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The Connection between Planarian and Human Stem Cell Differentiation

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Abstract

Stem cell research stands at the forefront of regenerative medicine, offering the potential to address a broad spectrum of diseases, injuries, and genetic disorders. Pluripotent stem cells, including embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs), are particularly valuable for their ability to differentiate into any cell type, providing opportunities for regenerative therapies, drug discovery, and personalized medicine. However, the clinical application of these stem cells faces significant challenges, including ethical concerns, immune rejection, and a high risk of tumorigenesis. A promising alternative model for regenerative medicine is provided by Planarians, flatworms known for their remarkable ability to regenerate entire bodies from small fragments, driven by neoblasts—multipotent stem cells that can regenerate tissues without tumor formation. This review explored the molecular mechanisms that control Planarian regeneration, including telomerase activity, chromatin modification, and key signaling pathways like the TOR pathway and ERK kinase. These mechanisms regulate the proliferation and differentiation of neoblasts, highlighting the networks that enable precise control of stem cell fate. Additionally, Planarian stem cells share molecular similarities with human stem cells, such as hierarchical differentiation pathways and the roles of Piwi homologous in maintaining stem cell function, suggesting conserved regenerative processes across species. By comparing Planarian and human stem cell biology, this review identified how the unique regenerative capabilities of Planarians could inform safer and more effective human stem cell therapies, particularly by reducing the risks of tumorigenesis and immune rejection. Furthermore, despite the promising potential, significant research gaps remain, including the challenges of translating these mechanisms to humans, particularly given differences in body size adaptation and physiological responses. This review ultimately underscored the value of Planarian regenerative mechanisms in advancing regenerative medicine, offering novel strategies for improving the safety, efficacy, and ethical acceptability of stem cell-based therapies.

Keywords: Neoblasts, Planarians, Transcription Factors, Nanogs, Neoblast, and Muse Cells

1. Introduction

Stem cells are currently one of the most studied topics in the medical field due to their potential to revolutionize regenerative medicine and their ability to transform into a variety of cell types. A stem cell is an undifferentiated cell capable of differentiating into multiple specialized cell types (Alba et al., 2020). The types of stem cells primarily include pluripotent and adult stem cells. Pluripotent stem cells are cells that can give rise to almost any cell type in the body. Among pluripotent stem cells are embryonic stem cells, derived from the inner cell mass of the blastocyst-stage embryo. Embryonic stem cells are invaluable for their ability to become virtually any type of cell in the body, but their use is accompanied by ethical concerns due to the destruction of human embryos. An alternative is induced pluripotent stem cells (iPSCs), which are somatic cells, such as skin or blood cells, that have been reprogrammed to an embryonic stem cell-like state. This reprogramming is achieved by introducing specific transcription factors, namely Oct4, Sox2, Klf4, and c-Myc (collectively known as OSKM) (Cai et al., 2015). The biggest advantage of

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iPSCs is that they circumvent the ethical issues associated with embryonic stem cells while still offering the potential for pluripotency, which is the ability to differentiate into any cell type. However, both embryonic stem cells and iPSCs present significant challenges in regenerative medicine, including complex reprogramming processes and the risk of tumorigenesis—the formation of tumors. This risk arises because the same properties that allow stem cells to proliferate and differentiate can also lead to uncontrolled cell growth if not properly regulated. This paper aims to bridge the gap in research by exploring Planarian stem cells as a model to address the issue of tumorigenesis in human stem cell therapies. Specifically, it examined the molecular mechanisms behind Planarian regeneration and how these mechanisms could aid the development of safer, more effective human stem cell therapies that avoid the risks associated with tumor formation. By studying Planarians, new strategies for harnessing stem cell potential while minimizing tumorigenic risks can be discovered.

