Avian and human influenza A virus receptors in trachea and lung of animals

Sukanya Thongratsakul[1, 2, 3], Yasuo Suzuki[4, 5], Hiroaki Hiramatsu[4], Thavajchai Sakpuaram [3], Theerapol Sirinarumitr[3], Chaithep Poolkhet[3], Pattra Moonjit[3], Rungrueang Yodsheewan[6] and Thaweesak Songserm[3]

Summary

Background: **Influenza A viruses are capable of crossing the specific barrier between human beings and animals resulting in interspecies transmission. The important factor of potential infectivity of influenza A viruses is the suitability of the receptor binding site of the host and viruses. The affinities of avian and human influenza virus to bind with the receptors and the distributions of receptors in animals are different.**

Objective: **This study aims to investigate the anatomical distribution of avian and human influenza virus receptors using the double staining lectin histochemistry method.**

Methods: **Double staining of lectin histochemistry was performed to identify both SA α2,3 Gal and SA α2,6 Gal receptors in trachea and lung tissue of dogs, cats, tigers, ferret, pigs, ducks and chickens.**

Results: **We have demonstrated that avian and human influenza virus receptors were abundantly present in trachea, bronchus and bronchiole, but in alveoli of dogs, cats and tigers showed SA α2,6 Gal only. Furthermore, endothelial cells in lung tissues showed presence of SA α2,3 Gal.**

Conclusion: **The positive sites of both receptors in respiratory tract, especially in the trachea, suggest that all mammalian species studied can be infected with avian influenza virus. These findings suggested that dogs and cats in close contact with humans should be of greater concern as an intermediate host for avian influenza A in which there is the potential for viral adaptation and reassortment.** ***(Asian Pac J Allergy Immunol 2010;28:294-301)***

Key words: *Influenza A viruses, receptors, host, lectin histochemistry, trachea, lung.*

From the [1]Center for Agricultural Biotechnology, Kasetsart University, Thailand.
[2]Center of Excellence on Agricultural Biotechnology: (AG-BIO/PERDO-CHE), Bangkok, Thailand.
[3]Faculty of Veterinary Medicine, Kasetsart University, Thailand.
[4]Department of Biomedical Sciences, College of Life and Health Sciences, and Health Science Hills, Chubu, University, Japan
[5]Global COE Program for Innovation in Human Sciences, University of Shizuoka School of Pharmaceutical Sciences, Japan
[6]Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
Corresponding author: Thaweesak Songserm
E-mail: fvettss@ku.ac.th
Submitted date: 14/5/2010
Accepted date: 9/11/2010

Introduction

Influenza A virus is an important pathogen which can infect a wide variety of avian species, mammals and human beings. In animals, the virus can be divided into two groups based on its virulence or pathogenicity, that is highly pathogenic and low pathogenic avian influenza (AI) viruses. Subtypes of AI virus are differentiated by characteristics of their two crucial proteins, hemagglutinin (HA) and neuraminidase (NA). At present, there are 16 H and 9 N among AI viruses. Avian strains, such as highly pathogenic avian influenza (HPAI) H5N1 and H7N7, have been reported to be zoonotic to human beings.[1-4] HPAI H5N1 can naturally and experimentally infect several mammalian species such as tigers, cats, dogs and ferrets.[5-10] The virus can be detected in or isolated from respiratory organs, especially trachea and lungs. Contrary to HPAI H5N1 virus transmitting from poultry to human beings and mammals, a new strain of H1N1 virus continuously spreading among human beings can transmit from human beings to animals such as pigs[11] turkeys, and cats.[12] Exposure to the viruses has been reported in mammals such as dogs, cats and tigers that were fed with infected poultry carcasses during the outbreak of a highly pathogenic avian influenza (H5N1) in Thailand. The viral antigen can be detected in lung tissue of

infected animals.[7-9] This finding indicates that the HPAI H5N1virus can cross host species barriers by ingestion of infected carcasses and contact with oronasal secretion from infected animals.

One factor in the potential infectivity of AI is the receptor binding site of the host and AI virus. In general, avian strains bind preferentially to sialic acid (SA) α2,3 Gal, while human strains favor sialic acid (SA) α2,6 Gal.[13-14] It has been previously reported that several species such as chickens, ducks, quail, and pigs can be infected with both avian and human influenza viruses and can play an important role as a 'mixing vessel' or intermediated host.[15] The distributions of the avian influenza and human influenza virus receptors in different animals were not the same. There have been no studies thus far in companion animals, especially in domestic dogs and cats, or in wildlife such as tigers, particularly in the target organs trachea and lung tissue compared to target organs in avian species.

