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| **Microglial-to-neuronal CCR5 signaling regulates autophagy in neurodegeneration** | |
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| Presenter: Wei-Jie Chen | Date/Time: 2024/05/02, 15:10 -16:00 |
| Commentator: Dr. Chun-Hsien Chu | Location: Room 601, Med College Building |

**Background:**

Neurodegenerative diseases are characterized by the accumulation of aggregate-prone proteins in the neuronal cytoplasm. Neurons possess protective mechanisms to prevent the accumulation of toxic aggregate-prone proteins, like macroautophagy, a major intracytoplasmic protein degradation pathway. Recently, defects in multiple steps of the autophagy pathway have been identified in the early stages of many neurodegenerative diseases.

**Objective:**

Due to previous studies showing that brain cells can regulate the function of these cells through bidirectional neuron-microglia communication by secreting soluble factors, the authors hope to identify which cytokine is involved in the autophagy pathway.

**Results:**

To stimulate changes associated with Alzheimer's disease, the authors used Lipopolysaccharide and Interferon-γ to activate and induce microglia derived from induced pluripotent stem cells in mice and humans. They found that microglia can secrete factors that inhibit Neuronal Autophagy. Subsequent RNA sequencing identified three upregulated chemokines: CCL3, CCL4, and CCL5. After verification using primary neurons and microglia, it was discovered that these chemokines also showed significant upregulation. The receptor for these chemokines, CCR5, inhibits cell autophagy through the mTORC1 pathway in transmitting cell signals. This phenomenon was observed in both HD mouse model and PS19tau Tauopathy model, where the CCR5-mTORC1 pathway affects Neuronal Autophagy. Additionally, the authors found that CCR5 enters the autophagy pathway through transport to recycling endosomes and is ultimately degraded by autophagosomes.

**Conclusion:**

Taken together, the author found that the microglial-derived CCL-3/-4/-5 bind and activate neuronal CCR5, which in turn promotes mTORC1 activation and disrupts autophagy and aggregate-prone protein clearance.