1.1 Planarian Regeneration

In contrast to human stem cells, the regenerative abilities of Planarians offer a fascinating natural model of pluripotency without these drawbacks. Planarians are a type of flatworm belonging to the phylum Platyhelminthes, characterized by their flat, soft-bodied, triploblastic body plan (Rink, 2013). These organisms possess an extraordinary ability to regenerate entire body parts, an ability driven by pluripotent stem cells known as neoblasts. Neoblasts constitute about 20% of the Planarian body and are remarkable because they can differentiate into nearly any cell type, similar to human pluripotent stem cells. This capacity for regeneration is surprising because pluripotency was initially thought to be confined to embryonic stem cells (Rink, 2013). Neoblasts are sometimes referred to as "dividing cells," and specific markers, such as phosphoHistone H3 Ser10 (H3P), BrdU incorporation, and PCNA, help identify these cells (Newmark & Alvarado, 2000; Orii et al., 2005; Salvetti et al., 2000). Planarians' neoblasts challenge our understanding of pluripotency as being limited to embryonic stages. Their regenerative capabilities raise intriguing questions about the molecular mechanisms that enable these cells to maintain and deploy their pluripotency so efficiently and safely. By studying Planarians, researchers hope to uncover insights that could transform human stem cell therapies. The ability of Planarian neoblasts to regenerate without forming tumors is particularly intriguing. If scientists can decipher the molecular pathways and transcription factors that allow neoblasts to function so effectively, they could potentially apply this knowledge to human cells. By modifying similar pathways in human cells, it might be possible to induce regenerative capabilities without the need for embryonic material or the complex reprogramming associated with iPSCs. This approach could offer a safer, more efficient means of developing stem cell therapies, reducing the risks of tumorigenesis and improving the reliability of these treatments. Furthermore, Planarians provide a unique platform for understanding the balance between proliferation and differentiation, crucial for effective regeneration. These insights could lead to breakthroughs in treating degenerative diseases and injuries where tissue regeneration is needed, offering hope for more effective and ethical treatments in human medicine. In conclusion, the study of Planarians and their remarkable regenerative capabilities offers a promising avenue for advancing stem cell research and therapy. By learning from these simple yet sophisticated organisms, we may unlock new potential in human regenerative medicine, providing safer and more ethical solutions to some of the most pressing challenges in healthcare today. As research continues, the lessons learned from Planarians could pave the way for groundbreaking advancements in how we understand and harness the power of stem cells.

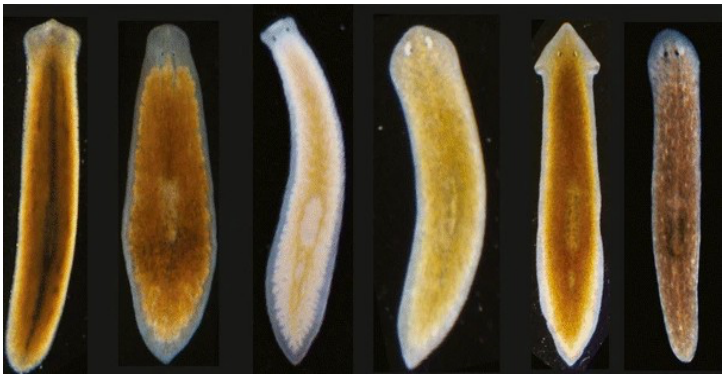

Figure 1. Planarian species from Europe. Left to right: *Polycelis* sp., *Planaria torva*, *Dendrocoelum lacteum*, *Schmidtea polychroa*, *Dugesia gonocephala*, *Schmidtea mediterranea* (Rink, 2013).

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2. Methods

This literature review was conducted using PubMed and Google Scholar, focusing on studies published between 2000 and the present that investigated neoblasts, planarians, and transcription factors. The search included both review and original research articles that examined the role of neoblasts or pluripotency factors in regeneration and stem cell function, with a preference for studies including advanced methods like RNA interference, gene expression analysis, and stem cell tracking. A total of 35 studies were included, and conflicting findings were compared based on the recency and credibility of the studies, with more recent research given priority. The review prioritized studies with high experimental reliability, and differences were noted as likely arising from differences in experimental design or model organism variations. Limitations of the review included the rapid pace of discovery in the field and the complexity of gene expression in planarians, which can lead to variability in results. Additionally, the focus on primary research may have limited the scope of broader trends in the field that could have been explored in review articles.

