Proceedings of the 2nd International Conference on Modern Medicine and Global Health
DOI: 10.54254/2753-8818/8/20240390

Exploring the parabiosis model's evolution, applications and effects

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Abstract. The parabiosis model, a surgical technique that has been in use for 150 years, has emerged as a helpful tool for examining the complex interactions across many biological systems. Through the surgical fusion of the circulatory systems of two viable species, commonly mice, this methodology facilitates the transfer of blood, cells, and soluble components between the interconnected entities. This comprehensive review provides a thorough examination of the parabiosis model, including its historical development and various applications in contemporary research. Additionally, it delves into the role of the parabiosis model in elucidating the potential rejuvenating effects of young blood on aged tissues, as well as its implications for age-related diseases. The study aims to elucidate the significant insights that have been provided by the mouse parabiosis model and underlines its promise as an experimental platform for deciphering the intricacies of inter-species interactions. The field of study exhibits promising potential for future discoveries, providing vital knowledge that has the potential to lead to new achievements.

Keywords: Parabiosis Model, Stem Cell, Blood, Aging, Regenerative Medicine.

1. Introduction

The exploration of biological phenomena has consistently been motivated by the pursuit of understanding the complex interactions among many systems within live creatures. The parabiosis model has gained significance as a surgical technique over the course of the last 150 years. It offers a distinct and helpful method for investigating intricate interconnections. The procedure entails the surgical anastomosis of the circulatory systems of two viable creatures, frequently employing mice as experimental models, thereby facilitating the reciprocal transfer of essential constituents, including blood, cells, and soluble substances.

The primary objective of this extensive research is to offer a thorough examination of the Parabiosis model, elucidating its historical roots and evolutionary progression. This study will explore the various uses of this phenomenon in current research, where it has significantly contributed to the comprehension of important biological features such as tissue regeneration and the effects of aging on the human body. The Parabiosis model is of significant interest due to its exploration of the rejuvenating effects of youthful blood on elderly tissues, presenting a potential avenue for addressing age-related disorders. Through the examination of inter-species interactions' impact on tissue regeneration and immunological response, this experimental platform has unveiled promising prospects for innovative therapeutic approaches. This paper will now proceed to examine the historical context, methodological issues, and

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current breakthroughs that have led to the increasing importance of the Parabiosis model in modern scientific research.

In contemporary scientific research, the parabiosis model has garnered significant interest owing to its adaptable nature and notable capacity to elucidate diverse physiological and pathological processes. The historical progression of this phenomenon has witnessed its transformation from an initial experimental novelty to a potent instrument that holds the potential to expand the horizons of knowledge. By comprehending the potential and constraints of this technique, researchers can successfully utilize it to investigate fundamental inquiries about interactions between different species and explore novel possibilities for breakthroughs in regenerative medicine and other related fields [1].

