Role of Autophagy in Immunity, Disease and Pathogen Replication

Abstract

Autophagy is a cellular homeostasis process which plays an important role in energy balance, especially during critical time such as starvation or nutrient stress. It also prevents the accumulation of damaged organelles or misfolded proteins in cytoplasm through lysosomal digestion. Autophagy recycles superfluous or damaged organelles and utilizes their hydrolyzed products for cellular vital functions. Autophagy also plays an important role in immune response and prevents the invasion of pathogens. However defective autophagy may lead to various diseases. Various pathogens subvert autophagy for their efficient replication. In this current mini review pathogen who exploits autophagy for their replication, autophagy related diseases and natural compound which use autophagy for disease amelioration is highlighted.

Keywords: Autophagy; Autophagy related disease; Virus; Bacteria; Natural compounds; Medicinal plants

Mini Review

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Introduction

Autophagy is essential cellular homeostasis, through which superfluous cytoplasmic components, damaged organelles or misfolded proteins are sequestered, enzymatically digested and recycled [1,2]. Generally, autophagy occurs at low basal levels in almost all cells but it is rapidly upregulated when cells need intracellular nutrients or energy such as during starvation [3]. Autophagy is divided into three types such as macroautophagy, microautophagy, and chaperone-mediated autophagy. Among them, macroautophagy is well studied and, usually referred as autophagy [2]. There are about 31 autophagy-related (Atg) genes have been identified in yeast which are conserved from yeast to plants and animals [2,4]. Atg gene translates into autophagy-related proteins. Many of these proteins are gathered at a site in cytoplasm and form preautophagosomal structure (PAS) [5] which lead to autophagosome formation.

Atgs gene expression are regulated by a series of complex cellular signaling events such as the activation of the class III PI3 kinase, hVps34, in association with Beclin1 or inactivation of mammalian target of rapamycin (mTOR) [6]. mTOR is a serine/threonine kinase and inhibits the autophagy [7]. mTOR phosphorylates Atg13 at multiple residues causing a reduced affinity between Atg1 and its binding proteins. Reduced affinity between Atg1 with its binding proteins results in suppression of autophagy [8]. Under starvation, mTOR became inactive, which leads to suppression of Atg13 phosphorylation and induce localization of Atg1, Atg17 and other essential autophagy factors to the PAS [9]. PAS formation cause autophagy initiation (Figure 1). Another pathways which lead autophagy is Beclin 1 signaling pathway. The Beclin 1 is a mammalian Atg6/Vps30 (vacuolar protein sorting 30) ortholog and a subunit of the class III PI3-kinase complex [2]. Under normal condition, the activity of Beclin 1 is reduced through anti-apoptotic protein, Bcl-2 [10]. Bcl-2 bind to Beclin 1 through BH3 domain and make it unavailable for autophagy. During starvation Bcl-2 and Beclin 1 interaction is reduced. Which leads the release of Beclin 1 [11-13], freely available Beclin 1 initiate the autophagy (Figure 1).

Role of Autophagy in Immunity

Autophagy is cellular homeostasis process, alone with homeostasis, autophagy also play an important role in innate and adaptive immune response. Previous studies have shown that autophagy is induced by toll-like receptors (TLR) [14], nucleotide-binding oligomerization domain (NOD)-like receptors [15], retinoic acid-inducible gene I (RIG-I)-like receptors [16] and damage associated molecular patterns [17]. The interaction of single-stranded RNA with TLR7 was found as most potent effector in autophagy induction [18]. The autophagy is also induced by LPS through a Toll/interleukin-1 receptor domain containing adaptor inducing interferon beta (TRIF) dependent or myeloid differentiation factor 88 (MyD88) independent TLR4 signaling pathway [19]. It has also been shown that during adaptive immune response autophagy facilitates the antigen presentation by increasing the antigen recognition through MHCII molecule with enhanced T cell activation and proliferation [20,21]. Similarly, the knocking down of Agt 5 in mice showed reduction in total thymocytes and peripheral T and B lymphocytes [22].