This study aims to investigate the anatomical distribution of avian SA α2,3 Gal and human SA α2,6 Gal influenza virus receptors using the double staining lectin histochemistry method.

Methods

Animal tissue preparation

Tissues were directly collected from donated animals at Kasetsart University Veterinary Teaching Hospital (KUVTH) and necropsy unit, Center of Veterinary Research and Diagnosis (CVRD), Faculty of Veterinary Medicine, Kasetsart University. The samples were collected from dogs, cats, pigs, chickens, and ducks, five each. Samples from two tigers were collected from the Khao Kheow Open Zoo, Chonburi, Thailand and one ferret from the Faculty of Medicine Siriraj Hospital, Mahidol University. Trachea and lung tissues were fixed in 10% neutral buffered formalin, and then processed using an automatic tissue processor (Shandon Citadel 1000) before being embedded in paraffin wax. All processes of tissue collection from the animals used in this study were approved by the committee of ethics and animal experimentation of Kasetsart University.

Detection of SA α2,3 Gal and SA α2,6 Gal receptors

The tissue blocks were sectioned using a rotary microtome (Shandon AS325, Runcorn, UK) at 5 μm in thickness and were mounted on glass slides. The methods to detect sialic acid receptors have been previously described[16-17] with few modifications. Briefly, the sections were deparaffinized and rehydrated. Biotinylated *Sambucus nigra agglutinin* (SNA) (Vector Laboratories Burlingame, CA, US), specific for binding human SA α2,6 Gal, and digoxigenin (DIG)-labeled *Maackia amurensis agglutinin* (MAA) (Roche Diagnostics GmbH, Germany), specific for binding avian SA α2,3 Gal, were used for lectin histochemistry. The sections were then incubated in a solution of biotinylated SNA at 5 μg/ ml and digoxigenin (DIG)-labeled MAA at 10 μg/ ml for 1 hour in phosphate-buffered saline (PBS), pH 7.2-7.4 containing 0.5 % bovine serum albumin (BSA). After 1 hour of incubation at room temperature the sections were rinsed with phosphate-buffered saline included 0.05% tween20 (PBST) for 3 times of 5 minutes each and then incubated with horseradish peroxidase (HRP)-conjugated streptavidin (Invitrogen, Carlsbad, CA) and alkaline phosphatase (AP)-conjugated anti-DIG antibody (Roche Diagnostics GmbH, Germany) diluted with 0.5% BSA/PBS. Using diaminobenzidine (DAB) (Amresco, Solon, OH, USA) and a combination of Nitro blue tetrazolium chloride) and 5-Bromo-4-chloro-3-indolyl phosphate p-Toluidine Salt (NBT/BCIP) (Roche Diagnostics GmbH, Germany) as chromogenic substrate for HRP and AP, respectively, negatives were created by omitting the primary antigen. The slides were counterstained with nuclear fast red or hematoxylin, dehydrated and mounted in per mount.

Simultaneous detection of SA α 2,3 Gal or SA α2,6 Gal receptors and highly pathogenic avian influenza H5N1 virus antigen

The paraffin embedded lung tissues of the infected chickens and ferret were examined immuno-histochemically for avian influenza H5 antigen and receptors. The methods to detect avian influenza virus antigen and influenza A receptor have been previously described[7-8, 16-17] with minor modifications. In brief, the sections were blocked with 2.5 % BSA/ PBS for 30 minutes. The sections were then incubated in a solution of DIG-labeled MAA at 10 μg/ ml or SNA at 5 μg/ ml for 1 hour in 0.5% BSA/ PBS. After 1 hour incubation at room temperature and washing with 0.05% PBST for 3 times of 5

Table 1. Distribution of influenza A receptors in the respiratory tract of animals

	Trachea		Bronchus/ Bronchioles		Alveoli		Endothelial cells	
Species	SAα2,3	SAα2,6	SAα2,3	SAα2,6	SAα2,3	SAα2,6	SAα2,3	SAα2,6
Dog	+	+	+	+	-	+	+	+
Cat	+	+	+	+	-	+	+	+
Tiger	+	+	+	+	-	+	+	+
Pig	+	+	+	+	+	+	+	+
Ferret	+	+	+	+	+	+	+	+
Chicken	+	+	+	+	+	+	+	+
Duck	+	+	+	+	+	+	+	+

