1. **No.**

   FP01901021

2. **Title**

   Studies on Proteins Which Regulate the Development of Lung Cancer Caused by Smoking

3. **Period**

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4. **Summary**

Novel high-affinity tryptophan (Trp) uptake into cells results in extracellular Trp depletion and immune suppression. Although this system is highly expressed in interferon-γ (IFN-γ)-treated cells and indoleamine 2,3-dioxygenase 1 (IDO1)-expressing cells, its identity remains incompletely understood. Tryptophanyl-tRNA synthetase (TrpRS) is also highly expressed in IFN-γ-treated cells and also has high affinity and selectivity for Trp. In this project, we investigated the effects of human TrpRS expression on Trp uptake into IFN-γ-treated cells. Inhibition of human TrpRS expression by TrpRS-specific siRNAs decreased and overexpression of TrpRS increased Trp uptake into the cells. We demonstrated that the addition of purified TrpRS to uptake assay buffer increases Trp uptake into cells, suggesting that extracellular TrpRS plays an important role in high-affinity Trp uptake into human cells. Moreover, we found that overexpression of IDO1 in HeLa cells drastically enhances high-affinity Trp uptake upon addition of purified TrpRS protein to uptake assay buffer. We also clarified that high-affinity Trp uptake by Trp-starved cells is significantly enhanced by the addition of TrpRS protein to the assay buffer. Furthermore, we showed that high-affinity Trp uptake is also markedly elevated by the addition of TrpRS protein to the assay buffer of cells overexpressing another Trp-metabolizing enzyme, tryptophan 2,3-dioxygenase. Taken together, we conclude that Trp deficiency is crucial for high-affinity Trp uptake mediated by extracellular TrpRS.