3. Enzymes and Transcription Factors in Planarians Figure 2

Planarians are flatworms renowned for their extraordinary regenerative abilities, largely attributed to a unique population of neoblasts which can differentiate into any cell type, enabling Planarians to regenerate lost or damaged tissues, even entire organs. Understanding the molecular pathways and signals that control neoblast differentiation and proliferation is important for studying regeneration and potentially applying this knowledge to regenerative medicine. The enzyme telomerase was found to be highly responsive to modes of both regeneration and reproduction, highlighting its role in maintaining genomic stability and facilitating cellular proliferation during tissue repair (Tan et al., 2012). Chromatin modifiers further regulate gene expression by altering chromatin structure, ultimately controlling the accessibility of DNA to transcriptional machinery (Rink, 2013). Piwi homologous, such as Smedwi-1, Smedwi-2, and Smedwi-3, are critical neoblast markers (Rink, 2013). Smedwi-1 is highly expressed in neoblasts, while knockdown of Smedwi-2 and Smedwi-3 results in the destruction of Neoblasts, demonstrating their essential role in neoblast maintenance and proliferation (Nakagawa et al., 2012; Palakodeti et al., 2008; Reddien et al., 2005). Neoblasts also share molecular similarities with germ cells, including the presence of chromatoid bodies involved in post-transcriptional gene regulation (PTGR) and reliance on nanos, a protein responsible for germline fate transition (Handberg-Thorsager & Saló, 2007; Sato et al., 2006; Wang et al., 2007). The TOR pathway is pivotal in regulating neoblast responses to wounding and regeneration (González-Estévez et al., 2012; Peiris et al., 2012; Tu et al., 2012). It regulates cell growth and division by detecting nutrient availability, energy status, and stress conditions, emphasizing its role in managing cellular reactions to environmental fluctuations (Peiris et al., 2012).This pathway is conserved across eukaryotes, including humans, underscoring its evolutionary significance (Zoncu et al., 2011). Other key regulators include SMED-EGFR-1 and Dj-P2X, which modulate neoblast responses to environmental cues, and FGF receptors, which are also expressed in neoblasts (Fraguas et al., 2011; Sakurai et al., 2012; Wagner et al., 2012). When scientists silenced SMED-EGFR-1, they found that the eye pigment cells in Planarians regenerated at a slower rate (Fraguas et al., 2011). SMED-inx11, a gap junction protein, plays a role in local niche signals, ensuring communication between cells (Oviedo & Levin, 2007). The transition from dividing neoblasts to early progeny requires SMED-p53, while Erk kinase helps cells exit the proliferative state, coordinating the progression from stem cell to differentiated cell (Pearson & Sánchez Alvarado, 2010).

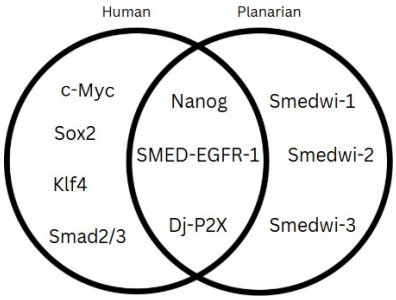

Figure 2. Transcription Factors.
*Made on Canva

Another significant signaling pathway is the Basic Fibroblast Growth Factor (bFGF) pathway, which supports pluripotency by activating the PI3K/AKT pathway while inhibiting ERK activity and GSKβ dephosphorylation (Armstrong et al., 2006; Greber et al., 2007; Kang et al., 2005; Levenstein et al., 2006; Li et al., 2007). The PI3K/AKT pathway is vital in influencing pluripotency, as it upregulates Nanog, a vital transcription factor for maintaining