+ Detected, - Not detected

minutes each,the sections were incubated with AP-conjugated anti-DIG antibody (Roche Diagnostics GmbH, Germany) diluted with 0.5% BSA/PBS for 1 hour and incubated with a mouse polyclonal antibody anti-nucleoprotein (NP) of influenza A H5N1 (Laboratory for Research and Technology Development, Faculty of Medicine Siriraj Hospital, Thailand) diluted 1:200 in PBS as a primary antibody. Polyclonal goat anti-mouse immunoglobulin G labeled with peroxidase (DAKO A/S, Glostrup, Denmark) as a secondary antibody. DAB and NBT/BCIP was used as a substrate for HRP and AP respectively.

Results

I. Influenza A receptors SA α2,3 Gal and SA α2,6 Gal in trachea and lung tissues of the animals.

The anatomical distribution of receptors in trachea and lung of the animals is presented in Table 1. Both receptors are detected in the epithelial cells of trachea, bronchus, bronchiole, alveoli cells and endothelial cells. Generally, most animals have both receptors in the respiratory tract, except that dogs, cats and tigers do not have SA α2,3 Gal in alveoli cells (Table1).

Dogs and Cats

The predominant positive stain of SA α2,3 Gal and SA α2,6 Gal receptors in both species are ciliated pseudostratified columnar epithelial cells and goblet cells. Some of them expressed both receptors in a single cell. Mixed glands in the submucosal layers were also found with both receptors. However, the most positive area was ciliated pseudostratified columnar epithelial cells (Figure 1a, 1d).

In the lung tissue of dogs and cats, we found predominant stain for both receptors SA α2,3 Gal and SA α2,6 Gal in epithelial cells of bronchi and bronchioles. Second and tertiary bronchi were lined with ciliated pseudostratified columnar epithelial cells while the terminal bronchioles were lined with ciliated cuboidal epithelial cells. They demonstrated strong staining with SA α2,3 Gal and SA α2,6 Gal when longitudinally sectioned (Figure 2a, 2b). The alveoli displayed the distinct SA α2,6 Gal in simple squamous epithelial cells with flattened nuclei or type I pneumocyte (Figure 2c). The avian influenza virus receptors SA α2,3 Gal were shown in endothelial cells of small blood vessels (Figure 2c) but were not found in epithelium of alveolar cells of dogs and cats (Figure 1b, 1e).

Tigers

In the trachea of tigers, the mucosal layer consists of ciliated pseudostratified columnar cells, goblet cells and basal cells. Human influenza receptors are present at the basal cells, which show strong staining with SA α2,6 Gal, but the free surface of ciliated pseudostratified cells showed SA α2,3 Gal which are specific for avian influenza receptors (Figure 1g). In the lung, SA α2,6 and SA α2,3 Gal were detected in the epithelium of terminal bronchioles whereas only SA α2,6 Gal was detected in alveolar cells (Figure 1h).

Pigs

The SA α2,6 Gal was mostly detected in the ciliated pseudostratified cells in the mucosa of swine trachea whereas a few stains of SA α2,3 Gal were found in the same area. In the mixed glands of the submucosa layer, which are seromucous glands, both receptors and endothelial cells of blood vessels were detected. In the swine lung tissue, including bronchus, secondary and terminal bronchiole, SA α2,6 Gal was mostly detected in the epithelial cells but SA α2,3 Gal was detected in the endothelial cells. In alveolar cells SA α2,6 Gal was predominantly found (Figure 1j, 1k) and SA α2,3 Gal was found in a few areas.

