Listeria monocytogenes is a foodborne pathogen responsible for human listeriosis. At the cell level, Listeria has the ability to invade and replicate in both phagocytic and non-phagocytic cells. Listeria intracellular life cycle involves interference with various host cell components. Here, we aim to characterize host cell proteome modifications in cells infected by Listeria. We focused our research on the activation of host proteases and the degradation of host cell proteins in response to infection. We identified more than 90 proteins degraded in response to the listeriolysin O, a pore-forming toxin secreted by Listeria monocytogenes. We anticipate that the degradation of these proteins, involved in different host pathways, can significantly impact the infection process through the modification of host cell physiology. In parallel, we identified that Listeria impairs lysosomal functions during infection. We demonstrate that extracellular Listeria, via the secretion of LLO, alter lysosomal integrity in epithelial cells. LLO induces lysosomal membrane permeabilization and the release of lysosomal content, such as cathepsins proteases, in the host cytosol. Altogether, those results highlight how Listeria reshapes the host proteome by altering the activation or localization of host proteases and by inducing protein degradations.