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COMMENTARY

Perspective on Death: A Gateway to a New Biology

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ABSTRACT

Organismal death has long been considered the irreversible ending of an organism's integrated functioning as a whole. However, the persistence of functionality in organs, tissues, and cells postmortem, as seen in organ donation, raises questions about the mechanisms underlying this resilience. Recent research reveals that various factors, such as environmental conditions, metabolic activity, and inherent survival mechanisms, influence postmortem cellular functionality and transformation. These findings challenge our understanding of life and death, highlighting the potential for certain cells to grow and form new multicellular entities. This opens new avenues in biology and medicine, expanding our comprehension of life's complexity.

1 | Introduction

Organismal death has traditionally been regarded as the loss of integrated biological processes. However, some organs, tissues, and cells remain functional even after an organism's demise. This resilience begs the question: what mechanisms underlie the continued functionality observed postmortem? A recent review posits that a myriad of factors influence the functionality and resilience of cells or tissues after death [1].

These factors include environmental conditions, metabolic activity, preservation techniques, and inherent survival mechanisms. Furthermore, a significant influence is exerted by the circumstances surrounding the organism's death: duration of the dying process, trauma, infection, time elapsed since death, and the nature of the entity itself. Notably, considerations of energy requirements, alongside demographic factors such as age, health, sex, and species, further shape the postmortem landscape. Unraveling the intricate interplay of these variables remains a paramount challenge, necessitating further inquiry into their collective impact on underlying mechanisms. Two intriguing revelations gleaned from these research findings are shown below.

2 | Two Intriguing Revelations

First, some cells continue to grow after organismal death. For example, activation and outgrowth of microglial and astrocytic glial cells have been reported in human brains 24 h postmortem [2]. It is reasonable to assume that the growth of glial cell processes is likely due to active transcription. These cells play essential roles in maintaining homeostasis, supporting neuronal function, and responding to injury and disease. Previous research indicates the activation of genes occurring postmortem in several animals [3, 4], suggesting the widespread potential for growth among diverse cell types. However, the prevalence of cells actively growing across various cell types in the human body is not yet known or fully understood. Interestingly, it is well established that some cells can enter a dormant state and have regenerative capacity. For example, skeletal muscle stem cells in the mouse [5] and fibroblast cells from sheep [6] can be cultured 14 to 17 days and 41 to 160 days postmortem, respectively. However, dormant cells and those that have the capacity to be cultured are physiologically different from cells actively growing after organismal death.

Second, certain cells exhibit the capacity to transform into multicellular entities with novel functionalities postmortem

when provided with essential nutrients, oxygen, endogenous bioelectricity, or biochemical cues [7]. Although the organism is technically dead, the cells attain a new life form without changes to their genetic/genomic background. Biologists are accustomed to developmental transformations like caterpillars metamorphosing into butterflies or tadpoles evolving into frogs, but there are few instances where organisms undergo changes divergent from these predetermined pathways. Here, are two examples of postmortem transformations representative of this phenomenon.

Example 1. Levin et al. [8, 9] have extracted skin cells from deceased frog embryos. Although the embryos have ceased to be, their cells retained functionality. In the controlled environment of a laboratory dish, these cells displayed remarkable adaptability, spontaneously reorganizing into novel multicellular structures with cilia. These cellular entities, named "Xenobots," exhibited behaviors far beyond their original biological roles. They navigated their surroundings, repaired damage, and defied expectations by utilizing cilia for locomotion rather than their usual function of mucus transport.

Example 2. Levin et al. [10] showed the transformative potential extends to adult human lung epithelial cells. Cultivated in a specialized environment and submerged in a fluid medium, a solitary cell undergoes self-assembly, culminating in the emergence of a miniature, motile multicellular organism named an "Anthrobot." These Anthrobots, displaying a diverse repertoire of behaviors and morphologies, transcended the boundaries of conventional cellular function. They not only navigated their surroundings with precision but also demonstrated the unprecedented ability to repair cellular damage and address neural injuries. This findings challenge our understanding of cellular capabilities, revealing hitherto unrecognized potentials inherent in human lung cells.

These revelations suggest that the boundary between life and death is far more indistinct than traditionally believed, challenging our conventional understanding of cellular behavior, and organismal identity. The continuum where life persists and even transforms beyond apparent death is evident. From cells that continue to grow and function postmortem to the emergence of novel multicellular entities from "dead" organisms, we see a pattern of life's tenacity and adaptability. This blurring of lines between life and death invites us to reconsider fundamental questions about the potential of cellular life, and the very definition of what it means to be alive or dead [11].

3 | Implications for Biology and Medicine

Living organisms are self-organized and internally unified systems that regulate themselves [12]. They are seen as "wholes," where each part works together for the benefit of the entire organism. In organismal death, the interdependence among the organism's parts breaks down, and organs, tissues, and cells are no longer coordinated together (i.e., loss of systematic unity). The organism transitions to a state where its components participate in natural processes.

The continued activity and growth of cells after organismal death, and their potential to form new multicellular entities, highlight important nuances in the complexity and multi-layered nature of biological organization and how biological processes change after organismal death. While the death of an organism signifies the end of its systematic unity as a whole, individual cells can retain life processes and contribute to new forms of life, reflecting both their autonomy and their role in the broader web of natural purposes.

