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Beneficial Effects of Wharton's Jelly Mesenchymal Stem Cell Conditioned Medium on Developing Zebrafish Embryos: Antioxidant, Survival and Regenerative Impacts

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Abstract

Exploring the Therapeutic Potential of Stem Cell Cultured Conditioned Media: Insights from Zebrafish Embryo Evaluation Conditioned media obtained from stem cell cultures offer promising prospects as innovative therapeutic interventions against a range of diseases, owing to their rich reservoir of growth, trophic, and protective factors. Crucially, thorough in vivo assessment of these products' effects and safety is imperative. Zebrafish emerges as an ideal testing ground for high-throughput toxicological analysis, presenting an opportunity to minimize reliance on mammalian models while maintaining reliability. In this study, we delved into the biological ramifications of exposing zebrafish embryos to conditioned medium derived from Wharton's jelly mesenchymal stem cells. Employing a multifaceted approach involving molecular, embryological, behavioral, and in vivo imaging techniques, we unearthed a spectrum of outcomes arising from non-toxic/non-lethal dosages of the conditioned medium. Notably, this exposure triggered an array of responses including antioxidant fortification, anti-apoptotic activity, and pro-regenerative potential. This was underscored by the upregulation of several genes associated with antioxidant defense, glycolysis, and cell survival (bcl2l1, mcl1a, and bim). Simultaneously, the conditioned medium downregulated pro-apoptotic markers. Of note, this comprehensive investigation marks the pioneering attempt to thoroughly analyze the effects of conditioned medium on an entire organism, encompassing developmental, molecular, and behavioral perspectives. We hold a strong belief that these findings will lay a robust foundation for the future therapeutic utility of conditioned media.

Keywords: Conditioned medium • Zebrafish • Antioxidant

Introduction

The clinical applications of mesenchymal stem cells within regenerative medicine have burgeoned, with ongoing clinical trials addressing an array of conditions, from heart ailments to COVID-19 and beyond. Intriguingly, the efficacy of these treatments largely hinges on the spectrum of bioactive molecules secreted by mesenchymal stem cells into the growth medium, a milieu termed the conditioned medium (hereafter referred to as CM). Presenting a departure from cell-based therapies, the cell-free approach grounded in CM has garnered remarkable attention. This owes much to its ability to circumvent the common challenges tied to mesenchymal stem cell administration, such as rejection and malignant transformations, thereby markedly enhancing patient safety. Moreover, this avenue underscores the advantageous prospect of achieving substantial quantities of CM for cell-free therapies, utilizing a notably smaller cohort of mesenchymal stem cells in contrast to the quantities typically necessitated by cell-based therapeutic regimens. Notably, the CM that is conventionally discarded as spent culture medium during mesenchymal stem cell expansion can be rescued and repurposed, providing an economical and robust reservoir of bioactive agents for therapeutic application [1].

Investigating the benefits of mesenchymal stem cell-derived conditioned medium on zebrafish embryos given this premise, the preclinical evaluation of the safety and effectiveness of these products in vivo is of paramount importance. In this context, the zebrafish (Danio rerio), a small freshwater cyprinid, emerges as an optimal platform for efficient toxicological analysis. This system not only facilitates the reduction of reliance on mammalian models while maintaining reliability, but also offers key advantages such as straightforward lab management, high reproductive rate, external fertilization, rapid life cycle, and a substantial degree of genome conservation with mammals [2]. Remarkably, around 99% of zebrafish genes crucial for embryonic development are analogous to those in humans. Adding to its attributes, zebrafish embryos possess optical transparency and permeability to water-soluble molecules, enabling non-invasive live imaging of morphogenetic processes and outcomes following exposure to conditioned medium (CM).

Description

In this study, we explored the biological implications of exposing developing zebrafish embryos to CM derived from Wharton's jelly mesenchymal stem cells obtained from human umbilical cords. These cells, in comparison to mesenchymal stem cells from other sources, exhibit exceptional secretion of growth, trophic, and protective factors. Importantly, the use of umbilical cords for research is ethically sound, as they are typically discarded after birth [3].

Using a blend of molecular, cellular, embryological, behavioral, and in vivo imaging techniques, we thoroughly assessed the multifaceted outcomes triggered by CM exposure. These encompassed beneficial impacts like antioxidant reinforcement, pro-survival effects, and pro-regenerative influence, all affecting specific marker gene expression. Particularly noteworthy was the upregulation of a cluster of genes linked to antioxidant defense (nrf2, brg1, sirt1, sirt6, foxO3a, sod2, and cat), alongside the glycolytic gene ldha. Additionally, CM treatment induced the elevation of pro-survival elements within the bcl2 family (bcl2l1, mcl1a, and bim), accompanied by the downregulation of established pro-apoptotic markers (baxa, caspase-3a, and caspase-8).

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In the realm of regenerative and protective medicine, cell-free strategies involving CM from various sources are rapidly emerging as attractive therapeutic options, circumventing challenges tied to handling and delivering intact mesenchymal stem cells to recipients [4]. Recently, CM sourced from Wharton's jelly mesenchymal stem cells extracted from human umbilical cords has gained attention due to its rich content of bioactive molecules, making it a theoretically optimal candidate for treating diverse disorders and injuries [5]. However, most studies have remained confined to cell culture systems, leaving potential mechanisms influenced by CM components in whole organisms largely unexplored. In a stark departure, our study delved into the biological effects occurring during exposure of developing zebrafish embryos and larvae to CM from Wharton's jelly mesenchymal stem cells.

Foremost among our findings is that CM treatment appears to have minimal toxic or lethal effects on zebrafish larvae, even up to concentrations of 75 µg/mL. While a minor delay in yolk reabsorption was noted in some CM-treated embryos at 72 hours post-fertilization (hpf), this condition largely normalized by 120 hpf, suggesting reversibility. Importantly, no change in hatching rates during CM exposure reaffirmed the absence of disturbances in embryonic anatomy and physiology. The hatching process is pivotal during zebrafish embryogenesis, necessitating coordinated enzyme expression and locomotion for chorion rupture.

Interestingly, CM exposure induced hyperactivity in zebrafish larvae, indicated by increased heartbeat frequency and locomotor parameters. However, two lines of evidence refute potential adverse outcomes. Firstly, morphological and morphometric analysis indicated no developmental defects in CM-treated individuals, aligning with the notion that behavior is a sensitive endpoint in zebrafish toxicity assessment. Secondly, no disorganization was observed in the global swimming pattern of CM-treated larvae, excluding any behavioral responses tied to heightened fear or anxiety [6].

Conclusion

To encapsulate, our comprehensive exploration of CM-treated zebrafish embryos has unveiled a spectrum of outcomes encompassing antioxidant fortification, pro-survival enhancement, and pro-regenerative activation. Remarkably, this constitutes the pioneering endeavor to scrutinize the effects of CM sourced from Wharton's jelly mesenchymal stem cells within an entire living vertebrate organism, spanning developmental, molecular, and behavioral dimensions. Our findings engender strong confidence in the potential of our evidence to chart a course toward forthcoming therapeutic applications.

Acknowledgment

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Conflict of Interest

None.

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