Autophagy and Disease

Autophagy is essential cellular homeostasis which also help in mounting good immune response, however defective autophagy is associated with a number of diseases [1]. The impaired maturation or defective lysosomal acidification of autophagy may lead to Vici syndrome or Alzheimer's disease [23,24], while dysregulation of the autophagy pathway cause Parkinson's disease or Crohn's disease [25,26]. Autophagy has dual roles in cancer pathology, initially autophagy act a tumor suppressor by preventing the accumulation of damaged proteins and organelles but once a tumor develops, the cancer cells could utilize autophagy for their own cytoprotection and proliferation [27,28].

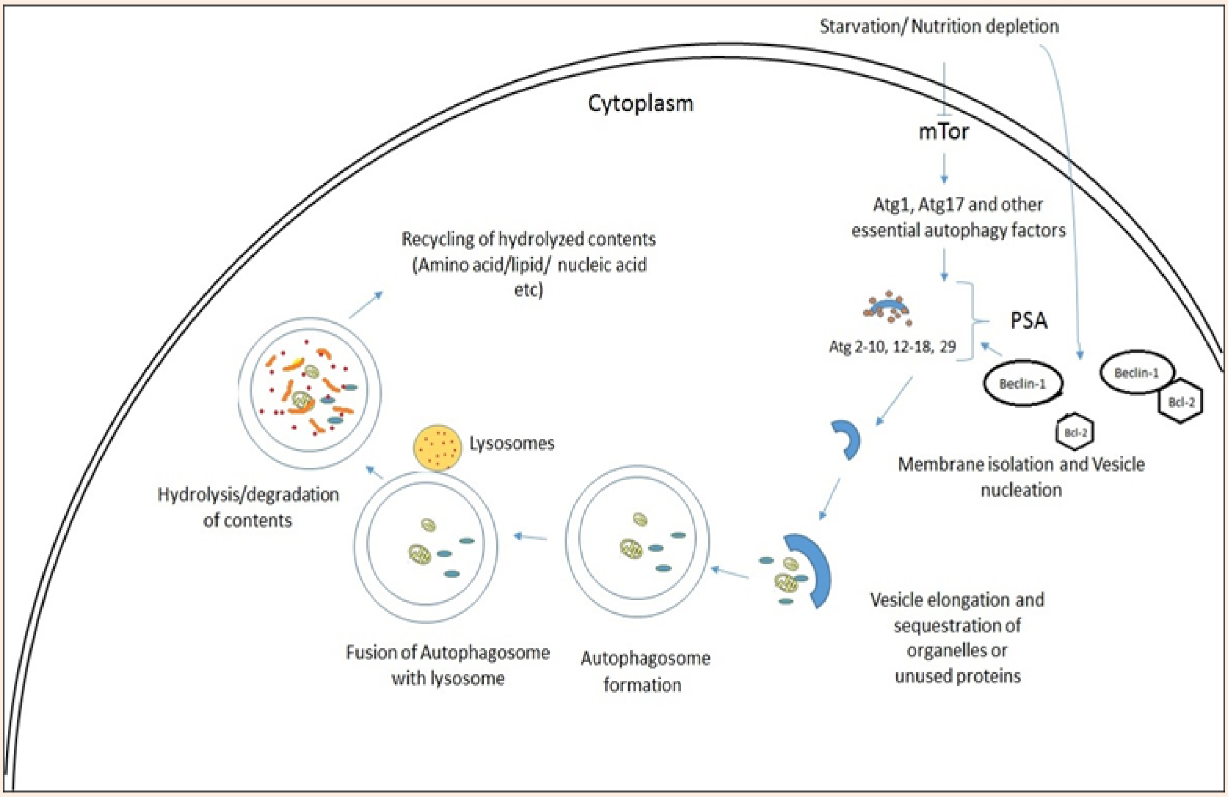

Figure 1: Steps in Autophagosome formation.

Exploitation of autophagy by viruses for their efficient replication

Autophagy play an important in innate and adaptive immune response against a variety of pathogens including bacteria or viruses [29,30]. But there are number of viruses which exploits the autophagy for their efficient replication [31]. Autophagy is utilized for replication of poliovirus [32,33], coxsackieviruses [34] and viruses belongs to flaviviridae family such as Hepatitis C virus [35], dengue virus [36,37], and Japanese encephalitis virus [38]. The virus of veterinary importance such as classical swine fever and Bovine virus diarrhea virus, which cause persistent infection and immunosuppression in infected host cause, also utilize the autophagy for their efficient replication [39-43].

