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Role of Autophagic Lysosome Reformation for Cell Viability in an in vitro Infection Model

Authors : Muhammad Awais Afzal, Lorena Tuchscherr De Hauschopp, Christian Hübner

Abstract : Introduction: Autophagy is an evolutionarily conserved lysosome-dependent degradation pathway, which can be induced by extrinsic and intrinsic stressors in living systems to adapt to fluctuating environmental conditions. In the context of inflammatory stress, autophagy contributes to the elimination of invading pathogens, the regulation of innate and adaptive immune mechanisms, and regulation of inflammasome activity as well as tissue damage repair. Lysosomes can be recycled from autolysosomes by the process of autophagic lysosome reformation (ALR), which depends on the presence of several proteins including Spatacsin. Thus ALR contributes to the replenishment of lysosomes that are available for fusion with autophagosomes in situations of increased autophagic turnover, e.g., during bacterial infections, inflammatory stress or sepsis. Objectives: We aimed to assess whether ALR plays a role for cell survival in an in-vitro bacterial infection model. Methods: Mouse embryonic fibroblasts (MEFs) were isolated from wild-type mice and Spatacsin (Spg11-/-) knockout mice. Wild-type MEFs and Spg11-/- MEFs were infected with Staphylococcus aureus (multiplication of infection (MOI) used was 10). After 8 and 16 hours of infection, cell viability was assessed on BD flow cytometer through propidium iodide intake. Bacterial intake by cells was also calculated by plating cell lysates on blood agar plates. Results: in-vitro infection of MEFs with Staphylococcus aureus showed a marked decrease of cell viability in ALR deficient Spatacsin knockout (Spg11-/-) MEFs after 16 hours of infection as compared to wild-type MEFs (n=3 independent experiments; $p < 0.0001$) although no difference was observed for bacterial intake by both genotypes. Conclusion: Suggesting that ALR is important for the defense of invading pathogens e.g. S. aureus, we observed a marked increase of cell death in an in-vitro infection model in cells with compromised ALR.

Keywords : autophagy, autophagic lysosome reformation, bacterial infections, Staphylococcus aureus
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