

Epitopes of Enzymes Involved in Sialylation with Special Reference to Lung Cancer

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Abstract

Environmental pollutants, poor air quality, urban growth, deforestation, burning of fuel and indoor air pollution lead to different respiratory diseases including lung cancer with fatal consequences. Almost 2 million people die every year due to harmful effects of indoor air pollutants. Especially an enormous number of children are being affected. Environment pollution is not only reported to affect the lungs but also damage the stem cells and their niche thus causing a permanent damage to the cell renewal system of our body. Thus, on one hand, it is important to understand the effect of pollutants causing cancer, and on the other hand, it is very important to understand the biochemical changes that are associated with the biology of lung cancer in order to search for strategies to halt the cancer progression and improve the quality of life. Altered expression of sialic acid is reported to be a hallmark in lung cancer and in other cancer. Post-translational sialylation are reported to be dysregulated leading to alteration of sialylation in receptor in lung cancer which is associated with their altered functioning. At this point, it seems the understanding of the epitopes of the enzymes involved in sialylation pathway and targeting them by specifically designed antibodies could be a probable strategy to halt lung cancer. In this study, the epitopes for different enzymes involved in sialylation of biomolecules are reported using a bioinformatics approach. More research focused on design of antibodies targeted to these epitopes in order to target these enzymes needs to be studied so that effective means of control of lung cancer can be designed forms the scope of future research.

Keywords: Sialic acids, stem cells, pollutants, lung cancer and environment

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INTRODUCTION

Environmental pollution and indoor air pollution bear detrimental consequences on the human health causing myriads of disorders of the lungs, including lung cancer [1, 2]. Indoor air pollution not only is cancerous, but it can also affect the stem cells and its niche thereby completely losing the chances of regeneration of lung cells to replace the damaged cells [1-3]. Around 14 million new cases of lung cancer in both men and women and 8.2 million deaths in 2012 have been reported with an expected rise in the numbers in the next decade are predicted [4] contributing to 1.59 million deaths out of the 8.2 million deaths from cancer worldwide. reported in 2012 [5]. The World Health Organization (WHO) statistics shows that indoor air pollutants are the causative agents for lung disorders causing morbidity and mortality globally. Around 3 billion people use open fire

to cook and heat homes of which around 4 million people die prematurely. More than 50% of premature deaths due to pneumonia among children under-5 of age years are caused by the particulate matter like soot inhaled from household air pollution [4, 5]. 3.8 million premature deaths occur annually from noncommunicable diseases including pneumonia (12%), stroke (34%), ischaemic heart disease (26%), chronic obstructive pulmonary disease (COPD, 22%) and lung cancer (6%) and are attributed to exposure to household air pollution [4, 5]. Approximately 17% of annual premature lung cancer deaths in adults are attributable to exposure to carcinogens from household air pollution caused by cooking with solid fuels like wood, charcoal or coal. The risk for women is higher, due to their role in food preparation [4, 5]. The situation in India is also alarming [6].

Thus, it is very important to understand and target lung cancer, and thus both basic and applied research for early detection and targeting of biomolecules with aberrant expression in lung cancer is imperative and forms the basic interest of research.

