developing ascites and peritoneal dissemination associated with the transdifferentiation process.[16] This is because cancer stem cells (CSC) have the potential to transdifferentiate into other lineage cells for promoting tumor growth and metastasis in some tissue contexts instead of only recruiting stromal cells from local or distant tissues.[17]

Transdifferentiation is also associated with atherosclerosis and diverse age-associated diseases by age-related accumulation of epigenetic alterations, implicating abnormal DNA methylation, changes in DNA methylation at promoters, enhancers, gene bodies and sites that control high-order chromatin structure.[18] Alterations during mitosis are associated with this cell reprogramming process. The formation of dysfunctional telomeres is necessary for human fibroblast to develop characteristics of myofibroblasts and is necessary for tumorigenesis.[19] Oncogenic cells must acquire telomere DNA maintenance mechanisms in order to counteract telomere shortening, avoiding DNA damage repair systems like p53 induced apoptosis.[20]

As humans age, oxidative stress accumulates reactive oxygen species (ROS) which leads to DNA damage, and eventually

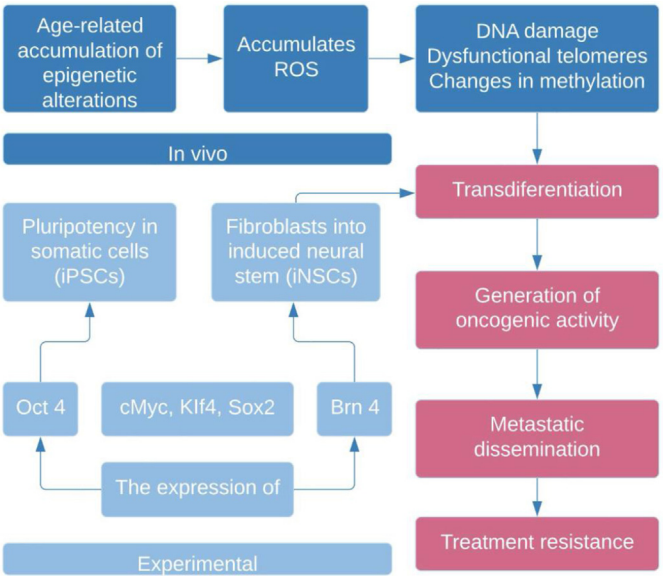


Fig. 4. Transdifferentiation in humans: experimental and in vivo research.[11,21]

influences telomere length as well[21] bringing with it an increased risk for developing transdifferentiation and oncogenic activity (Fig. 4).

Discussion

Why does jellyfish *T. dohrnii* manage to use transdifferentiation to trick nature while in humans it increases oncogenic activity through aging? Cellular reprogramming in the jellyfish had DNA synthesis and related mechanisms genes overexpressed, but

cell division and mitotic related genes were under expressed.[1] There,DNA quality it's a priority over cellular division. In humans, DNA damage like telomere dysfunction, it's what promotes transdifferentiation and also links it to oncogenic activity,[20] although it is not exclusive. Translational medicine seeks to convert these concepts into practical aspects and, why not say, the clinicians involved represent a change in the evolution of diseases in people in general and in the elderly in particular. A good example can be referred to in relation to bioengineering and thymic regeneration as an alternative to improve the immune response to many clinical situations in humans, including the increased production of naive cells.

Conclusion

The regeneration of these jellyfish is mainly by transdifferentiation. This mechanism is related to its ability to rejuvenate. However, in humans it fosters the generation of oncogenic activity and metastatic dissemination, due to a predisposition of damaged DNA during the cell reprogramming process associated with shortness of telomerase and ROS increased activity. The model of the jellyfish *T. dohrnii* is an excellent principle and a research opportunity to ensure that people can have not only a longer life expectancy, but a better quality of life in old age. In the future, studies are required to broaden the concept of transdifferentiation and its application to the process of pathological aging, thereby seeking to modify the course of chronic diseases such as dementia or oncological disease, among others.

Statement

During the preparation of this work the author(s) used ChatGPT to check grammar, it wasn't used for any further writing purposes. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

None.