2. History of Parabiosis Model

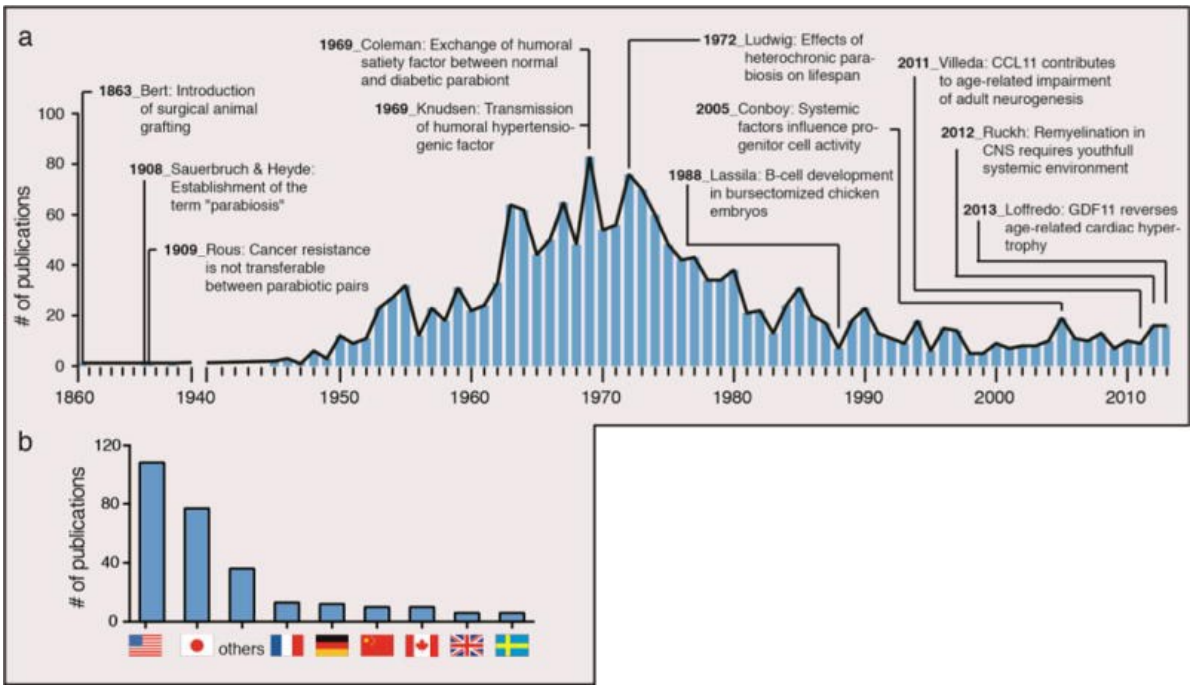

Figure 1. The annual frequency of publications related to parabiosis from 1860 to 2013 [2].

The figure 1 depicts the annual frequency of publications related to parabiosis from 1860 to 2013. Prominent studies that have produced groundbreaking findings are specifically highlighted. Furthermore, this study presents a compilation of papers that focus on parabiosis investigations, which have been grouped based on the nations in where they were conducted [2].

In 2005, a research group headed by Professor Thomas Rando from the Department of Neurology at the Stanford University School of Medicine established vascular anastomoses between young and aged rats. After a period of five weeks, the researchers saw a notable phenomenon wherein the older rats exhibited a rejuvenated state of stem cells in their livers and skeletal muscles. Furthermore, these rats had a nearly equivalent capacity to heal muscle injury as their younger counterparts, hence highlighting a surprising outcome. The juvenile mice, on the other hand, exhibited signs of accelerated aging and displayed a reduction in muscle regeneration that was not consistent with their chronological age.

In 2013, a study was conducted by Amy Wagers, a researcher affiliated with Harvard University, wherein experiments were performed on conjugated rats. The findings revealed that older rats exhibited a certain degree of rejuvenation when they shared blood with younger rats, as certain elemental factors in their blood were found to be shared. The study revealed that across several tissues, including the heart, brain, and muscles, the blood obtained from young rats exhibited rejuvenating effects on aging organs,

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resulting in enhanced strength, cognitive abilities, and overall health in the older rats. According to the source cited [3], the intervention resulted in an improvement in the luster of their fur.

In 2014, a significant study on parabiosis was conducted by Tony Wyss-Coray, a neuroscientist affiliated with Stanford University in California. The experimental findings revealed that older mice exhibited potential enhancements in memory and learning capabilities subsequent to the administration of plasma derived from younger mice. The findings of this work indicate a potential expedited approach for conducting comparable research, wherein the recurrent administration of plasma from younger animals serves as a straightforward and viable method for conducting xenobiotic experiments [4].

3. Various applications of the Parabiosis Model in modern research

The process of parabiosis has been observed to have positive effects on cognitive performance, muscle strength, and bone healing in aged mice. Additionally, it has been discovered that parabiosis has the ability to reverse DNA methylation aging in several organs inside the mouse body. In order to investigate the systemic impacts of parabiosis on various organs and cells, the investigators conducted a study using mice at two different stages of life: 4 months and 19 months, which can be considered analogous to 25 and 65 years of age in humans, respectively. The mice were subjected to a parabiosis experiment for a duration of 5 weeks. The cells from a total of 20 distinct organs and tissues were subjected to flow sorting in this study. These included the bladder, brain, brown fat, gonadal fat, heart, kidney, colon, muscle, liver, lung, tongue, thymus, trachea, as well as several other tissues. The utilization of single-cell type annotation facilitated the examination of cellular and genetic expression patterns in disparate symbiosis-induced rejuvenation mechanisms, expedited aging processes, and typical aging processes [4].

The study involved the examination of 49 distinct cell types in juvenile mice in comparison to Heterochronic parabiosis juvenile mice, as well as the analysis of 51 distinct cell types in typical elderly mice and Heterochronic parabiosis elderly mice. Hepatocytes exhibited the highest degree of prominence among cell types in both normal aging and in reaction to senescent blood at the cellular level. Furthermore, hepatocytes demonstrated the most significant reversal of senescence gene-related effects following exposure to youthful blood. In contrast, endothelial cells exhibit distinct transcriptional sensitivities to either young or elderly blood in a tissue-specific manner, primarily as a result of their restricted exposure to blood. Adipose mesenchymal stem cells, among other cell types, exhibit significant variations in gene expression within adipose tissue. One of the defining characteristics of the aging process is the progressive accumulation of immune cells in various organs. The researchers observed notable alterations in gene expression patterns in both lymphocytes and myeloid cells in mice via parabiosis tests. The process of aging has been observed to induce various changes in certain cell types within the blood. The researchers' establishment of the parabiosis single cell atlas provides confirmation that blood has the capacity to modify nearly all cells, including those that do not have direct contact with blood [5].