Sialic acids comprise of a family of monosaccharide acidic sugars with a 9-carbon backbone, with 43 derivatives of the sugar neuraminic acid amongst which the most common is N-acetylneuraminic acid, in vertebrates. They are known as bio-markers in different cancer [7-10] and their role in altered cellular physiology in cancer [11–14] together other alteration in cell surface with glycoproteins and lipids and have been reported throughout the entire stages of oncogenic development, metastasis and transformation. Altered sialylation of proteins and lipids during cancer are due to altered enzymatic activity of different types of sialidase, sialyltransferase [10–14]. Sialylation is a post-transcriptional modification of proteins and lipids mediated by a battery of enzymes controlling the biochemical pathway for sialylation [10]. Altered sialylation of proteins and lipids has been reported as markers enabling diagnosis, prognosis and post treatment monitoring in various cancers [10–17]. Aberrant sialic acid expression in lung cancer has been reported [18–20] and has been found to be associated with poor prognosis in non-small lung cancer [18]. Fungal lectin *Psathyrella velutina* (PVL) with specificity towards the GlcNAcβ1-3Gal epitope indicated their expression in lung carcinomas [20]. Polysialic acid (polySia) has been reported of their expression on several malignant tumors of neuroendocrine origin including small cell lung cancer, and finds relevance as effective targeting by oncolytic adenovirus in tumors in mice models an proving as an effective therapy of disseminated lung cancer [21]. Sialylation and fucosylation of epidermal growth factor receptor (EGFR) receptors in lung cancer has been reported to suppress the normal function of the receptor [22]. Sialylation on EGFR phosphorylation has been recently shown to be associated with resistance to tyrosine kinase inhibition, thus affecting the signalling process [23]. Although studies confirm the sialylation

lung and also targeting in cancer sialyltransferase by inhibitors [24] in lung cancer are reported; extensive studies have not been undertaken to understand the enzymes involved in sialylation in lung cancer. Thus enzymes involved in sialylation process could be potential targets to control of activation of metastatic pathways in lung cancer. In the current study, we have studied the epitopes of these enzymes through a bioinformatics approach. At this point, it seems imperative to study the different enzymes in the sialylation process and their epitope involved, so that effective antibody may be designed to target the enzymes as a strategy to halt lung cancer by targeting these sialylation enzymes.

MATERIALS AND METHODS

Immune epitope database analysis resource (IEDB) is a database, which enables prediction and analysis of B cell and T cell epitopes. It allows easy searching of experimental data characterizing antibody and T cell epitopes studied in humans, non-human primates, and other animal species. Epitopes for the enzymes involved in sialic acid synthesis and sialyltransferase enzymes in human were searched for in the database [25].

RESULTS

Results from this study reveal the different epitopes for enzymes involved in sialic acid synthesis and sialyltransferase enzymes, regulating the sialylation process. From the Database of Immune Epitope database and Analysis Resource [25], the following protein epitopes of the different enzymes controlling sialylation of proteins and lipids were found (Table 1). From the analysis, we report the epitopes for enzymes involved in the sialic acid synthesis and sialylation pathway. NeuAc-alpha-2,3-Gal-beta-1,3-GalNAc-alpha-2.6-sialyltransferase alpha2.6-sialyltransferase [26] is involved in the transfer of sialic acid from CMP-sialic acid to galactose-containing substrate showing specificity towards the Neu5Ac-alpha-2,3-Gal-beta-1,3substrate GalNAc and the enzyme reveals nine epitopes database. Alpha-N-acetylfrom the neuraminyl-2,3-beta-galactosyl-1,3-N-acetylgalactosaminide alpha-2,6-sialyltransferase, commonly termed as ST6GalNAcIV is coded by ST6GALNAC4 gene, and transfers CMP-

NeuAc with an alpha-2,6-linkage to GalNAc residue on NeuAc-alpha-2,3-Gal-beta-1,3-GalNAc of glycoproteins and glycolipids and shows preference to glycoproteins over glycolipids [27]. The enzyme reveals three epitope from the database. CMP-Nacetylneuraminate-poly-alpha-2,8-

sialyltransferase also termed as ST8SiaIV coded by the gene ST8SIAIV catalyzes the polycondensation of alpha-2,8-linked sialic acid required for the synthesis of polysialic acid (PSA), located on embryonic neural cell adhesion molecule (N-CAM), for neural cell plasticity [25]. It reveals 19 epitopes from the database. Sialic acid synthase coded by the NANS gene and its isoforms have role in sialic acid synthesis pathway. It uses Nacetylmannosamine-6-phosphate and mannose-6-phosphate to produce phosphorylated forms of N-acetylneuraminic acid and 2-keto-3-deoxy-D-glycero-D-galacto-nononic acid (KDN) [28]. Isoform CRA_a is one of the isoforms. This enzyme reveals 6 epitopes from the database. N-acetylneuraminic acid phosphate synthase catalyses the formation of Neu5Ac-9phosphate [29] from N-acetylmannosamine-6phosphate and phosphoenolpyruvate [30] and reveals 6 epitopes. Beta-galactoside alpha-2,6sialyltransferase 1 also called as ST6GalI, encoded by the ST6GAL1 gene is the main enzyme mediating transfer of sialic acid from CMP-sialic acid to galactose-containing acceptor substrates [31, 32] revealing the highest 25 number of epitopes. Betagalactoside alpha-2,6-sialyltransferase 2, also termed as ST6GalII, is a type II transmembrane