Autophagy and bacterial infection

Autophagy is one of the most remarkable tools of against the intracellular bacteria. However, like may viruses, several bacterial pathogens also manipulate autophagy for their survival and replication. *Coxiella burnetii*, which cause of Q fever in humans utilize autophagic pathway to form parasitophorous vacuoles (PV) and prevent its fusion to lysosome. Lack of lysosomal fusion to PV prevents acidification of vacuoles and help intracellular bacterial survival [44]. Similarly, *Brucella spp*., is another intracellular bacterial which is responsible for reproductive disorders in animals and humans. It is prevalent throughout the worlds including North America, Europe, Africa and Asia [45-48]. Studies revealed that Brucella melitensis 16M trigger autophagosome formation and enhanced autophagy for its replication [49]. In contrast, various bacterial pathogens such as *Escherichia coli, Anaplasma phagocytophilum, Listeria monocytogenes, Shigella spp, Legionella spp* subvert the autophagy for their survival [50-54]. Similarity, helminthic co-infections, which is also prevalent worldwide, has been shown to impair autophagy-mediated bacterial killing [55-58].

Autophagy and natural compounds

There are number of natural compounds or medicinal plants, which have been known to possess antibacterial, antiviral, anthelmintic, anti-cancerous or anti-stress activity [59-67]. Research findings have shown that few of these medicinal plants have such properties to modulate autophagy machinery for host benefit [68-70].

Conclusion

Autophagy is an essential cellular homeostasis process which also prevent the invading pathogens, however various pathogen utilize autophagy for their efficient replication. Along with it, defective autophagy may lead to various diseases. Currently there are number of research are going on to understand more

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about autophagy and its molecular mechanism and regulatory network. The current knowledge and further research findings may provide in-depth knowledge of autophagy so that we can utilize this machinery as a potential pharmacological target to treat various diseases. Such example has been observed to reduce disease severity in avian influenza infection [71], this virus has been shown highly pathogenic to birds as well as to human [72].

