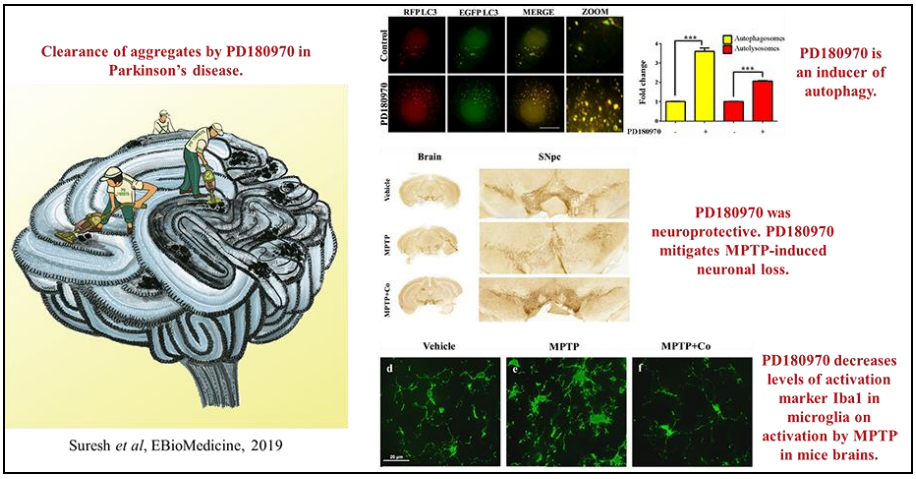
JNCASR scientists find a way to boost innate immune system against intracellular infection

A promising way to deal with intracellular pathogens including multi-drug- resistant bacteria is to induce a pathway of the human immune system known as xenophagy say researchers at the Autophagy laboratory, Molecular Biology and Genetics Unit of the Jawaharlal Nehru Centre for Advanced Scientific Research, Bangalore, an autonomous unit of the Department of Science and Technology.

Xenophagy is the selective degradation of intracellular pathogens such as bacteria which are captured and degraded by autophagy — an intracellular process responsible for lysosomal mediated degradation of cellular cargoes. Autophagy related discoveries earned Prof. Yoshinori Ohsumi the 2016 Nobel prize for physiology or medicine. JNCASR scientists have found a pharmacological tool to modulate autophagy, which can help induce xenophagy. They have filed a patent for this process, which is pending at present.

Inducing xenophagy is effective against a wide range of bacterial species and also in viruses and parasites — unlike antibiotics that act only on select pathogens. Furthermore, combining the effects of xenophagy with antibiotics has shown positive effects in treating infections.



While xenophagy has been studied to an extent, the molecular principles behind this process are poorly understood. This is further complicated by the fact that each pathogen has its unique way of subverting xenophagy, necessitating the need to identify tools to induce the process during infection.

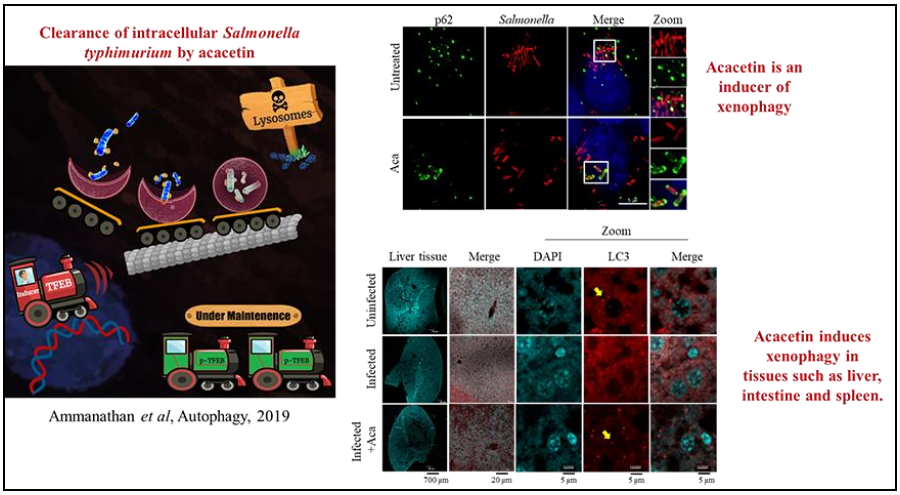
In the present work, acacetin, a plant-derived flavonoid, was used to induce xenophagy against *Salmonella typhimurium* infection. The efficacy of this small-molecule compound has been demonstrated both *in cellulo* and *in vivo*.

While xenophagy occurs in the cytoplasm, the present work published in *Autophagy* on 19 November 2019, highlights nuclear control of the process through a master transcriptional regulator called TFEB.

TFEB, considered as a master regulator of autophagy and lysosomal genes, was kept in a transcriptionally inactive form during infection by typhoid causing bacteria. Rescuing TFEB function during infection-induced xenophagic capture of bacteria as well as lysosomal biogenesis, and both these steps are critical in eliminating the intracellular bacteria.

The identified drug-like compound was further tested for their potential in disease models such as intracellular *S. typhimurium* infection in epithelial and macrophage cell lines. The compound does not directly affect the growth of bacteria but induced host xenophagy machinery to capture the bacteria and increased its fusion with lysosomes. Additional experiments revealed activation of TFEB to induce active lysosomal population inside cells.

Although the process is shown to restrict infection, there are no well-studied compounds that could induce the process during *in vivo* infection. Interestingly, the basal level of xenophagy in tissues such as intestine, liver, and spleen are low, which are also regions that are commonly affected during bacterial infection. It is, therefore, essential to induce the process transiently during infection to be effective in curbing intracellular infection.



This research group has also identified novel genetic as well as pharmacological modulators of autophagy. Pilot-scale screening of essential genes identified two protein complexes, namely septin (Barve *et al.*, J Cell Sci., 2018) and exocyst (Singh *et al.*, J Mol Biol., 2019) that are involved in autophagosome biogenesis. Furthermore, a high throughput screening of more than 2,00,000 compounds comprising of 16 libraries have identified multiple autophagy modulators that could temporally and transiently regulate the process (Mishra *et al.*, Autophagy, 2017; Suresh *et al.*, Autophagy, 2017; Vats *et al.*, Mol Biol Cell, 2019).

Publication:

Ammanathan V, Mishra P, Chavalmane AK, Muthusamy S, Jadhav V, Siddamadappa C, Manjithaya R. Restriction of intracellular Salmonella replication by restoring TFEB-mediated xenophagy. Autophagy. 2019. Nov 19:1-14. doi: 10.1080/15548627.2019.1689770.

Patent details:

“Method for modulating autophagy and applications thereof” Patent number: US20180369186A1.

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