The Lysosomal Positioning of mTOR Regulator and Regulation of Autophagy

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Lysosomes are key cellular organelles that play a role in catabolism by degrading extracellular and intracellular material. Specially, mechanistic target of rapamycin complex 1 (mTOR) localizes in its active form to the surface of lysosome, which regulates energy level, growth signal, and nutrient etc [1]. In addition, there are reports related to a tight crosstalk between mTOR activity and lysosomal function.

The intracellular amino acid level is the essential signal for regulating mTOR kinase activity [2]. The kinase activity of mTOR is also controlled by growth factors. In many cell types, leucine appears to be the main regulatory amino acid for mTOR [3]. The regulatory effect of amino acids on mTOR is declined by lowering the leucine concentration. Leucyl-tRNA synthetase (LRS) has a major role in not only providing Leu-tRNA but also activating mTORC1 through intracellular leucine sensing [4]. Recent studies indicate that LRS may act as a leucine sensor for the mTORC1 pathway, potentially providing an alternative strategy to overcome rapamycin resistance in cancer treatments [5]. Biochemical studies related to the leucine sensing have been published enough. However, there is still a lack of visualization data. Therefore, we observed LRS positions with and without leucine through transmission electron microscopy (TEM) with immuno-staining.

As a result, LRS was translocated to lysosome when leucine was added. This is a direct visualization LRS’s translocation to lysosome by leucine, it suggests LRS can affect to activation of mTORC1. Then, in order to confirm the activation of mTORC1, we monitored the number of autophagy by TEM and demonstrated the relationship between leucine sensing, LRS translocation, and mTORC1 activation. TEM is one of the most accurate methods for the quantification of autophagy. The decrease of autophagy can be evidence for mTOR’s activation; in contrast, the increase of autophagy suggests its inactivation. This study showed that the decrease of autophagy after treating of leucine indicated mTORC1 can be regulated by LRS’s translocation to lysosome through leucine (figure 1). This work was supported by the Bio & Medical Technology Development Program of the National Research Foundation (NRF) & funded by the Korean government (MSIP&MOHW) (No. 2016M3A9B6904244).

References

Figure 1. LRS immuno-gold labelled lysosome was increased in presence of Leucine. We showed that LRS’s translocation to lysosome after treatment of leucine by immuno-EM. We monitored the number of autophagy with and without leucine (red arrow). The result showed decrease of autophagy after treatment of leucine. It suggests mTORC1 can be regulated by LRS’s translocation to lysosome through leucine.