References

1. Mikuła-Pietrasik J, Pakuła M, Markowska M, Uruski P, Szczepaniak-Chicheł L, Tykarski A, et al. Nontraditional systems in aging research: an update. Cell Mol Life Sci. 2021;78:1275–304, http://dx.doi.org/10.1007/s00018-020-03658-w. Epub 2020 Oct 9. PMID: 33034696; PMCID: PMC7904725.
2. Calcinotto A, Kohli J, Zagato E, Pellegrini L, Demaria M, Alimonti A. Cellular senescence: aging, cancer, and injury. Physiol Rev. 2019;99:1047–78, http://dx.doi.org/10.1152/physrev.00020.2018. PMID: 30648461.
3. Cai Y, Song W, Li J, Jing Y, Liang C, Zhang L, et al. The landscape of aging. Sci China Life Sci. 2022;65:2354–454, http://dx.doi.org/10.1007/s11427-022-2161-3. Epub 2022 Sep 2. PMID: 36066811; PMCID: PMC9446657.
4. Petralia RS, Mattson MP, Yao PJ. Aging and longevity in the simplest animals and the quest for immortality. Ageing Res Rev. 2014;16:66–82, http://dx.doi.org/10.1016/j.arr.2014.05.003. Epub 2014 Jun 5. PMID: 24910306; PMCID: PMC4133289.
5. Guest PC. Of mice, whales, jellyfish and men: in pursuit of increased longevity. Adv Exp Med Biol. 2019;1178:1–24, http://dx.doi.org/10.1007/978-3-030-25650-0_1. PMID: 31493219.
6. Reid A, Tursun B. Transdifferentiation: do transition states lie on the path of development? Curr Opin Syst Biol. 2018;11:18–23, http://dx.doi.org/10.1016/j.coisb.2018.07.004. PMID: 30386832; PMCID: PMC6202785.
7. Matsumoto Y, Piraino S, Miglietta MP. Transcriptome characterization of reverse development in *Turritopsis dohrnii* (Hydrozoa, Cnidaria). G3 (Bethesda). 2019;9:4127–38, http://dx.doi.org/10.1534/g3.119.400487. PMID: 31619459; PMCID: PMC6893190.
8. Pascual-Torner M, Carrero D, Pérez-Silva JG, Álvarez-Puente D, Roiz-Valle D, Bretones G, et al. Comparative genomics of mortal and immortal cnidarians unveils novel keys behind rejuvenation. Proc Natl Acad Sci USA. 2022;119:e2118763119. doi:10.1073/pnas.2118763119. Epub 2022 Aug 29. Erratum in: Proc Natl Acad Sci USA. 2023 Apr 4;120(14):e2303228120. Erratum in: Proc Natl Acad Sci USA. 2023 Sep 26;120(39):e2314776120. PMID: 36037356; PMCID: PMC9459311.
9. Matsumoto Y, Miglietta MP. Cellular reprogramming and immortality: expression profiling reveals putative genes involved in *Turritopsis dohrnii's* life cycle reversal. Genome Biol Evol. 2021;13:evab136, http://dx.doi.org/10.1093/gbe/evab136. PMID: 34132809; PMCID: PMC8480191.
10. Belpaire A, van Geel N, Speeckaert R. From IL-17 to IFN-γ in inflammatory skin disorders: Is transdifferentiation a potential treatment target? Front Immunol. 2022;13:932265, http://dx.doi.org/10.3389/fimmu.2022.932265. PMID: 35967358; PMCID: PMC9367984.
11. Yang R, Pan J, Wang Y, Xia P, Tai M, Jiang Z, et al. Application and prospects of somatic cell reprogramming technology for spinal cord injury treatment. Front Cell Neurosci. 2022;16:1005399, http://dx.doi.org/10.3389/fncel.2022.1005399. PMID: 36467604; PMCID: PMC9712200.
12. Han JK, Shin Y, Kim HS. Direct conversion of cell fate and induced endothelial cells. Circ J. 2022;86:1925–33, http://dx.doi.org/10.1253/circj.CJ-21-0703. Epub 2021 Nov 3. PMID: 34732599.
13. Velychko S, Kang K, Kim SM, Kwak TH, Kim KP, Park C, et al. Fusion of reprogramming factors alters the trajectory of somatic lineage conversion. Cell Rep. 2019;27:30–9, http://dx.doi.org/10.1016/j.celrep.2019.03.023, e4. PMID: 30943410.
14. Hayward MK, Muncie JM, Weaver VM. Tissue mechanics in stem cell fate, development, and cancer. Dev Cell. 2021;56:1833–47, http://dx.doi.org/10.1016/j.devcel.2021.05.011. Epub 2021 Jun 8. PMID: 34107299; PMCID: PMC9056158.
15. Lamouille S, Xu J, Derynck R. Molecular mechanisms of epithelial-mesenchymal transition. Nat Rev Mol Cell Biol. 2014;15:178–96, http://dx.doi.org/10.1038/nrm3758. PMID: 24556840; PMCID: PMC4240281.
16. Mogi K, Yoshihara M, Iyoshi S, Kitami K, Uno K, Tano S, et al. Ovarian cancer-associated mesothelial cells: transdifferentiation to minions of cancer and orchestrate developing peritoneal dissemination. Cancers (Basel). 2021;13:1352, http://dx.doi.org/10.3390/cancers13061352. PMID: 33802781; PMCID: PMC8002484.
17. Huang Z, Wu T, Liu AY, Ouyang G. Differentiation and transdifferentiation potentials of cancer stem cells. Oncotarget. 2015;6:39550–63, http://dx.doi.org/10.18632/oncotarget.6098. PMID: 26474460; PMCID: PMC4741845.
18. Ehrlich M. DNA hypermethylation in disease: mechanisms and clinical relevance. Epigenetics. 2019;14:1141–63, http://dx.doi.org/10.1080/15592294.2019.1638701. Epub 2019 Jul 8. PMID: 31284823; PMCID: PMC6791695.
19. Razdan N, Vasilopoulos T, Herbig U. Telomere dysfunction promotes transdifferentiation of human fibroblasts into myofibroblasts. Aging Cell. 2018;17:e12838, http://dx.doi.org/10.1111/acel.12838. Epub 2018 Sep 22. PMID: 30244523; PMCID: PMC6260909.
20. De Vitis M, Berardinelli F, Sgura A. Telomere length maintenance in cancer: at the crossroad between telomerase and alternative lengthening of telomeres (ALT). Int J Mol Sci. 2018;19:606, http://dx.doi.org/10.3390/ijms19020606. PMID: 29463031; PMCID: PMC5855828.
21. Gao X, Yu X, Zhang C, Wang Y, Sun Y, Sun H, et al. Telomeres and mitochondrial metabolism: implications for cellular senescence and age-related diseases. Stem Cell Rev Rep. 2022;18:2315–27, http://dx.doi.org/10.1007/s12015-022-10370-8. Epub 2022 Apr 23. PMID: 35460064; PMCID: PMC9033418.