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Binding affinities of hydrophilic pulmonary surfactant proteins with surface proteins of microbes, pollen allergens and lipid ligands using molecular docking studies

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Abstract

Hydrophilic Surfactant proteins, SP-A and SP-D, are collagen like C-type (calcium dependent) lectins called collectins, which contribute significantly in host defence mechanism. Binding studies of SP-A and SP-D with the surface proteins of microorganisms, pollen allergens and lipid ligands were studied. Out of which SP-A was found to bind with a higher affinities with Influenza A- Virus (-542.48kcal/mol) and Di-lauroyl phosphatidyl choline (-114.622 kcal/mol) than SP-D, but Birch pollen allergen (-593.08kcal/mol) bound strongly with SP-D. Rotavirus and Carrot pollen allergen have negative binding with SP-A and positive binding with SP-D.

Keywords: Surfactant protein, Binding affinities, microbes, Pollen allergens, Lipids.

INTRODUCTION

Pulmonary surfactant is found in the fluid lining, the alvelolar surface of the lungs primarily composed of lipids and proteins. Majority of lipids are phospholipids which are essential for reducing the surface tension in the lungs. Four surfactant proteins SP-A, SP-B, SP-C and SP-D were secreted by alveolar type II cells of the lung, in which SP-B and SP-C are hydrophobic, SP-A and SP-D are hydrophilic in nature [1, 2]. Both *in vitro* and *in vivo* studies show that SP-A and SP-D, as well as MBL, enhance the uptake of particles and pathogens and that they do so by at least three different mechanisms: by opsonizing pathogens; by functioning as activation ligands, and by regulating cell-surface-receptor expression.

SP-A and SP-D consist of carbohydrate recognition domains which binds to various carbohydrate ligands present on the foreign substances such as Influenza Viruses, Rotavirus and Bacteria [3, 4]. The interaction of SP-A and SP-D with different strains of Influenza A virus (IAV) appears to depend on the structures of their surface expressed hemagglutinin, neuraminidase and their levels of glycosylation [5, 6,12, 13]. Both SP-A and SP-D, via their CRDs, bind to the carbohydrate structures on the surfaces of a broad spectrum of Gram-positive and Gram-negative bacteria [7]. This interaction has different effects depending on the bacteria and the surfactant protein involved. It can cause agglutination of bacteria, hindering their entry into host cells and dissemination. It may lead to killing by making the cell walls permeable, increasing the respiratory burst by macrophages and neutrophils, and enhancing their opsonization by phagocytic cells.

SP-A and SP-D appear to offer protection against allergenic challenge at various levels, suggesting a hierarchical role for these two molecules of innate immunity [8]. These protective mechanisms seem to involve allergen scavenging, inhibition of allergen-IgE cross-linking in addition to the release of histamine, suppression of the activation of sensitized basophils, mast cells or eosinophils, suppression of Band T-cell proliferation, modulation of DCs and macrophages. [9, 10, 11].

MATERIALS AND METHODS

Interaction of surfactant protein (SP-A and SP-D) with surface proteins of microbes and pollen allergens

In this study, surfactant proteins, surface proteins of microbes and pollen allergens were retrieved from Protein Data Bank, based on the presence of ligand, X-ray diffraction, resolution and Ramchandran Plot (Table 1). Interaction of surfactant proteins (SP-A and SP-D) with surface proteins of microbes and pollen allergens were carried out using Hex software version 5.0. Hex is an interactive Molecular Graphics program for calculating the docking scores of protein-protein interactions.

