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Inhibition of autophagy ameliorates acute lung injury caused by avian influenza A H5N1 infection

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The threat of a new influenza pandemic has existed since 1997, when the highly pathogenic H5N1 strain of avian influenza A virus infected humans in Hong Kong and spread across Asia, where it continued to infect poultry and people. The human mortality rate of H5N1 infection is about 60%, whereas that of seasonal H1N1 infection is less than 0.1%. The high mortality rate associated with H5N1 infection is predominantly caused by acute lung injury; however, how viral infection contributes to this disease pathology is unclear and the effective treatment for human H5N1 infection is currently lacking. Here, we used electron microscopy to show the accumulation of autophagosomes in H5N1-infected lungs from a human cadaver and mice, as well as in infected A549 human epithelial lung cells. Then, we showed that H5N1, but not seasonal H1N1, induced autophagic cell death in alveolar epithelial cells through a pathway involving the kinase Akt, the tumor suppressor protein TSC2, and the mammalian target of rapamycin. Additionally, we suggest that the hemagglutinin protein of H5N1 may be responsible for stimulating autophagy. When applied prophylactically, reagents that blocked virus-induced autophagic signaling substantially increased the survival rate of mice and substantially ameliorated the acute lung injury and mortality caused by H5N1 infection. At the same time, we also showed that chloroquine (CQ), an anti-malaria drug used in clinic for 65 years, was highly effective when administered therapeutically. We conclude that the autophagic cell death of alveolar epithelial cells likely plays a crucial role in the high mortality rate of H5N1 infection, and we suggest that autophagy-blocking agents might be useful as prophylactics and therapeutics against infection of humans by the H5N1 virus.

Biography

Chengyu Jiang is a Chair and professor of Department of Biochemistry and Molecular Biology, Peking Union Medical College (PUMC) and Chinese Academy of Medical Sciences. She obtained her PhD from Brown University in 1997 and followed by postdoctoral training at Massachusetts General Hospital, affiliated to Harvard Medical School before joining PUMC in 2003. Her research is to elucidate molecular pathogenesis of RNA viruses such as SARS-CoV, Avian Flu H5N1, S-OIV-H1N1, and Ebola, as well as to explore the molecular pathogenesis of acute lung injury induced by nanoparticles. Dr. Jiang has published extensively in numerous peer reviewed journals including Nature, Nature Medicine, Science Signaling, and PNAS. She is also an inventor of a number of international patents. Some of the patents are exclusively licensed to a top 5 international pharmaceutical company and an international biotech company. She has served as member of WHO IARC fellowship committee in Lyon, France from 2005 to 2008 and as the chair in the year of 2007/2008. She received numerous honors including “Cheung Kong” Scholar, the young woman scientist of China, and national outstanding young award fund.

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