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Article / Book Information

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論 文 要 旨
THESIS SUMMARY

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要旨（英文 800 語程度）
Thesis Summary (approx.800 English Words)

5-Aminolevulinic acid (ALA) is extensively utilized in healthcare, serving diagnostic and therapeutic purposes. ALA is also recognized as a safe compound for the human body, as it is naturally produced endogenously in our bodies. The use of exogenous ALA is often accompanied by co-addition of ferrous iron, related with its ability to increase heme biosynthesis function. The application of ALA and the additional ferrous iron combination has become an interesting topic because it has provided promising results, especially in cancer and other health issues. This study is focusing into two different types of ferrous iron, such as sodium ferrous citrate (SFC) and hemin. Result shows that the combination of ALA-SFC and ALA-hemin demonstrated significant improvement effects across various applications, including iPS MELAS syndrome, adipogenesis in pre-adipocyte 3T3-L1 cells, and treatment of TMK-1 gastric cancer cells.

In Chapter 2, the combination of ALA and SFC improves mitochondrial functions in iPS MELAS syndrome by increasing the relative expression level of OXPHOS system complex proteins, HO-1, and affects the iPS cell differentiation process. The OXPHOS system is fundamentally important for MELAS syndrome, while HO-1 is essential in heme catabolism and ALA processing. It is suggested that heme biosynthesis in cells improved after ALA and ALA-SFC treatment. In the OXPHOS system, complex proteins II, III, IV, and cytochrome c are known to contain heme. Therefore, the expression in the OXPHOS system might be attributed to the increased rate of heme production.

In Chapter 3, the administration of ALA and its combination with SFC can reduce the fatty acid as a byproduct of adipogenesis using the 3T3-L1 cells model. Heme is known to be one of the key regulators in adipogenesis. Heme oxygenase 1 is also plays an essential role in heme biosynthesis and ALA processing. Therefore, the increased rate of heme production might affect the improvement of complex proteins and genes related to adipogenesis.

In Chapter 4, it is discovered that the other source of ferrous iron, hemin, with a combination of ALA, can improve the utilization of photodynamic therapy (PDT) on TMK-1 cells. The combination of ALA and hemin reduces the cell viability of TMK-1 gastric cancer cells. PpIX accumulation increases by ALA addition in TMK-1 cells, while ROS production and Fe2+ accumulation are significantly induced after the addition of hemin. Hemin enhances ROS production through the Fenton reaction, leading to lipid peroxidation and iron-mediated cell death. In addition, increased iron supply affects the expression of iron homeostasis-related genes, such as IRP, Tfr1, Ferritin, and mitochondrial-related proteins NFS1 and SDHB. Therefore, co-addition of ALA and hemin enhances phototoxicity in TMK-1 cells. The combination triggers cell death, increased PpIX and ROS, and significant changes in iron homeostasis.

In this study, two different sources of ferrous ions were utilized: sodium ferrous citrate (SFC) and hemin. Both SFC and hemin act as iron providers, facilitating the enhancement of cellular functions dependent on iron metabolism. The degradation of free iron ions (Fe^{2+}), in conjunction with ALA administration, influences the heme biosynthesis pathway within cells, potentially optimizing the metabolism and therapeutic outcomes. This combined approach is important to addressing complex conditions like iPS MELAS syndrome, regulating adipogenesis in 3T3-L1 pre-

adipocytes, and enhancing the efficacy of treatment strategies for TMK-1 gastric cancer cells.

For future consideration, additional experiments can be conducted to further support and expand upon the current findings. Potential experiments such as the investigation of ABCG2 and related transporters can be done to help clarify the mechanisms behind PpIX buildup in cancer cells and identify potential targets for enhancing the efficacy of ALA-based treatments. The other experiments that can be conducted are respiratory function measurement and in vivo application to understand the mechanism for further applications in medical purposes. Additionally, similar treatments can be applied to different cell types to investigate their effects on various diseases related to mitochondrial function. By exploring a more comprehensive range of cell models and conditions, researchers can better understand the utilization and potential applications of ALA and ferrous iron supplementation in treating mitochondrial dysfunction and other related disorders.