Table 1 List of proteins selected

Origin	Name of the protein	Source of organism	PDB ID
Surfactant proteins	SP-D	Human	2GGU
	SP-A	Human	1R14
Microbial surface proteins	VP7	Rotavirus	3GZT
	Hemagglutinin	Influenza A Virus	3HTT
	Gp B(glyco protein B)	Herpes simplex Virus	2GUM
	PknD (Protein kinase D)	MycobacteriumTuberculosis	1RWL
Surface proteins of allergens	Bet v 1	Betula pendula	1FM4
	EXPB1	Zea mays	2HCZ
	DAU C 1	Daucus carota	2WQL
	Phl p 7	Phelum pratense	1K9U

Interaction of surfactant protein (SP-A and SP-D) with Lipid ligands

To study the protein-lipid interactions ISIS Draw 2.3 software (www.mdli.com) was used to draw the chemical structures of the lipids. 2D structures were converted to 3D structures by ProDrg2sever (http://davapc1.bioch.dundee.ac.uk/prodrg/). Docking studies were carried out using Molegro Virtual Docker 4.0.0. Eight lipid ligands such as Di-stearoyl phosphatidylcholine, palmitoyl phosphatidyl choline, di-lauroyl phosphatidyl choline, phosphatidyl ethanolamine, phosphatidyl serine, phosphatidyl glycerol, di-palmitoyl phosphatidyl choline, phosphatidyl ethanolamine, and α-Tocopherol were taken for docking studies with SP-A and SP-D.

RESULTS AND DISCUSSIONS

Interactions of SP-A and SP-D with microbial surface proteins

The Hex scoring results of protein-protein interactions of surfactant proteins such as SP-A (1R14) and SP-D (2GGU), with microbial surface proteins of Influenza-A virus (3HTT), Rotavirus (3GZT), Herpes simplex virus (2GUM), and Mycobacterium (1RWL) tuberculosis are given in Table 2

Table 2 Hex scores of interaction of surfactant proteins (SP-A & SP-D) with Microorganisms

Surfactant Proteins	Hex scores of Influenza –A- Virus(kcal/mol).					
	Etotal	Eshape	Eforce	Eair	Vshape	VcIash
SP-A (1R14)	-542.48	-503.36	-39.12	0.00	584.63	0.00
SP-D (2GGU)	-401.32	-461.32	51.54	0.00	645.04	0.00
	Hex scores of Rotavirus (kcal/mol).					
SP-A (1R14)	0.00	0.00	0.00	0.00	14.27	3.17
SP-D (2GGU)	-118.43	-118.41	-0.02	0.00	202.48	3.03
	Hex scores of Herpes Simplex Virus (kcal/mol).					
SP-A (1R14)	-336.22	-355.87	19.65	0.00	456.54	0.00
SP-D (2GGU)	-270.12	-280.19	-10.07	0.00	265.13	0.00
	Hex scores of Mycobacterium Tuberculosis (kcal/mol).					
SP-A (1R14)	-347.72	-315.91	-31.80	0.00	373.16	0.00
SP-D (2GGU)	-341.85	-530.06	-1 .79	0.00	650.81	0.00

Jo Rae Wright reported [2] that both SP-A and SP-D recognize the Influenza A virus and Mycobacterium tuberculosis. Rotavirus binds with SP-D but not with SP-A and Herpes simplex virus binds with SP-A but not with SP-D. Our studies predicted the binding affinities scores of SP-D with Rotavirus, Influenza A virus and Mycobacterium tuberculosis (-118.43, -401.32 and -341.85 kcal/mol). Present investigations also predicted unknown binding affinities of Herpes simplex virus (-270.12kcal/mol) with SP-D. SP-A with Influenza A virus, Herpes simplex virus, Mycobacterium tuberculosis showed positively (-542.48, -336.22, -347.72 kcal/mol respectively) and also predicted unknown binding affinity of Rotavirus. A comparative study explains that SP-A has more affinity towards the microbes than SP-D except Rotavirus. Among all these microbes, Influenza A virus showed highest binding affinity (-542.48 kcal/mole) with SP-A , when compared with SP-D.

Interactions of SP-A and SP-D with Pollen allergens

The binding energies of protein-protein interactions of SP-A (1R14) and SP-D (2GGU) with pollen allergens such as Birch pollen allergens, Maize pollen allergens, Carrot pollen allergen, Grass pollen allergen are tabulated in Table 3.