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pluripotency, and prevents apoptosis through AKT activity (Paling et al., 2004; Romorini et al., 2016; Storm et al., 2007, 2009). Differentiation into specific cell lineages involves various transcription factors, such as ERG, HOXA5, HOXA9, HOXA10, LCOR, RUNX1, and SPI1 (Peng et al., 2023). These factors are typically detected in myeloid, B, and T cells of engrafted recipients, confirming their role in lineage specification and commitment during differentiation (Varzideh et al., 2023). However, it is important to note that such factors are absent in Planarians, highlighting the complexity and specificity of the differentiation process in higher organisms, particularly in the context of hematopoietic lineage differentiation. Overall, the network of molecular pathways and signals governing human stem cell differentiation is fundamental to understanding stem cell biology and its therapeutic potential. These pathways not only regulate pluripotency and self-renewal but also guide the precise differentiation into specific cell types, crucial for regenerative medicine and tissue engineering applications.

4. Parallels between Planarian and Human Stem Cell Differentiation

Planarians, with their remarkable regenerative abilities, are an interesting model for studying stem cell biology. This comparison is particularly intriguing when exploring how similar mechanisms might be used in human medicine. The differentiation of human stem cells is a complex process controlled by various molecular pathways and signals. A key player in this process is the TGF-β/Activin A/Nodal pathway, which plays a crucial role in regulating pluripotency (Varzideh et al., 2023). This pathway activates Smad2/3, promoting the self-renewal of human embryonic stem cells (ESCs) by activating the expression of Nanog (Varzideh et al., 2023). Muse cells, known as "nontumorigenic pluripotent stem cells," also highlight the intricacy of stem cell differentiation (Simerman et al., 2016). Found in both humans and Planarians, these cells are present in all connective tissues and express Nanog, marking them as pluripotent stem cells (Simerman et al., 2016). This cross-species presence underscores the evolutionary conservation of certain stem cell mechanisms. Both humans and Planarians possess neuropeptides that play a crucial role in regulating critical biological processes. In humans, these neuropeptides are integral to the endocrine and lymphatic systems, which are essential for maintaining homeostasis and responding to various physiological challenges. A key similarity between Planarian and human stem cells is the presence of hierarchical differentiation pathways. Both types of stem cells begin with general pluripotency. This pluripotency gradually narrows as the stem cells specialize, ultimately leading to the formation of specific cell types. This process is vital for both tissue regeneration in Planarians and various regenerative medicine applications in humans.

Another interesting parallel in both humans and Planarians is the presence of Muse cells which are a type of pluripotent stem that is capable of differentiating into multiple cell types (Simerman et al., 2016). Their discovery in Planarians suggests a conserved mechanism across species that could have significant implications for regenerative medicine. Both human and Planarian stem cell proliferation models involve the ERK kinase pathway (Varzideh et al., 2023). This pathway is a crucial component of the signaling network that regulates cell growth, differentiation, and survival. Its conservation across species highlights its importance in maintaining the balance between stem cell proliferation and differentiation. Moreover, research has shown that Planaria species-Malta (PSM) extract can increase the expression of SPI1, a gene involved in stem cell differentiation (Suleiman et al., 2020). This finding is particularly important because SPI1 plays a critical role in the differentiation of pluripotent stem cells in humans (Peng et al., 2023). If it is possible to harness the ability of Planarian extracts to enhance SPI1 expression, it could potentially lead to new ways to promote stem cell differentiation in regenerative therapies. This cross-species comparison not only deepens our understanding of stem cell biology but also opens up new avenues for medical research and treatment.

5. Conclusion

The parallels between Planarian regeneration and human stem cells open up exciting possibilities for advancing regenerative medicine. Both systems share hierarchical differentiation pathways, involve neuropeptides, and utilize crucial signaling pathways like the ERK kinase, emphasizing the potential for cross-species insights to enhance human stem cell therapies. The discovery that Planaria species-Malta (PSM) extract can increase the expression of SPI1, a gene involved in pluripotent stem cell differentiation in humans, highlights a promising area of research that could have significant implications for human health.