The putative reasons some cells survive and continue to function are due to residual energy stores, autonomous functioning, delayed cessation of biological processes, gradual loss of homeostasis, and specific cell types' behavior. The fact that some cells can grow and transform after death reflects their partial autonomy. While they are integral parts of the organism, they also possess their own capacities for survival and growth. Life has emergent properties at multiple levels of organization [12, 13]. The organism as a whole and its individual cells can be seen as different levels of purposive systems. These abilities can be viewed as an extension of the organism's natural purposes and are aligned with the notion that nature is a system of interrelated purposes.

In the medical realm, cells sourced from adult human tissue hold promise for advancing personalization and technological innovation, referred to as "Medicine 3.0," a term coined by Peter Attia in "Outlive: The Science and Art of Longevity." These cells could potentially offer a safe avenue for drug delivery, mitigating immune responses. Applications range from clearing arterial plaque in atherosclerosis to alleviating mucus buildup in cystic fibrosis patients. Importantly, these multicellular organisms have a finite lifespan, naturally degrading after 4 to 6 weeks, ensuring safety.

Yet, the extent of cellular transformation postmortem remains uncertain. While select cells exhibit this capability, its prevalence across diverse cell types is still unclear. Of note, prior research suggests the activation of developmental genes in certain organisms postmortem [3, 14], hinting at broader transformative potential. As research continues to uncover the remarkable capabilities of cells postmortem, we stand on the brink of significant advancements in both our understanding of biological processes and the development of innovative medical therapies, potentially transforming the landscape of regenerative medicine and beyond.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

References

1. P. A. Noble, A. Pozhitkov, K. Singh, et al., "Unraveling the enigma of organismal death: insights, implications, and unexplored frontiers," *Physiology* 39: 313–323, https://doi.org/10.1152/physiol.00004.2024.

2. F. Dachet, J. B. Brown, T. Valyi-Nagy, et al., "Selective Time-Dependent Changes in Activity and Cell-Specific Gene Expression in human

Postmortem Brain," *Scientific Reports* 11, no. 1 (2021): 6078, https://doi.org/10.1038/s41598-021-85801-6.

3. A. E. Pozhitkov, R. Neme, T. Domazet-Lošo, et al., "Tracing the Dynamics of Gene Transcripts after Organismal Death," *Open Biology* 7, no. 1 (2017): 160267, https://doi.org/10.1098/rsob.160267.

4. P. G. Ferreira, M. Muñoz-Aguirre, F. Reverter, et al., "The Effects of Death and Post-Mortem Cold Ischemia on Human Tissue Transcriptomes," *Nature Communications* 9, no. 1 (2018): 490, https://doi.org/10.1038/s41467-017-02772-x.

5. M. Latil, P. Rocheteau, L. Châtre, et al., "Skeletal Muscle Stem Cells Adopt a Dormant Cell State Post Mortem and Retain Regenerative Capacity," *Nature Communications* 3 (2012): 903, https://doi.org/10.1038/ncomms1890.

6. M. Singh, X. Ma, E. Amoah, and G. Kannan, "In Vitro Culture of Fibroblast-Like Cells from Postmortem Skin of Katahdin Sheep Stored at 4°C for Different Time Intervals," *In Vitro Cellular & Developmental Biology Animal* 47: 290–293, https://doi.org/10.1007/s11626-011-9395-6.

7. M. Levin, "Life, Death, and Self: Fundamental Questions of Primitive Cognition Viewed through the Lens of Body Plasticity and Synthetic Organisms," *Biochemical and Biophysical Research Communications* 564 (2021): 114–133, https://doi.org/10.1016/j.bbrc.2020.10.077.

8. D. Blackiston, E. Lederer, S. Kriegman, S. Garnier, J. Bongard, and M. Levin, "A Cellular Platform for the Development of Synthetic Living Machines," *Science Robotics* 6, no. 52 (2021): eabf1571, https://doi.org/10.1126/scirobotics.abf1571.

9. S. Kriegman, D. Blackiston, M. Levin, and J. Bongard, "Kinematic Self-Replication in Reconfigurable Organisms," *PNAS* 118, no. 49 (2021): e2112672118, https://doi.org/10.1073/pnas.2112672118.

10. G. Gumuskaya, P. Srivastava, B. G. Cooper, et al., "Motile Living Biobots Self-Construct from Adult Human Somatic Progenitor Seed Cells," *Advanced Science* 11 (2023): e2303575, https://doi.org/10.1002/advs.202303575.

11. B. Gert, "Matters of 'Life' and 'Death'," *Hastings Center Report* 36, no. 3 (2006): 4.

12. P. A. Corning, S. A. Kauffman, D. Noble, J. A. Shapiro, R. I. Vane-Writght, and A. Pross, *Evolution "on Purpose": Teleonomy of Living Systems* (Cambridge: The MIT Press, 2023), https://doi.org/10.7551/mitpress/14642.001.0001.

13. S. A. Kaufmann, *The Origins of Order: Self-Organization and Selection in Evolution* (New York: Oxford University Press, 1993).

14. R. S. Bonadio, L. B. Nunes, P. N. S. Moretti, et al., "Insights into How Environment Shapes Post-Mortem RNA Transcription in Mouse Brain," *Scientific Reports* 11, no. 1 (2021): 13008, https://doi.org/10.1038/s41598-021-92268-y.