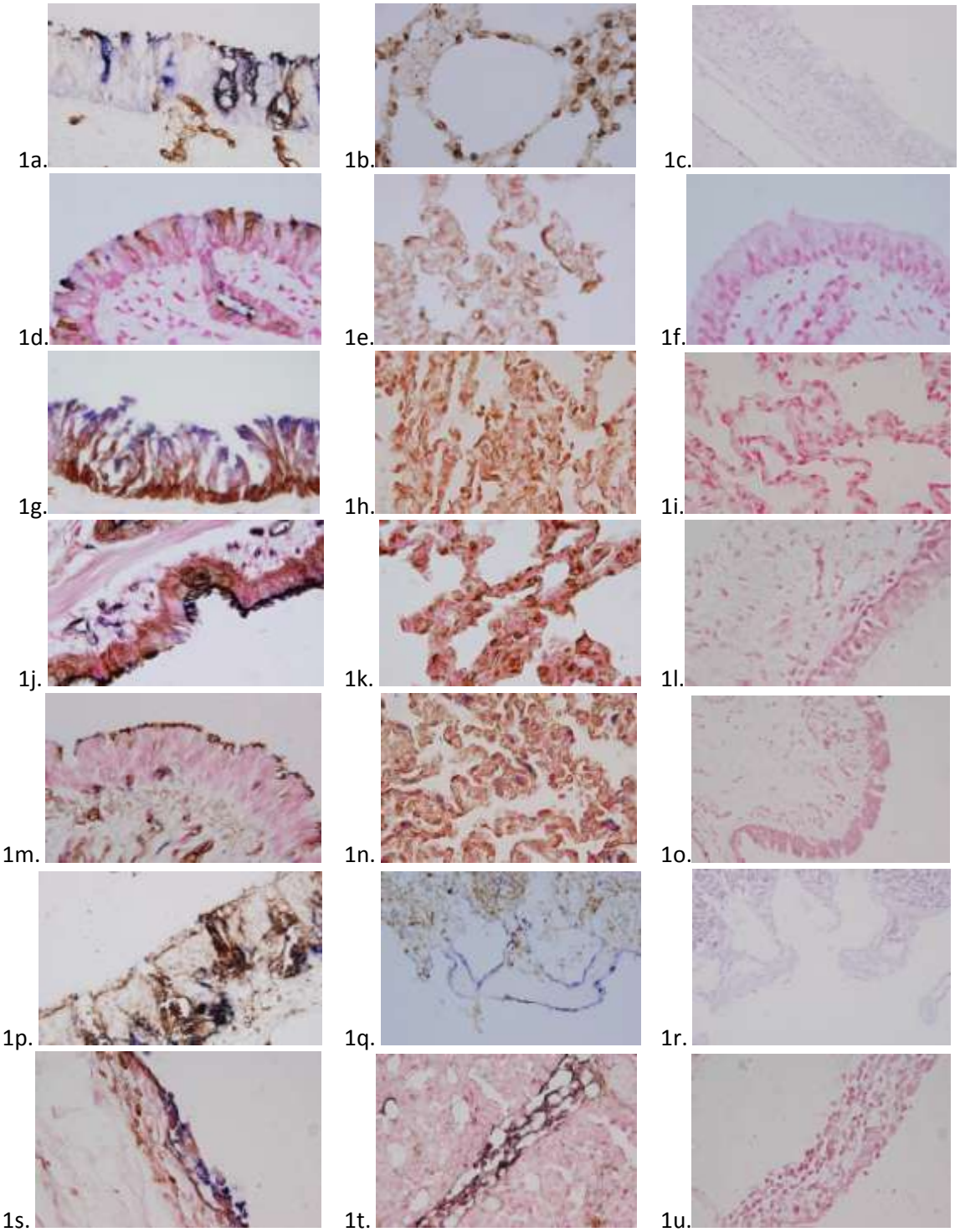

Figure 1. Comparison of lectin binding in trachea and lung tissues. Avian influenza virus receptor SA α2,3 Gal binding with *Macckia amurensis agglutinin* (MAA), is shown in blue and human influenza virus receptor SA α2,6 Gal binding with Sambucus nigra agglutinin (SNA) is shown in brown. The distribution in tissues of dogs, cats, tiger, pigs, ferret, chickens and ducks: Dog trachea (1a.), dog lung (1b.), cat trachea (1d.), cat lung (1e.), tiger trachea (1g.), tiger lung (1h.), pig trachea (1j.), pig lung (1k.), ferret trachea (1m.), ferret lung (1n.), chicken trachea (1p.), chicken lung (1q.), duck trachea (1s.), duck lung (1t.), the negative control of all species (1c.,1f.,1i.,1l.,1o.,1r.,1u.). Counter stain with hematoxylin or nuclear fast red (magnification x100)

Ferret

Avian influenza receptors, SA α2,3 Gal, were found in small amounts in epithelial cells in the mucosa of trachea (Figure 1m). Most epithelial cells showed marked staining with SA α2,6 Gal. In the lung, the non-ciliated cuboidal epithelium of the terminal bronchioles mainly expressed SA α2,6 Gal, while in alveoli epithelial cells expressed both SA α2,6 Gal and SA α2,3 Gal and alveolar macrophage also expressed SA α2,3 Gal (Figure 1n).