When considering the genetic aspect of parabiosis, it is observed that the infusion of young blood has the ability to counteract the decline in gene expression related to the subunits of the electron transport chain that occurs naturally with aging. Furthermore, the introduction of young blood has been observed to promote cell type-specific mitochondrial gene expression, providing evidence in favor of the notion that young blood has a wide positive impact on mitochondrial function. Various cell types, including endothelial cells, adipose mesenchymal stromal cells, and immune cells, demonstrate comparable transcriptional patterns across diverse tissues. For instance, the expression of collagen genes diminishes with advancing age, leading to significant cross-linking of collagen molecules, so compromising its physiological functions inside the organism.

The introduction of new cells and tissues into the body has the potential to decelerate or even reverse the natural progression of aging, thereby playing a crucial role in mitigating the susceptibility to illnesses and preserving overall well-being. The researchers employed single-cell RNA sequencing to analyze a comprehensive set of over 20 distinct organs and tissues in heterochronic parabiosis mice. Through this approach, they were able to identify distinct cellular reactions to both young and old blood. Notably,

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adipose mesenchymal stromal cells, hematopoietic stem cells, and hepatocytes were found to exhibit heightened sensitivity to blood. Furthermore, through the examination of alterations in gene expression, the investigators have discovered that mitochondrial function assumes a significant role in the process of rejuvenation. This is evident from the observation that the collective expression of genes associated with mitochondrial function is diminished in aged blood, whereas young blood reinstates gene expression in distinct cell types. The aforementioned global data serve as the basis for a comprehensive comprehension of the interaction between substances present in the bloodstream and the maintenance of cellular structure and function.

4. Impact of the Parabiosis Model on Age-Related Diseases

In accordance with the alternative hypothesis positing that the revitalization of aged mice in heterochronic parabiosis experiments can be attributed to the mitigation or annulment of deleterious proteins in the bloodstream of older mice through the introduction of younger blood, researchers Michael J. Conboy and Irina M. Conboy from the Department of Bioengineering at the University of California, Berkeley, undertook a comprehensive investigation into the impacts of heterochronic parabiosis experiments on the well-being of mice. The pair undertook a comprehensive investigation. The researchers were inclined to favor this hypothesis due to their discovery in a study where blood was transferred between young and old animals without any physical connection. The results indicated that the young animals exhibited signs of aging, implying that the presence of young blood circulating within young veins was unable to counteract the detrimental components present in the older blood, thus allowing them to dominate [6].

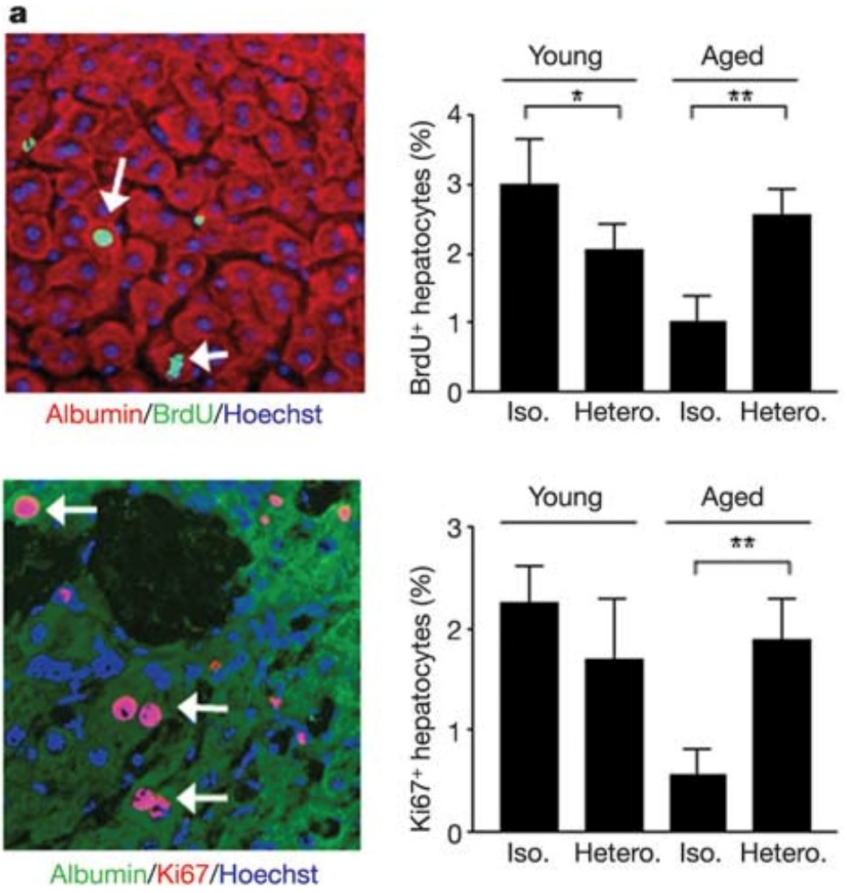

Figure 3. The process of parabiotic matching involving individuals of varying ages [7].

