Potential role of Inosine-5′-monophosphate dehydrogenase 2 (IMPDH2) in autophagy regulation

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Autophagy is a cellular recycling process activated upon stress to supply nutrients supporting vital biochemical pathways. Under growth conditions, autophagy is inhibited by the mechanistic target of rapamycin complex 1 (mTORC1), which serves as an integration point for different cellular stimuli including energy, amino acid and growth factors levels. It was recently described that mTORC1 activity is dependent on cellular GTP pools. IMPDH2 is the rate limiting enzyme of the *de novo* synthesis of GTP. Thus, its inactivation may indirectly lead to mTORC1 inactivation by lowering the intracellular GTP concentration. However, previous work in our lab revealed a potential direct link between mTORC1 and IMPDH2. Mass spectrometry-based proteomic analysis of the IMPDH2 interactome revealed that in optimal growth conditions IMPDH2 might interact with NPRL2, a component of the GATOR1 complex, an inhibitor of mTORC1. Thus, by binding to NPRL2, IMPDH2 might sequester it and positively affect mTORC1 activity. However, in autophagy-promoting conditions, IMPDH2 seemed to be targeted by p62/SQSTM1 for its lysosomal degradation, thus releasing NPRL2 and promoting the inhibition of mTORC1 to further activate autophagy.

The aim of this study was is to corroborate these results and to verify the direct role of IMPDH2 in mTORC1 and autophagy regulation. Despite that we were not able to demonstrate the aforementioned regulatory role, we found that IMPDH2 might bear a post-translational modification that may regulate its function, stability or subcellular localization in stress conditions. Although further work is needed to verify the role of IMPDH2 in autophagy and the nature and physiological function of this biochemical modification, this work might have unveiled a new regulatory mechanism of IMPDH2 activity.

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