Chickens and Ducks

Chicken trachea has abundant intraepithelial mucous glands which were shown to have a positive stain of SA α2,3 Gal, whereas ciliated pseudostratified columnar epithelial cells had SA α2,6 Gal (Figure 1p). By contrast, duck trachea had both receptors in its epithelial cells (Figure 1s) and the upper or apical surface of ciliated pseudostratified columnar epithelial cells revealed SA α2,3 Gal and SA α2,6 Gal. The smooth muscle and squamous cells of the parabronchus and tertiary bronchi of chickens showed strong positive staining for SA α2,3 Gal (Figure 1q) whereas respiratory epithelial cells predominantly expressed SA α2,6 Gal (Figure 1q). In the lungs of ducks, the mesobronchus has a ciliated pseudostratified epithelial cell lining which markedly demonstrated both receptor types. A few areas of pulmonary parenchyma were positive to both receptor types, especially in septum lung lobule (Figure 1t).

II. Avian influenza virus antigen and influenza A virus receptors in highly pathogenic avian influenza H5N1 infected animals

In general, the NP of avian influenza virus antigen and the SA α2,3 Gal receptor in the same area of infected chicken and ferret lung tissue were detected. MAA bound strongly with SA α2,3 Gal receptor in pneumocytes is shown in blue and the avian influenza virus antigen is shown in brown in Figure 3a, 3c. In contrast the relationship between avian influenza virus antigen and SA α2,6 Gal receptors was not found (Figure 3b, 3d).

Lung tissue of the infected chickens

In the serial sections of chicken lung, we found the NP antigen in respiratory epithelial cells and MAA bound strongly with SA α2,3 Gal receptors in the same area (Figure 3 a).

Lung tissues of the infected ferret

In ferret lung tissues, the NP antigen and SA α2,3 Gal receptors were detected in alveoli cells in the same location. However, SNA bound strongly to SA α2,6 Gal receptors in the epithelial cells of the bronchioles of ferrets but the NP antigen was not detected in the same area (Figure 3d)

Discussion

In this study, the SA α2,3 Gal and SA α2,6 Gal were detected in respiratory tissues but the positive sites varied between animal species. SA α2,6 Gal was detected in the alveoli of all animals studied whereas SA α2,3 Gal was only found in

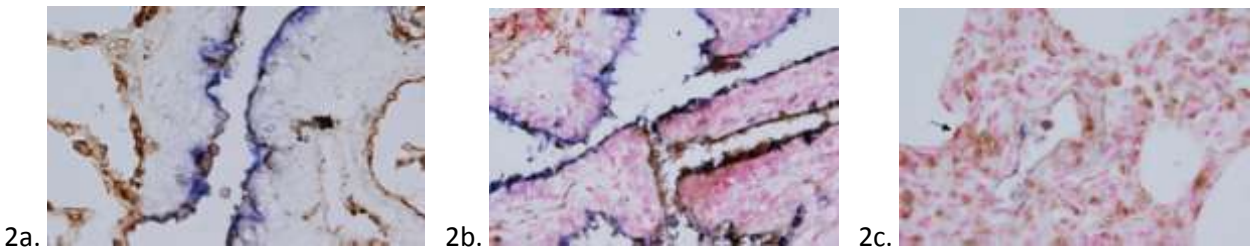

Figure 2. Lung tissue of dogs and terminal bronchioles showing staining of SA α2,3 Gal and SA α2,6 Gal in ciliated cuboidal epithelium (Figure 2a.,b.). Pneumocyte type I with flattened nuclei show strong positive stain in brown color of biotinylated *Sambucus nigra agglutinin* (SNA) as DAB is chromogenic substrate (arrow) (Figure 2c.) (magnification x100)

chickens, ducks, pigs and ferrets. The positive sites for both receptors in the upper respiratory tract, especially in the trachea, suggest that all mammalian species can be infected with avian influenza virus. On the other hand, avian species can also be infected with human influenza A virus. However, susceptibility to those viruses of each species needs to be further studied in animal experiments.