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In figure 3, the process of parabiotic matching involving individuals of varying ages has been found to facilitate the proliferation of liver precursor cells in old individuals, while also restoring the activation of molecular mechanisms associated with young liver regeneration. Following a period of 5 weeks of pairing, the mice were subjected to BrdU injections at varying intervals of 5, 3, and 1 day prior to their death. The liver slices were analyzed to assess hepatocyte proliferation by employing dual staining techniques with albumin and either BrdU or Ki67. The doubly labeled cells were identified by arrows pointing to their nuclei [7].

In order to validate this hypothesis, the researchers, Conboys et al., proposed the concept of neutral blood exchange. Rather of completely substituting the blood of older mice with that of younger mice, the researchers opted to replace only half of the plasma in the older mice with a combination of saline and albumin. The research investigation revealed that the process of neutral blood exchange yielded notable improvements in the well-being of the elderly mice, exhibiting outcomes akin to the anti-aging benefits shown when receiving blood from younger mice. According to Conboy, the anti-aging mechanism of neutral blood exchange can be understood as a molecular reset button. This process effectively reduces the levels of various pro-inflammatory proteins that tend to accumulate with age, while simultaneously increasing the presence of beneficial proteins that facilitate blood vessel formation. The process of neutral blood exchange conducted in elderly mice exhibits similarities to the therapeutic plasma exchange (TPE) procedure employed in clinical settings for the treatment of various diseases. TPE involves the substitution of a patient's plasma with saline and purified albumin, thereby restoring blood cells to the patient while diluting the proteins present in the circulating blood. This process ensures that the patient's blood cell composition remains unaltered, while simultaneously eliminating detrimental factors such as cytokines, auto-reactive antibodies or toxins, as well as the underlying causes of specific diseases.

The Conboys and their research team conducted proteome studies on plasma samples obtained from individuals undergoing therapeutic plasma exchange (TPE) in a clinical setting. The objective of their study was to gain insights into the alterations occurring in blood proteins during plasma replacement.The TPE therapy facilitates a comprehensive alteration in the proteomic profile, leading to the rejuvenation of the biological system. This rejuvenation encompasses various beneficial effects, such as the enhancement of regenerative potential, mitigation of inflammatory processes, decrease in the levels of circulating biomarkers associated with neurodegeneration and cancer, preservation of circulating cells in the bone marrow and lymphatic system, attenuation of cellular senescence, and mitigation of DNA damage.

The characteristics of older blood encompass persistent inflammation, heightened DNA damage in peripheral blood mononuclear cells, and immunological dysregulation, all of which contribute to an elevated susceptibility to various diseases. The TPE procedure effectively restores the systemic environment to a state resembling youthfulness through the quick and significant reduction of age-related inhibitors in the conventional pathways responsible for regulating tissue maintenance and repair. The initial impact of this intervention is a decrease in inflammation, which is subsequently followed by enhanced cellular and molecular homeostasis through regulated intercellular signaling communication and a decrease in biological variability [8].

According to the Conboys' research findings, instead of subjecting individuals to the potential risks associated with the infusion of young plasma, a more viable approach involves diluting the detrimental proteins present in older plasma. This dilution process would effectively mitigate the adverse health consequences associated with these proteins, enhance the overall blood environment, and facilitate the production of more advantageous proteins.

5. Conclusion

In conclusion, the Parabiosis Model is a surgical approach that has been employed for more than a century and a half, and has significantly contributed to the advancement of biological research. Through the meticulous suturing of the circulatory systems of two animals of disparate ages, the exchange of blood, organs, and cells occurs, so facilitating an enhancement in the overall health and vitality of the

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older organism, rendering it more youthful. In this extensive analysis, we explore the historical progression of the parabiosis model, its contemporary utilization in scientific investigation, and its wide-ranging ramifications for human beings. Moreover, the parabiosis model exhibits considerable promise as a research topic, and its efficacy in non-human creatures suggests its potential applicability to humans as well. Nevertheless, it is imperative to thoroughly contemplate the ethical implications of implementing this surgical experiment on human subjects, as it entails a significant degree of cruelty. Furthermore, it is crucial to acknowledge that such an endeavor may necessitate substantial sacrifices while yielding only marginal advantages [7].

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