References

1. Kudchodkar SB, Levine B (2009) Viruses and autophagy. Rev Med Virol 19(6): 359-378.
2. Mizushima N (2007) Autophagy: process and function. Genes Dev 21(22): 2861-2873.
3. Li L, Chen Y, Gibson SB (2013) Starvation-induced autophagy is regulated by mitochondrial reactive oxygen species leading to AMPK activation. Cell Signal 25(1): 50-65.
4. Kabeya Y, Kawamata T, Suzuki K, Ohsumi Y (2007) Cis1/Atg31 is required for autophagosome formation in *Saccharomyces cerevisiae*. Biochem Biophys Res Commun 356(2): 405-410.
5. Kim J, Huang WP, Klionsky DJ (2001) Membrane recruitment of Aut7p in the autophagy and cytoplasm to vacuole targeting pathways requires Aut1p, Aut2p, and the autophagy conjugation complex. J Cell Biol 152(1): 51-64.
6. Beatman E, Oyer R, Shives KD, Hedman K, Brault AC, et al. (2012) West Nile virus growth is independent of autophagy activation. Virology 433(1): 262-272.
7. Nazio F, Strappazzon F, Antonioli M, Bielli P, Cianfanelli V, et al. (2013) mTOR inhibits autophagy by controlling ULK1 ubiquitylation, self-association and function through AMBRA1 and TRAF6. Nat Cell Biol 15(4): 406-416.
8. Kamada Y, Funakoshi T, Shintani T, Nagano K, Ohsumi M, et al. (2002) Tor-mediated induction of autophagy via an Apg1 protein kinase complex. J Cell Biol 150(6): 1507-1513.
9. Kamada Y, Yoshino K, Kondo C, Kawamata T, Oshiro N, et al. (2010) Tor directly controls the Atg1 kinase complex to regulate autophagy. Mol Cell Biol 30(4): 1049-1058.
10. Liang XH, Kleeman LK, Jiang HH, Gordon G, Goldman JE, et al. (1998) Protection against fatal Sindbis virus encephalitis by beclin, a novel Bcl-2-interacting protein. J Virol 72(11): 8586-8596.
11. Maiuri MC, Le Toumelin G, Criollo A, Rain JC, Gautier F, et al. (2007) Functional and physical interaction between Bcl-X(L) and a BH3-like domain in Beclin-1. EMBO J 26(10): 2527-2539.
12. Oberstein A, Jeffrey PD, Shi Y (2007) Crystal structure of the Bcl-XL-Beclin 1 peptide complex: Beclin 1 is a novel BH3-only protein. J Biol Chem 282(17): 13123-13132.
13. Pattingre S, Tassa A, Qu X, Garuti R, Liang XH, et al. (2005) Bcl-2 antiapoptotic proteins inhibit Beclin 1-dependent autophagy. Cell 122(6): 927-939.
14. Delgado MA, Elmaoued RA, Davis AS, Kyei G, Deretic V, et al. (2008) Toll-like receptors control autophagy. Embo J 27(7): 1110-1121.
15. Suzuki T, Nunez G (2008) A role for Nod-like receptors in autophagy induced by *Shigella* infection. Autophagy 4(1): 73-75.
16. Jounai N, Takeshita F, Kobiyama K, Sawano A, Miyawaki A, et al. (2007) The Atg5 Atg12 conjugate associates with innate antiviral immune responses. Proc Natl Acad Sci U S A 104(35): 14050-14055.
17. Tang D, Kang R, Coyne CB, Zeh HJ, Lotze MT (2012) PAMPs and DAMPs: signal 0s that spur autophagy and immunity. Immunol Rev 249(1): 158-175.
18. Deretic V (2011) Autophagy in immunity and cell-autonomous defense against intracellular microbes. Immunol Rev 240(1): 92-104.
19. Xu Y, Jagannath C, Liu XD, Sharafkhaneh A, Kolodziejska KE, et al. (2007) Toll-like receptor 4 is a sensor for autophagy associated with innate immunity. Immunity 27(1): 135-144.
20. Paludan C, Schmid D, Landthaler M, Vockerodt M, Kube D, et al. (2005) Endogenous MHC class II processing of a viral nuclear antigen after autophagy. Science 307(5709): 593-596.
21. Miller MJ, Hejazi AS, Wei SH, Cahalan MD, Parker I (2004) T cell repertoire scanning is promoted by dynamic dendritic cell behavior and random T cell motility in the lymph node. Proc Natl Acad Sci U S A 101(4): 998-1003.
22. Pua HH, Dzhagalov I, Chuck M, Mizushima N, He YW, et al. (2007) A critical role for the autophagy gene Atg5 in T cell survival and proliferation. J Exp Med 204(1): 25-31.
23. Wolfe DM, Lee JH, Kumar A, Lee S, Orenstein SJ, et al. (2013) Autophagy failure in Alzheimer's disease and the role of defective lysosomal acidification. Eur J Neurosci 37(12): 1949-1961.
24. Cullup T, Kho AL, Dionisi-Vici C, Brandmeier B, Smith F, et al. (2013) Recessive mutations in EPG5 cause Vici syndrome, a multisystem disorder with defective autophagy. Nat Genet 45(1): 83-87.
25. Lynch-Day MA, Mao K, Wang K, Zhao M, Klionsky DJ, et al. (2012) The role of autophagy in Parkinson's disease. Cold Spring Harb Perspect Med 2(4): a009357.
26. Fritz T, Niederreiter L, Adolph T, Blumberg RS, Kaser A (2011) Crohn's disease: NOD2, autophagy and ER stress converge. Gut 60(11): 1580-1588.
27. White E (2012) Deconvoluting the context-dependent role for autophagy in cancer. Nat Rev Cancer 12(6): 401-410.
28. Yang ZJ, Chee CE, Huang S, Sinicrope FA (2011) The role of autophagy in cancer: therapeutic implications. Mol Cancer Ther 10(9): 1533-1541.
29. Deretic V (2005) Autophagy in innate and adaptive immunity. Trends Immunol 26(10): 523-528.
30. Deretic V, Levine B (2009) Autophagy, immunity, and microbial adaptations. Cell Host Microbe 5(6): 527-549.
31. Vescovo T, Refolo G, Romagnoli A, Ciccosanti F, Corazzari M, et al. (2014) Autophagy in HCV infection: keeping fat and inflammation at bay. Biomed Res Int 2014: 265353.
32. Jackson WT, Giddings TH, Taylor MP, Mulinyawe S, Rabinovitch M, et al. (2005) Subversion of cellular autophagosomal machinery by RNA viruses. PLoS Biol 3(5): e156.
33. Taylor MP, Kirkegaard K (2007) Modification of cellular autophagy protein LC3 by poliovirus. J Virol 81(22): 12543-12553.
34. Wong J, Zhang J, Si X, Gao G, Mao I, et al. (2008) Autophagosome supports coxsackievirus B3 replication in host cells. J Virol 82(18): 9143-9153.
35. Ait-Goughoulte M, Kanda T, Meyer K, Ryerse JS, Ray RB, et al. (2008)

Hepatitis C virus genotype 1a growth and induction of autophagy. J Virol 82(5): 2241-2249.