An avian influenza virus antigen detected in the trachea of beagles experimentally infected with H3N2, and in lung of tigers, cats, and dogs have been reported in natural infection with HPAI H5N1.[7-9, 18-19] This evidence supports the view that the avian influenza virus receptor SA α2,3 Gal is abundant in trachea, bronchi and bronchiolar epithelial and alveolar cells. In this study, we have shown that SA α2,6 Gal was present in trachea and bronchi of cats and dogs. This suggests that the recently identified human strain of influenza H1N1 can infect cats.[12]

Our findings are in accordance with those of Kuchipudi *et al*.'s study (2009), in that chicken tracheal epithelial cells expressed predominantly SA α2,6 Gal by using the SNA binding method, and chicken alveoli expressed both receptors.[20] Duck trachea, however, expressed a greater abundance of SA α2,3 Gal in ciliated epithelial cells. Furthermore, our results showed that in ducks, the trachea has both avian and human influenza virus receptors (Figure 1s, 1t) and in the tracheal mucosa gland of chickens we found that SA α2,3 Gal was predominantly expressed (Figure 1p).

Additionally in this report, we demonstrated a direct relationship between avian influenza virus and influenza A receptor SA α2,3 Gal and SA α2,6 Gal in the same area of infected animal tissues (Figure 3). These results confirm that the presence of influenza A receptors in respiratory tract are major predilection site for avian influenza virus infection. In the initial step of avian influenza virus infection the viruses need to attach to the specific receptors. Therefore, this might explain why the replication of avian influenza viruses in humans is limited.[21]

The source of lectin should be investigated by its suppliers, since so many companies provide isoforms of MAA. Generally, MAA I specifically binds with SA α2,3 Galβ(1-4) GlcNAc[20, 22] and MAA II specifically binds for SA α2,3 Galβ (1-3) GlcNAc.[23] The different isoforms of MAA from different suppliers produce differential staining results.[24] The studies showed a varied distribution of MAA I and MAA II which were supplied by Vector Laboratories, and MAA I isoform supplied by Roche and EY laboratories produced different results. MAA II isoform may not detect some of the H5N1 influenza virus binding SA α2,3 terminated oligosaccharides that can be recognize by MAA I in trachea of humans. Other study recommends using both MAA I and MAA II for detecting avian influenza receptors in trachea and lung tissue.[24]

In dog and cat lung tissue, the molecular structure of the avian influenza receptor SA α 2,3 Gal is SA α2,3 Galβ (1-4) GlcNAc.[25] Therefore

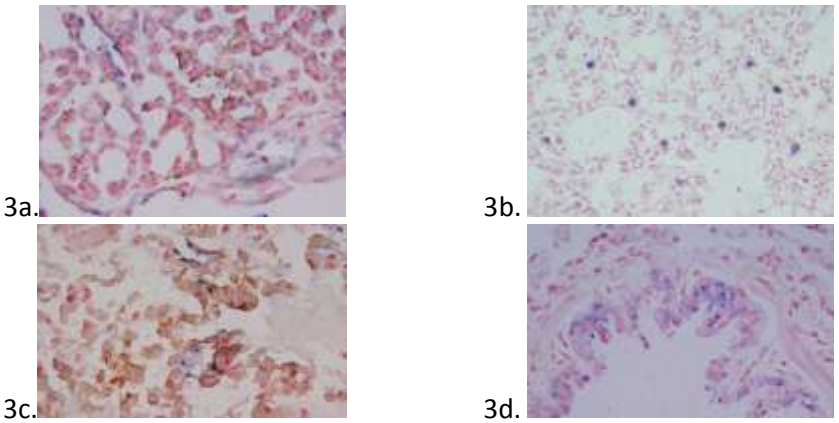

Figure 3. Double staining of avian influenza virus antigen and receptor in tissues of infected animals. Avian influenza virus antigen is shown in brown and avian influenza virus receptor SA α2,3 Gal binding with *Macckia amurensis agglutinin* (MAA) is shown in blue (3a., 3c.). Chicken lung (3a, 3b.). Ferret lung (3c., 3d.). Human influenza virus receptor SA α2,6 Gal binding with *Sambucus nigra agglutinin* (SNA) is shown in blue (3b., 3d.) (magnification x100)

in this study we used MAA I, which can detect SA α2,3 Gal in lung tissue if the avian influenza receptor has been detected. We also confirmed that the MAA II isoform did not detect SA α2,3 Gal in the lung tissue of dogs and cats. However, we have found an avian influenza virus receptor in the trachea of dogs, cats, pigs and ducks by using the MAA I isoform supplied by Roche.

