International Journal of Microbiology Research, ISSN: 0975-5276, Volume 1, Issue 2, 2009, pp-18-19

Current insight into the antigenicity and virulence of *H5N1 Virus*

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Abstract- The Influenza virus is highly potent in causing epidemics and pandemics. It has caused three major pandemics with one more into light. The Spanish pandemic during 1918-19 caused around 50 million deaths world wide. A lot has been studied on influenza but yet it forms a major obstacle to prevent it from spreading its menace repeatedly. Sometime back the H5N1 strain was considered to be the agent of pandemic but yet again the sporadic evolution of A/H1N1 strain spread its menace unexpectedly with an efficient human to human transmission. A lot of studies have been done in molecular levels about the virulence of influenza but yet difficult to control. This is the time to revive our knowledge on influenza and the target of this review is the H5N1 strain of virus because of its extreme virulent nature and thus could be the agent of next pandemic.
Keywords- Influenza, Pandemic, H5N1, Flu, Antigenicity, Virulence, Avian

Introduction

Influenza virus possesses two membrane glycoprotein namely, Haemagglutinin (HA) and Neuraminidase (NA) at a ratio of 4:1 [1].HA mediates the binding of the virus particle to the host cell via sialic acid containing receptors while NA functions in the release of virions by cleaving off the sialic acid from virus and spread infection to the new cells. HA is also the antigenic part which stimulates the production of antibodies in the host [2].There are various subtypes of HA and NA (16 HA subtypes and 9 NA subtypes). Several combinations of HA and NA has produced a number of subtypes of influenza and continues to exhibit their endless capacity to change. The influenza type A virus is quite rich and diverse in its ecology [3] and causes infection from ducks (avian influenza), pigs (swine influenza) and other terrestrial animals. Not only in land they have spread their menace to the aquatic world as well by infecting seals and whales [4].Their intensity is further fuelled up by their ability of crossing species barriers and get adapted to the newly infected hosts [10]. The current subtype which forms a matter of great concern is H5N1 strain. This is considered to be highly pathogenic and agent for the next pandemic if they gain the capacity of efficient human to human transmission. The success of influenza virus to cause epidemics is due to two forms of antigenic variations it exhibits: antigenic shift and antigenic drift. Antigenic shift involves the co-infection of a single host with two different strains of influenza virus which results in the evolution of a third type of influenza virus. Since a wide range of HA and NA are circulating in nature, the chance of antigenic shift always resides and promotes the evolving of a more virulent strain. Antigenic drift refers to the gradual point mutation responsible for the change of one or the other character. This result in the sequentially variant strain of the same virus circulates in the environment for several decades. The genes encoding HA and NA are the subject to mutation. Apart from H5N1, two other strains which are considered extremely virulent are H9N2 and H7N7 [5, 6]. These two strains are common in poultry and promote human diseases frequently. HA forms the key component for initiating infection. Research has revealed that H5N1 strains which are highly pathogenic in mice possess a series of basic residues close to the HA cleavage site which renders HA to be cleaved by numerous trypsin-like proteases. The above statement is further confirmed as the recombinant H5N1 strains lacking those residues were found to be non-virulent in mice [7]. In NA the active site of the moiety possesses some specialized amino acids at particular points which enhance its action. The presence of three arginine residues at particular points as 118,292 and 371 promotes in binding of the virus to the carboxylate group of the sialic acid residue in the host cells. Also arginine at 152 interacts with the acetamido group and glutamic acid at 276 forms hydrogen bonding with the 8^{th} and the 9^{th} hydroxyl groups of the host substrate which promotes its activity [1]. Recently molecular studies has revealed that apart from the above mentioned structural glycoprotein, another non-structural protein which remained unnoticed may contribute to the virulence of H5N1 strains partially. The protein NS1 which is synthesized in the infected host cells and functions in inhibiting the action of two cellular proteins which are absolutely required for the post-transcriptional modification of the cellular mRNAs at the 3' end [8]. This results in the reduced production of interferon-β-mRNA, a compound produced by the host in response to viral invasion [12]. Thus the virus escapes the immune response and renders its pathogenicity [13]. Further it was found that the carboxyl end of the NS1 protein of most of the avian H5N1 strains possessed sequence motif composed of four amino acids, namely Glu-Ser-Glu-Val. These residues mediate the binding of the NS1 protein to several cellular proteins which possess a special region called the PDZ domain. A number