Table 3 Hex scores of SP-A&SP-D with surface proteins of pollen allergens

Surfactant Proteins	*Hex scores of Birch pollen allergen (kcal/mol)*					
	Etotal	Eshape	Eforce	Eair	Vshape	VcIash
SP-A (1R14)	-296.28	-243.75	-52.54	0.00	280.35	0.00
SP-D (2GGU)	-593.08	-586.51	-6.56	0.00	602.86	0.00
	Hex scores of Maize pollen allergen(kcal/mol)					
SP-A (1R14)	*-354.80*	*26.18*	*-380.98*	*0.00*	*378.34*	*0.00*
SP-D (2GGU)	*-516.49*	*2.06*	*-519.09*	*0.00*	*596.21*	*0.00*
	Hex scores of Carrot pollen allergen(kcal/mol)					
SP-A (1R14)	0.00	0.00	0.00	0.00	3.57	1.31
SP-D (2GGU)	-339.48	-288.91	-50.57	0.00	331.11	0.00
	Hex scores of Grass pollen allergen(kcal/mol)					
SP-A (1R14)	-369.72	-323.20	-46.52	0.00	344.88	0.00
SP-D (2GGU)	-589.48	-580.82	-8.66	0.00	645.71	0.00

SP-D shows positive binding with all pollen allergens. It has high binding affinity with Birch pollen allergen (-593.08kcal/mol). SP-A shows negative binding with Carrot pollen allergen, high affinity with Grass pollen allergen (-369.72kcal/mol) and moderate binding with remaining allergens. Comparative interaction studies shows that SP-D have high affinities than SP-A with all the pollen allergens.

Interactions of SP-A and SP-D with lipid ligands

The binding studies of SP-A and SP-D with various lipid ligands are carried out using the Molegro Virtual Docker and results obtained given in Table 4

Table 4 Interaction between SP-A and SP-D with lipid ligands

S.No	**Ligand name**	**Binding score (kcal/mol)**	
		SP-A	**SP-D**
1	Dipalmitoyl phosphatidyl choline(DPPC)	-101.581	-92.9502
2	Di-stearoyl phosphatidyl choline (DSPC)	-13.0316	25.1947
3	Palmitoyl phosphatidyl choline(PPC)	-90.8682	91.939
4	Di-lauroyl phosphatidyl choline(DLPC)	-114.622	-58.0762
5	Phosphatidyl Serine (PS)	-103.638	-93.0396
6	Phosphatidyl Ethanolamine (PE)	-99.6805	-89.5332
7	α-Tocopherol	-102.301	-83.0751
8	Phosphatidyl Glycerol(PG)	-121.176	-75.5345

The results indicates that SP-D binds towards Phosphatidyl Serine (-93.0396kcal/mol) and Palmitoyl phosphatidyl choline (+91.939 kcal/mol) with more and low affinities respectively. Further,SP-A binds towards Di-lauroyl phosphatidyl choline (-114.622 kcal/mol) and Di-stearoyl phosphatidyl choline (-13.0316 kcal/mol) with high and low affinities. Among all lipids, Di-lauroyl phosphatidyl choline has highest binding affinity with SP – A.

CONCLUSION

Present docking studies reveal that SP – A has more affinity than SP-D towards the microbes, Influenza A virus, Herpes simplex virus, Mycobacterium tuberculosis except Rotavirus. Rotavirus and Carrot pollen allergen have negative binding with SP-A and positive binding with SP-D. Among all, Influenza A virus has more binding affinity (-542.48kcal/mol). SP-D have high affinities than SP-A with all pollen allergens. Among pollen allergens, Birch Pollen allergen has high affinity (-593.08kcal/mol) with SP-D. SP-A has more affinity than SP-D towards all lipid ligands. Out of all lipid ligands used in the present study, Dilauroylphosphatidylcholine has highest affinity with SP - A (-114.622 kcal/mol). Docking studies are useful in identifying various possible proteins that bind with SP-A or SP-D with varied degree of affinities.

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