protein catalyzing the transfer of sialic acid from CMP to an oligosaccharide substrate, genetic polymorphisms are reported to be associated with variations in risperidone response in schizophrenic patients. It revealed 1 epitope. ST6 beta-galactosamide alpha-2,6sialyltranferase reveals 5 epitopes from the database. ST6 beta-galactosamide alpha-2,6sialyltransferase 1 involved in transfer of sialic acid from CMP-sialic acid to galactose-[25]. ST6 betacontaining substrates galactosamide alpha-2,6-sialyltransferase 2 mediates the attachment of sialic acid to glycoprotein chain [33]. Lactosylceramide alpha-2,3-sialyltransferase also termed as ST3GalV, encoded by the ST3GAL5 gene, a type II membrane protein with several isoforms, catalyzes the production of ganglioside GM3, (monosialodihexosylganglioside) using substrate lactosylceramide [25]. Mutation in this gene are associated with Amish infantile epilepsy syndrome, 'Salt & Pepper' syndrome [34] and reveal 2 epitopes from the database. Alpha-2,8-sialyltransferase 8F also termed as ST8SiaVI coded by the ST8SIA6 gene enables the synthesis of polysialic acid by catalyzing the polycondensation of alpha-2,8-linked sialic acid which contributes towards the adhesive properties of neural cell adhesion molecule (NCAM1). Two transcript variants encoding different isoforms [35-37]. It reveals 2 epitopes. B cell antigen CD 75 is a cell surface sialyltransferase functioning similar to alpha 2-6 sialyltransferase [38] and reveal 5 epitopes from the database.

Epitope	Object	Description	Starting	Ending	Antigen Name	Antigen ID
ID	Туре		Position	Position		
428540	Linear	YFQKARDTLY	139	148	NeuAc-alpha-2,3-Gal-beta-1,3-	GI:6002700
	peptide				GalNAc-alpha-2, 6-	
					sialyltransferase alpha2,6-	
					sialyltransferase	
443733	Linear	FEADVGQRSTL	111	121	Alpha-N-acetyl-neuraminyl-2,3-	GI:21759443
	peptide				beta-galactosyl-1,3-N-acetyl-	
					galactosaminide alpha-2,6-	
					sialyltransferase	
449472	Linear	TRMYPGLQVY	173	182	NeuAc-alpha-2,3-Gal-beta-1,3-	GI:6002700
	peptide				GalNAc-alpha-2, 6-	
					sialyltransferase alpha2,6-	
					sialyltransferase	
495617	Linear	TRMYPGLQV	173	181	NeuAc-alpha-2,3-Gal-beta-1,3-	GI:6002700
	peptide				GalNAc-alpha-2, 6-	
					sialyltransferase alpha2,6-	
					sialyltransferase	

 Table 1: Epitopes of Enzymes involved in Sialylation Pathway in Human IEDB(https://www.iedb.org)