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5.1 Future Directions

One of the key areas of future research should focus on identifying and modulating the transcription factors that enable Planarian neoblasts to maintain pluripotency. Understanding these factors could enable scientists to apply similar mechanisms in human stem cells, potentially by upregulating elements that promote pluripotency and downregulating those that limit cell differentiation. This approach could lead to more effective stem cell therapies and regenerative treatments. Developing advanced in vitro systems to culture and study Planarian neoblasts is another promising direction. By creating controlled environments for detailed molecular analysis, researchers can dissect the signaling pathways and gene networks involved in the pluripotent capabilities of neoblasts. Insights gained from these studies could be applied to human stem cells, enhancing our ability to guide their differentiation and proliferation in therapeutic contexts. Comparative genomics and proteomics studies between Planarians and humans offer another valuable research avenue. By identifying conserved genes and proteins involved in stem cell regulation, researchers can gain evolutionary insights that may reveal potential targets for enhancing human regenerative capacities. This approach could bridge the gap between Planarian biology and human medical applications, leading to innovative therapies for a variety of conditions. Investigating whether the regeneration pathways present in Planarians can be replicated or mimicked in human cells is also crucial. For instance, studying the role of specific pathways like TOR in Planarian regeneration might reveal new ways to enhance human cell regeneration. If these pathways can be successfully manipulated in human cells, they could lead to significant breakthroughs in regenerative medicine. To translate these findings into clinical applications, collaborative research efforts are essential. Future research also aims to develop in vitro conditions to further dissect these mechanisms and address challenges in maintaining a dynamic steady state between proliferating stem cells and differentiated cells (Rink, 2013). Molecular biologists, geneticists, and bioengineers must work together to develop novel techniques for stem cell manipulation. Such interdisciplinary collaborations can drive innovation and help bring the benefits of Planarian research into human medical practice.

5.2 Challenges and Questions

Planarian neoblasts offer valuable insights into regenerative medicine, particularly in understanding human stem cell capabilities. A key question is whether external or intrinsic mechanisms and signals control fate and differentiation. On-demand replacement is based on tissue needs, such as replacing dying cells, needing "replace me" signals. However, in the case of Planarians, if a cell type like photoreceptors is entirely replaced after head amputation, there is no "replace me" signal, yet the cells regenerate, suggesting that Planarians possess mechanisms beyond simple replacement cues (Rink, 2013). The challenge with intrinsic mechanisms is that it could lead to the same progenitor production in all the parts of the organism, potentially producing some cells in unneeded areas, like photoreceptors in the tail (Rink, 2013). These issues arise from assuming that cell fate specification occurs at a single point or stage, whereas it is hierarchical, with a progressively limited capacity for differentiation (Rink, 2013). In a hierarchical model, the process starts with general categories (neuronal, intestinal, muscle, eye) that become more specific at later stages (Rink, 2013). This approach allows for the integration of both signal-mediated external signals and cell-intrinsic signals, providing long-term stability of the lineage tree through intrinsic mechanisms and enabling on-demand fate choices through signal-mediated external signals at later stages (Rink, 2013). The molecular pathways and signals governing neoblast differentiation and proliferation in Planarians are complex, involving a delicate balance between intrinsic genetic programs and extrinsic environmental cues. Understanding these processes provides valuable insights into the fundamental biology of stem cells and regeneration. The hierarchical model of cell fate specification, with its integration of both intrinsic and extrinsic signals, offers a promising framework for comprehending how Planarians achieve their remarkable regenerative capabilities. Collaborations between molecular biologists, geneticists, and bioengineers will be key to developing novel stem cell manipulation techniques and translating them into clinical applications. However, significant challenges remain. The Planarian model presents unique challenges for translating regenerative insights into human applications, given differences in body size adaptation and physiological responses. The potential for tumorigenesis is another major concern, and ensuring safety is crucial before clinical use. Ethical considerations also come into play when modifying human stem cells. Additionally, the complexity of human tissues

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presents difficulties in applying Planarian mechanisms directly to humans, requiring careful navigation to avoid unintended consequences. Finally, any new techniques must be scalable and reproducible across different cell types and individuals to be viable for widespread therapeutic use. Addressing these challenges will require innovative approaches and a strong focus on safety and efficacy.

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