Suzuki (2005) reported that a single amino acid mutation at the receptor binding site of HA results in the switching of viral and host specificity between the human influenza virus receptor and the avian influenza virus receptor.[21] Therefore an understanding of the receptor distribution in different species of animals, including mammals and poultry, is important for monitoring the progression of the mutation and adaptation of the influenza viruses.

Overall, sialic acids on host cell membranes vary and have a high level of host specificity. In fact SA on the respiratory epithelial cell surface plays a role in the host specific barrier to influenza infection. The mechanisms of the host response to influenza viruses are very complex and involve both humoral and cell-mediated immunity. The first step of influenza infection occurs when the virus is preferentially attached to SA receptors in the epithelial cells. The virus infects the cells subsequently, inducing the production of cytokines and chemokines such as interferons (IFNs), interleukin (IL), and tumor necrosis factor (TNF).[26] The alveolar macrophages are present in the early stage as signal messengers in virus infected cells. These processes are associated with the recruitment of macrophages and neutrophils into the lung tissue and result in lung inflammation.[26]

Specific immune responses require coordination between humoral and cell mediated immunity during viral infection and replication of viruses in the host cells. Throughout influenza virus infection, dendritic cells (DCs) and macrophages secrete antiviral cytokines such as IFNs and TNF. However, when epithelial cells are infected, the virus can spread to DCs and macrophages. Therefore, macrophage and DCs cells have surface receptors which are the potential targets for influenza viruses and the virus can replicate very well in these cells.[26-29] Chemokines facilitate the infiltration of inflammatory cells, such as macrophages, monocytes, neutrophils lymphocytes and DCs into the alveolar space and proliferation of influenza-specific $CD8^+$ and $CD4^+$ cells in the lung.[26] Furthermore, HA and NA are the important surface proteins that are recognized by antigen presenting cells (APC). Subsequently MHC molecules will present the antigen to the surface stimulating T cells to become either $CD8^+$ cells or $CD4^+$ cells and activating B lymphocyte cells to produce immunoglobulins.[30-31] This indicates that the SA receptors on the surface of the host cells play an important role in the early development of viral infection because the virus could not infect the host if the receptors are absent.

In the respiratory tract, the cilia are involved in removing infectious agents and in mucus entrapment. Human bronchial mucin mostly contain SA α2,3 Gal which can inhibit influenza infection.[32] Moreover, surfactant collectin, such as surfactant proteins A and D (SP-A and D), and scavenger receptor-rich glycoprotein 340 (gp340) also inhibit influenza A viruses. Similarly to mucin activity, they provide an SA ligand which is attached to the HA and NA of the viruses.[33] Viral mutation and changes in the HA receptor binding domain occur continuously, hence they may also affect the receptor binding specificity. The information on influenza A receptors in different animals, in terms of types and locations, is very important in extrapolating the chance of infection and the susceptibility of various species. This needs to be investigated in order to understand pathogenesis in different animals. Cats and dogs in close contact with humans should be of greater concern as an intermediate host of avian and mammalian influenza A virus, since they have both viral receptors in the trachea and lung. These animals may potentially be a 'mixing vessel' in which viral adaptation and reassortment to cross-species barrier to influenza A viruses in mammals, including human beings. Alternative drugs, antibodies or substances like receptor sugar chain analogs may hold the potential to inhibit influenza infection as a prophylactic or as a cleaning and disinfection substance. Therefore, study of the viral receptors and knowledge of mechanism of host range specificity is very valuable.

Acknowledgements

The authors would like to thank the clinicians at the Kasetsart University Veterinary Teaching Hospital, Faculty of Veterinary Medicine, and Khao Kheow Open Zoo, Chonburi, Thailand. We

also would like thank to Professor Dr. Robert H. Orr for English editing. A part of this research was financially supported by Center of Advanced Studies for Agriculture and Food, Institute for Advanced Studies, Kasetsart University (CASAF, NRU-KU, Thailand) and the Center of Excellence on Agricultural Biotechnology Science and Technology Postgraduate Education and Research Development Office (PERDO), Commission on Higher Education Development Project, Ministry of Education, and Thailand.

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