36. Panyasrivanit M, Khakpoor A, Wikan N, Smith DR (2009) Co-localization of constituents of the dengue virus translation and replication machinery with amphisomes. J Gen Virol 90(Pt 2): 448-456.

37. Heaton NS, Perera R, Berger KL, Khadka S, Lacount DJ, et al. (2010) Dengue virus nonstructural protein 3 redistributes fatty acid synthase to sites of viral replication and increases cellular fatty acid synthesis. Proc Natl Acad Sci U S A 107(40): 17345-17350.

38. Li JK, Liang JJ, Liao CL, Lin YL (2012) Autophagy is involved in the early step of Japanese encephalitis virus infection. Microbes Infect 14(2): 159-168.

39. Pei J, Zhao M, Ye Z, Gou H, Wang J, et al. (2014) Autophagy enhances the replication of classical swine fever virus *in vitro*. Autophagy 10(1): 93-110.

40. Darweesh MF, Rajput MK, Braun LJ, Ridpath JF, Neill JD, et al. (2015) Characterization of the cytopathic BVDV strains isolated from 13 mucosal disease cases arising in a cattle herd. Virus Res 195: 141-147.

41. Rajput MK, Darweesh MF, Park K, Braun LJ, Mwangi W, et al. (2014) The effect of bovine viral diarrhea virus (BVDV) strains on bovine monocyte-derived dendritic cells (Mo-DC) phenotype and capacity to produce BVDV. Virol J 11: 44.

42. Chase CC, Thakur N, Darweesh MF, Morarie-Kane SE, Rajput MK (2015) Immune response to bovine viral diarrhea virus--looking at newly defined targets. Anim Health Res Rev 16(1): 4-14.

43. Rajput MKS (2013) Understanding the effect of BVDV on antigen presenting cells and cytoplasmic trafficking. PhD thesis, South Dakota State University, USA.

44. Berón W, Gutierrez MG, Rabinovitch M, Colombo MI (2002) Coxiella burnetii localizes in a Rab7-labeled compartment with autophagic characteristics. Infect Immun 70(10): 5816-5821.

45. McDermott JJ, Arimi SM (2002) Brucellosis in sub-Saharan Africa: epidemiology, control and impact. Vet Microbiol 90(1-4): 111-134.

46. Godfroid J, Käsbohrer A (2002) Brucellosis in the European Union and Norway at the turn of the twenty-first century. Vet Microbiol 90(1-4): 135-145.

47. Mikolon AB, Gardner IA, Hietala SK, Hernandez de Anda J, Chamizo Pestaña E,, et al. (1998) Evaluation of North American antibody detection tests for diagnosis of brucellosis in goats. J Clin Microbiol 36(6): 1716-1722.

48. Singh P, Rajput MKS, Shandilya S, Devrari A, Sharma D (2009) Prevalence of brucellosis in small ruminants in Tarai region of Uttarakhand. Vets Communications 4: 51.

49. Guo F, Zhang H, Chen C, Hu S, Wang Y, et al. (2012) Autophagy favors Brucella melitensis survival in infected macrophages. Cell Mol Biol Lett 17(2): 249-257.

50. Chargui A, Cesaro A, Mimouna S, Fareh M, Brest P, et al. (2012) Subversion of autophagy in adherent invasive *Escherichia coli*-infected neutrophils induces inflammation and cell death. PLoS One 7(12): e51727.

51. Niu H, Yamaguchi M, Rikihisa Y (2008) Subversion of cellular autophagy by Anaplasma phagocytophilum. Cell Microbiol 10(3): 593-605.

52. Choy A, Dancourt J, Mugo B, O'Connor TJ, Isberg RR, et al. (2012) The Legionella effector RavZ inhibits host autophagy through irreversible Atg8 deconjugation. Science 338(6110): 1072-1076.