428899	Linear peptide	YYDDLKYRY	316	324	CMP-N-acetylneuraminate-poly- alpha-2, 8-sialyltransferase isoform a precursor	GI:5031999
429095	Linear peptide	MPLEFKTLNVLHNRGAL	333	349	CMP-N-acetylneuraminate-poly- alpha-2, 8-sialyltransferase	GI:2494834
439362	Linear peptide	MPLEFKTLNVLHNR	333	346	CMP-N-acetylneuraminate-poly- alpha-2, 8-sialyltransferase	GI:2494834
439363	Linear peptide	MPLEFKTLNVLHNRG	333	347	CMP-N-acetylneuraminate-poly- alpha-2, 8-sialyltransferase	GI:2494834
439364	Linear peptide	MPLEFKTLNVLHNRGA	333	348	CMP-N-acetylneuraminate-poly- alpha-2, 8-sialyltransferase	GI:2494834
440647	Linear peptide	SPHRMPLEFKTLNVLHNRG	329	347	CMP-N-acetylneuraminate-poly- alpha-2, 8-sialyltransferase	GI:2494834
492945	Linear peptide	KRWTICTISL	6	15	CMP-N-acetylneuraminate-poly- alpha-2,8-sialyltransferase isoform b precursor	GI:28373099
512714	Linear peptide	DFITMNPSVVQRAFG	186	200	CMP-N-acetylneuraminate-poly- alpha-2, 8-sialyltransferase	GI:2494834
512715	Linear peptide	DFITMNPSVVQRAFGGF	186	202	CMP-N-acetylneuraminate-poly- alpha-2, 8-sialyltransferase	GI:2494834
515804	Linear peptide	FITMNPSVVQRAFG	187	200	CMP-N-acetylneuraminate-poly- alpha-2, 8-sialyltransferase	GI:2494834
515805	Linear peptide	FITMNPSVVQRAFGGF	187	202	CMP-N-acetylneuraminate-poly- alpha-2, 8-sialyltransferase	GI:2494834
519182	Linear peptide	ISHDLHSLLPEVSP	120	133	CMP-N-acetylneuraminate-poly- alpha-2, 8-sialyltransferase	GI:2494834
547328	Linear peptide	DFITMNPSVVQRAFGG	186	201	CMP-N-acetylneuraminate-poly- alpha-2, 8-sialyltransferase isoform a precursor	GI:5031999
547421	Linear peptide	FITMNPSVVQRAF	187	199	CMP-N-acetylneuraminate-poly- alpha-2, 8-sialyltransferase isoform a precursor	GI:5031999
547422	Linear peptide	FITMNPSVVQRAFGG	187	201	CMP-N-acetylneuraminate-poly- alpha-2, 8-sialyltransferase isoform a precursor	GI:5031999
547492	Linear peptide	GTKSDFITMNPSVVQRAFGG	182	201	CMP-N-acetylneuraminate-poly- alpha-2, 8-sialyltransferase isoform a precursor	GI:5031999
547872	Linear peptide	YDDLKYRYFSNASPHRM	317	333	CMP-N-acetylneuraminate-poly- alpha-2, 8-sialyltransferase isoform a precursor	GI:5031999
547873	Linear peptide	YDDLKYRYFSNASPHRMPL	317	335	CMP-N-acetylneuraminate-poly- alpha-2, 8-sialyltransferase isoform a precursor	GI:5031999
547874	Linear peptide	YDDLKYRYFSNASPHRMPLE	317	336	CMP-N-acetylneuraminate-poly- alpha-2, 8-sialyltransferase isoform a precursor	GI:5031999
464852	Linear peptide	FLHELNVPFF	121	130	N-acetylneuraminic acid synthase (sialic acid synthase), isoform CRA a	GI:119579270
464853	Linear peptide	FLHELNVPFFKV	121	132	N-acetylneuraminic acid synthase (sialic acid synthase), isoform CRA a	GI:119579270
470062	Linear peptide	RPMVISSGMQSM	151	162	N-acetylneuraminic acid phosphate synthase	GI:8453156
470063	Linear peptide	RPMVISSGMQSMDTM	151	165	N-acetylneuraminic acid phosphate synthase	GI:8453156
470207	Linear peptide	RYAEEVGIFF	100	109	N-acetylneuraminic acid synthase (sialic acid synthase), isoform CRA_a	GI:119579270
494043	Linear peptide	QRYAEEVGIFF	99	109	N-acetylneuraminic acid phosphate synthase	GI:8453156



