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參展科別 **醫學與健康科學**

作品名稱 **Investigation of the Role of Mammalian Siderophore 2,5-DHBA in Neurodegeneration**

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Abstract

Lipocalin 2 (LCN2), a 25-kDa secreted protein that belongs to the lipocalin family, is known to bind to a class of bacterial Fe-binding molecules known as siderophores. Iron is essential for bacterial growth. To obtain iron from host cells, bacteria produce siderophores, such as Enterochelin (Ent), to bind and transport host iron into the bacterial cell. In response, the host produces LCN2 to bind the iron-laden enterochelin, forming the tricomplex, LCN2: Ent: Fe^{3+}. This inhibits bacterial growth as iron has been sequestered by LCN2. Devireddy et.al. 2005, proposed the binding of the tricomplex, LCN2: Ent: Fe^{3+} with the LCN2 receptor (LCN2R). This resulted in the internalisation of the complex, releasing the bound iron into the cell. The increase of intracellular iron was reported to cause cell mortality. Recent publications postulated 2,5-dihydroxybenzoic acid (2,5-DHBA) to be an endogenous mammalian siderophore homologue in mouse *in vivo* and *in vitro* studies, which could sequester LCN2 and iron.

High iron concentrations in the brain have been consistently observed in Alzheimer's disease and Parkinson's disease. Accumulation of intracellular iron is known to be toxic to neurons, resulting in neurodegeneration. Hence, this study aims to determine the role of 2,5-DHBA as the mammalian siderophore in a cell culture model of neurodegeneration. We hypothesise that addition of 2,5-DHBA to cells exposed to LCN2 will result in increased iron uptake into neuronal cells, reducing cell viability.

SH-SY5Y (human neuroblastoma) cell line was used in our study. To determine if SH-SY5Y is a suitable cell line, endogenous levels of LCN2 and LCN2R mRNA and protein expression were determined using reverse transcription-polymerase chain reaction (RT-PCR) and Western Blot analysis respectively. Preliminary results showed presence of both the LCN2R mRNA and protein but absence of LCN2 mRNA. This

could be due to the low expression of LCN2 when not exposed to stress. Hence, to simulate conditions of neurodegeneration (by inducing high expression of LCN2), SH-SY5Y was treated with Kainic Acid (KA). After KA, LCN2 mRNA and protein expression levels will be detected again. With the successful upregulation of LCN2 gene expression, SH-SY5Y will be treated with 2,5-DHBA with KA treatment to determine cell viability using the MTS cell proliferation assay. A decreased cell viability or increased expression of pro-apoptotic genes would support the function of 2,5-DHBA as a mammalian siderophore in the brain.

Furthermore, KA treatment can also be applied to microglial or astrocyte cell lines, which are known to secrete high levels of LCN2 when treated with KA. Co-culturing these cells with SH-SY5Y can allow us to study the downstream effects of secreted LCN2 from glial cells binding to the LCN2R receptors on SH-SY5Y neuronal cells.

This study will help to further understanding of the relationship between 2,5-DHBA and cellular iron transport. If 2,5-DHBA is able to bind LCN2 and iron to increase intracellular iron levels in the neuronal cells, the formation of the tricomplex, LCN2: 2,5-DHBA: Fe^{3+}, could be targeted for therapeutic interventions in neurodegenerative diseases by reducing intracellular iron levels to help ameliorate the progression of neurodegenerative diseases.

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To study the role of mammalian Siderophore 25-DHBA neurodegeneration. They hypothesize that addition of 2.5-DHBA to cells exposed to Lipocalin 2 will result in increased iron uptake into neuronal cells, reducing cell viability.

This is an interesting study, however, don't have the clinical specimens or animal model to confirm their study.