of proteins in a cell that controls some of the vital activities in the cell as cell signaling (signal transduction) and maintaining the cell structure and morphology contain the PDZ domain. Similar PDZ domain binding motif was discovered in the NS1 protein of H5N1 strain virulent in humans but the amino acid in the second position was proline as Glu-Pro-Glu-Val. Also the low virulent influenza strain of human possessed Arg- Ser-Lys-Val which was found to be non PDZ binding domain. Comparing the above three instances of the motifs it can be concluded that the presence of a functional carboxyl-terminal PDZ –binding domain in NS1 protein of H5N1 strain contributes to its virulence by interfering in the cellular processes of various proteins. However the dilemma still sustains as the most pathogenic isolate of H5N1 till date, A/Vietnam/1203/04 do not possess both the PDZ binding sequence motifs [2, 9]. Another important membrane protein is the M2 channel protein which plays a significant role in uncoating the virus inside the host cell by permitting the protons to enter the virus particles [3]. This M2 protein is relatively conserved part and can form the target of a "universal" influenza vaccine as the "Holy Grail" influenza vaccine. However the M2 is present in very less number compared to HA and NA and thus is efficient upto a certain extent [4]. The genome of influenza virus consists of –ve sense ssRNA of eight segments. The RNA polymerase remains associated with each of the RNA strands which in turn consist of three specialized proteins namely, PB1, PB2 and PA. Studies have revealed that amino acid sequence of the three proteins involved in specific steps of the RNA synthesis or mediating interaction amongst themselves. It has been found that the H5N1 strains which were virulent in mice encode lysine at the position 627 in PB2 whereas those which are non-virulent encode glutamic acid in the same position. Thus substitute of amino acid in PB2 can attribute partially to the virulence of H5N1 strain. The thorough understanding of the above mentioned factors for virulence and antigenicity forms the top priority to develop an efficient influenza vaccine to combat the disease. Immunogen-design strategies are under pipeline to develop an efficient vaccine which would target the functionally conserved areas devoid of variations to prevent the next pandemic [11]. Also current focus should be laid more on universal influenza vaccine which covers a wide spectrum of strains. However the studies of the virulence and antigenicity at molecular level will continue and awaits a significant breakthrough.

Acknowledgement

I am thankful to Mr. Sekar Viswanathan, Pro-chancellor, VIT University for his enormous encouragement and Periyar EVR Central Library, VIT University for allowing the access to the latest information through journals of International repute.

References

[1] Russell R.J., Haire L.F., Stevens D.J., Collins P.J., Lin Y.P., Blackburn G.M., Hay A.J., Gamblin S.J., Skehel J.J. (2006) *Nature* 443, 45-49.

[2] Krug R.M.(2006)*Science* 311,1562.

[3] Regoes R.R. and Bonhoeffer S. (2006) *Science* 312,389.

[4] Doherty P.C.,Turner S.J., Webby R.G.,Thomas P.G.(2006) *Nat. Immunol*. 7,449-455.

[5] Butt K.M., Smith G.D., Chen H., Zhang L. J. , Leung Y. H.C.,. Xu K. M, Lim W., Webster R.G., Yuen K. Y., Malik Peiris J. S. and Guan Y. (2005) *J.Clin. Microbiol*. 43, 5760-5767.

[6] Fouchier R.A., Schneeberger P.M., Rozendaal F.W., Broekman J.M., Kemink S.G., Munster V., Kuiken T., Rimmelzwaan G.F., Schutten M., Doornum G.V.,Koch G., Bosman A., Koopmans M., Osterhaus A.E.(2004) *Proc. Natl. Acad. Sci. USA* 101,1356-1361.

[7] Hatta M., Gao P., Halfmann P..Kawaoka Y.(2001) *Science* 293,1840-1842.

[8] Krug R.M.,Yuan W., Noah D.L. Latham A.G.(2003) *Virology* 309(2),181-189.

[9] Obenauer J.C.,Denson J.,Mehta P.K.,Su X., Mukatira S., Finkelstein D.B., Xu X., Wang J., Ma J., FanY., Rakestraw K.M., Webster R.J., Hoffmann E., Krauss S., Zheng J., Zhang Z., Naeve. (2006) *Science* 311, 1576 -1580.

[10] Smith D.J.(2006) *Science* 312, 392-394.

[11] Hedestam G.B., FouchierR.M., Phogat S., Burton D.R., Sodroski J., Wyatt R.T.(2008) *Nat. Rev. Microbiol*. 6,143-155.

[12] Noah D.L., Twu K.Y., Krug R.M.(2003) *Virology* 307(2),386-395.

[13] ThanhT.T., DoornH.R., Jong M.D.(2008) *Internatl. J. Biochem. Cellbiol*. 40, 2671-2674.