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449472 Lin pep	ude				galactosaminida alpha 2.6	
449472 Lin pep					sialvltransferase	
pep	ear T	RMYPGLQVY	173	182	NeuAc-alpha-2,3-Gal-beta-1,3-	GI:6002700
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					sialvltransferase	
495617 Lin	ear '	TRMYPGLOV	173	181	NeuAc-alpha-2.3-Gal-beta-1.3-	GI:6002700
pep	tide				GalNAc-alpha-2, 6-	
r · r					sialyltransferase alpha2,6-	
					sialyltransferase	
428540 Lin	ear Y	YFQKARDTLY	139	148	NeuAc-alpha-2,3-Gal-beta-1,3-	GI:6002700
pep	tide				GalNAc-alpha-2, 6-	
					sialyltransferase alpha2,6-	
					sialyltransferase	
443733 Lin	ear F	EADVGQRSTL	111	121	Alpha-N-acetyl-neuraminyl-2,3-	GI:21759443
pep	tide				beta-galactosyl-1,3-N-acetyl-	
					galactosaminide alpha-2,6-	
					sialyltransferase	
449472 Lin	ear T	RMYPGLQVY	173	182	NeuAc-alpha-2,3-Gal-beta-1,3-	GI:6002700
pep	tide				GalNAc-alpha-2, 6-	
					sialyltransferase alpha2,6-	
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49561/ Lin	ear	TRMTPGLQV	1/3	181	NeuAc-aipna-2,5-Gai-beta-1,5-	GI:6002700
pep	ude				GainAc-aipna-2, 0-	
					sialyltransferase	
147407 Lin	ear WDI	IOFISPEFIOPNPP	74	90	beta-galactoside alpha-2 6-	GI-27765093
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513560	Linear peptide	DPSVYHSDIP	258	267	Beta-galactoside alpha-2,6- sialvltransferase 1	GI:115445
513561	Linear	DPSVYHSDIPKWYQNP	258	273	Beta-galactoside alpha-2,6-	GI:115445
513562	Linear	DPSVYHSDIPKWYQNPD	258	274	Beta-galactoside alpha-2,6-	GI:115445
513563	Linear	DPSVYHSDIPKWYQNPDYN	258	276	Beta-galactoside alpha-2,6-	GI:115445
513766	Linear	DSFKLQTKEFQVLKSLG	36	52	Beta-galactoside alpha-2,6-	GI:115445
520197	Linear	KPQMPWELWDIL	297	308	Beta-galactoside alpha-2,6-	GI:115445
521954	Linear	LRGLAKAKPEASF	81	93	Beta-galactoside alpha-2,6-	GI:115445
521955	Linear	LRGLAKAKPEASFQ	81	94	Beta-galactoside alpha-2,6-	GI:115445
521956	Linear	LRGLAKAKPEASFQV	81	95	stalyltransferase I Beta-galactoside alpha-2,6-	GI:115445
521957	peptide Linear	LRGLAKAKPEASFQVW	81	96	sialyltransferase 1 Beta-galactoside alpha-2,6-	GI:115445
524608	peptide Linear	QTLGSLRGLAKAKPEASF	76	93	sialyltransferase 1 Beta-galactoside alpha-2,6-	GI:115445
526270	peptide Linear	SLRGLAKAKPEASF	80	93	sialyltransferase 1 Beta-galactoside alpha-2,6-	GI:115445
526271	peptide Linear	SLRGLAKAKPEASFQ	80	94	sialyltransferase 1 Beta-galactoside alpha-2,6-	GI:115445
526272	Linear	SLRGLAKAKPEASFQVW	80	96	stalyltransferase 1 Beta-galactoside alpha-2,6-	GI:115445
527241	Linear	TDEDIYLLGKATLPGFR	386	402	stalyltransferase 1 Beta-galactoside alpha-2,6-	GI:115445
528951	Linear	VKHLNQGTDEDIYL	379	392	stalyltransferase 1 Beta-galactoside alpha-2,6-	GI:115445
546338	Linear	VYHSDIPKW	260	268	B cell antigen CD75	GI:29389
547497	Linear	HDAVLRFNGAPTANFQQ	204	220	B cell antigen CD75	GI:29389
547722	Linear	QTKEFQVLKSLGKLAMG	41	57	B cell antigen CD75	GI:29389
505803	Linear	HHFIDSSLY	354	362	Beta-galactoside alpha-2,6-	GI:166219772
442064	Linear	AAAPAGRAM	21	29	Lactosylceramide alpha-2,3-	GI:189047140
447658	Linear	RPKFAKTSM	121	129	Lactosylceramide alpha-2,3-	GI:189047140
484735	Linear	RTKGVTAYR	312	320	Alpha-2,8-sialyltransferase 8F	GI:48428578
493403	Linear	MRPGGALLAL	1	10	alpha-2,8-sialyltransferase 8F	GI:54234057
464852	Linear peptide	FLHELNVPFF	121	130	N-acetylneuraminic acid synthase (sialic acid synthase), isoform	GI:119579270
464853	Linear peptide	FLHELNVPFFKV	121	132	N-acetylneuraminic acid synthase (sialic acid synthase), isoform	GI:119579270
470062	Linear	RPMVISSGMQSM	151	162	N-acetylneuraminic acid	GI:8453156
470063	Linear	RPMVISSGMQSMDTM	151	165	N-acetylneuraminic acid	GI:8453156
470207	Linear peptide	RYAEEVGIFF	100	109	N-acetylneuraminic acid synthase (sialic acid synthase), isoform CRA a	GI:119579270
494043	Linear peptide	QRYAEEVGIFF	99	109	N-acetylneuraminic acid phosphate synthase	GI:8453156