53. Yoshikawa Y, Ogawa M, Hain T, Yoshida M, Fukumatsu M, et al. (2009) Listeria monocytogenes ActA-mediated escape from autophagic recognition. Nat Cell Biol 11(10): 1233-1240.

54. Ogawa M, Yoshimori T, Suzuki T, Sagara H, Mizushima N, et al. (2005) Escape of intracellular *Shigella* from autophagy. Science 307(5710): 727-731.

55. Su CW, Cao Y, Zhang M, Kaplan J, Su L, et al. (2012) Helminth infection impairs autophagy-mediated killing of bacterial enteropathogens by macrophages. J Immunol 189(3): 1459-1466.

56. Pant K, Rajput MKS, Kumar J, Sahu S, Rajkumari V, et al. (2009) Prevalence of helminthes in small ruminants in Tarai region of Uttarakhand. Veterinary World 2(7): 265-266.

57. Osazuwa F, Ayo OM, Imade P (2011) A significant association between intestinal helminth infection and anaemia burden in children in rural communities of Edo state, Nigeria. N Am J Med Sci 3(1): 30-34.

58. Harhay MO, Horton J, Olliaro PL (2010) Epidemiology and control of human gastrointestinal parasites in children. Expert Rev Anti Infect Ther 8(2): 219-234.

59. Prakash O, Rajput M, Kumar M, Pant AK (2010) Chemical Composition and Antibacterial Activity of Rhizome Oils From *Hedychium coronarium* Koenig and *Hedychium spicatum* Buch-Ham. Journal of Essential Oil Bearing Plants 13(2): 250-259.

60. Singh N, Singh JP, Rajput MKS (2008) Hematological alterations in broiler chicks during different seasons supplemented with herbal formulations. Veterinary World 1(4): 110-112.

61. Martin KW, Ernst E (2003) Antiviral agents from plants and herbs: a systematic review. Antivir Ther 8(2): 77-90.

62. Singh N, Bagherwal RK, Singh JP, Rajput MKS (2009) Feed consumption supplemented with herbal formulations during different seasons in broiler chicks Vets Communications 4: 35-37.

63. Upadhyay AK, Chaudhary S, Rajput MKS (2009) *In vitro* antitrematodal study of Butea frondosa extracts. Indian Vet J 86(8): 867-868.

64. Rajput MKS, et al. (2006) Evaluation of anthelmintic efficacy of some plants against Haemonchus contortus. Indian J Vet Med 26: 86-88.

65. Rajput , M.K.S. et al. (2008) Anthelmintic efficacy of the seed of Embelia ribes against Haemonchus contortus. Animal Science Reporter 3: 113-115.

66. Rajput, M.K.S. et al. (2007). "Amla: A solution of Heat stress in Poultry. Poultry line 5: 45-47.

67. Singh N, Bagherwal RK, Rajput MKS (2008) Antistress modulation of herbal formulations on bodyweight of broiler chicks during different seasons. Indian Journal of Veterinary Medicine. Indian J Vet Med 28: 52-53.

68. Kumar D, Shankar S, Srivastava RK (2014) Srivastava, Rottlerin induces autophagy and apoptosis in prostate cancer stem cells via PI3K/Akt/mTOR signaling pathway. Cancer Lett 343(2): 179-189.

69. Laconi S, Madeddu MA, Pompei R (2014) Autophagy activation and antiviral activity by a licorice triterpene. Phytother Res 28(12): 1890-1892.

70. Wang Y, Wang JW, Xiao X, Shan Y, Xue B, et al. (2013) Piperlongumine induces autophagy by targeting p38 signaling. Cell Death Dis 4: e824.

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71. Pan H, Zhang Y, Luo Z, Li P, Liu L, et al. (2014) Autophagy mediates avian influenza H5N1 pseudotyped particle-induced lung inflammation through NF-kappaB and p38 MAPK signaling pathways. Am J Physiol Lung Cell Mol Physiol 306(2): L183-L195.

72. ElBakrey RM, El Sisi MA, Mansour SM, Ahmed HH, Rajput M, et al. (2015) Cleavage site stability of Egyptian highly pathogenic avian influenza viruses in backyard chickens during 2009-2011. J Microbiol Immunol Infect 48(1): 28-35.

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