DISCUSSION

Although preliminary report at this point from published literature is indicative of altered sialylation, sialic acid expression [13-19], EGFR sialylation in lung cancer [22], no studies have been reported on the enzymes involved in sialylation in lung cancer. Thus it is important to understand the epitopes of enzymes involved in sialylation process so that effective target antibodies could be designed targeting them. We from this study, using a bioinformatics approach conclude the different epitopes of 13 enzymes studied so far in the database involved in sialylation pathway by a bioinformatics approach through in silico studies. From our study, amongst the thirteen enzymes studied for their epitopes. Betagalactoside alpha-2,6-sialyltransferase 1 reveal the maximum number of 25 epitopes and could be a potential target, in lung cancer.

At this point only one study records the expression of sialyltransferase [24] in lung cancer nothing is known about the nature of aberration of other enzymes controlling sialylation in lung cancer and which enzymes from the pathway is over expressed more in human lung cancer as compared to the normal cells. It remains to be seen which would be the most important enzyme, either single or more than one involved in the process of sialylation of proteins and lipids, in human lung cancer to be controlled or targeted in lung cancer and then it would be able to point out the particular epitope of interest to be targeted so that effective antibodies may be designed specifically targeted against this epitope in lung cancer. More research is required to understand the different sialyltransferases enabling the sialylation process, their levels of expression in lung cancer and designing of either a cocktail of antibody against all epitopes of all enzymes involved in sialylation in lung cancer or epitope of a specific enzymes in the sialylation pathway expressed in lung cancer over normal cells, which remains the future scope of this study.

CONCLUSION

Lung cancer due to environmental pollution and indoor air pollution are pressing across the globe. Therefore research focused on suitable targets of bio molecules expressed in lung cancer find importance in today's scientific biomedical basic and applied research. We have shown in this study all epitopes of enzymes involved in the sialylation pathway, in silico approaches using the IEDB database. The problems are manifold and the need of the hour is an innovation niche focused on production of low cost medicines, effective disease targeting, drugs, vaccines, regenerative medication. Our current study, finds fundamental relevance that antibodies targeted against these epitopes can be developed, tested, for detection, diagnosis and prognosis of lung cancer in an integrated set up of basic, applied and clinical studies targeting lung cancer.

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