Neuraminidases

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Neuraminidases (NEUs) are able to cleave off sugars termed sialic acids, which are terminally attached to glycolipids and -proteins. Glycoproteins and glycolipids on the cell surfaces of vertebrates and higher invertebrates contain α-keto acid sugars called sialic acids, terminally attached to their glycan structures. The actual level of sialylation, regulated through enzymatic removal of the latter ones by NEU enzymes, highly affects protein-protein, cell-matrix and cell-cell interactions. Thus, their regulatory features affect a large number of different cell types, including those of the immune system.

neuraminidase sialidase sialic acid sialylation desialylation glycosylation

1. Introduction

Vertebrate cell surfaces contain a complex array of sugar chains that are bound to lipids and proteins. Sialic acids are a diverse class of α-keto acid sugars characterized by a 9-C-backbone, widely found in animal tissues of all vertebrates [1][2]. They are essential components, positioned at the end of the sugar chains of many glycoproteins, glycolipids and gangliosides at the cell surface or at soluble proteins. Their ubiquitous distribution in glycoconjugates of various origins indicates that a variety of biological functions are associated with them [2]. Sialic acids play important roles in many physiological and pathological processes, e.g., cellular communication, cell assembly and development, mediation of viral and bacterial infections. In particular, they play a crucial role in the development of cardiovascular diseases, as they serve as ligands for leukocytes in the endothelium and are therefore involved in inflammation, atherosclerosis and reperfusion injuries [3][4][5]. NEUs are enzymes able to remove sialic acids, a process which is called desialylation, thus regulating the function of numerous different molecules [6][7].

The endothelial surface layer (ESL) is an important part of the vascular barrier. Coating the intimal surface in blood vessels, thereby creating a barrier separating endothelial cells, blood and neighbouring cells from each other, the ESL plays an important role in various immune reactions, including cardiovascular ones. As one component of the ESL, endothelial cells synthesize the polysaccharide-rich glycocalyx, which surrounds all eukaryotic cells. Consisting of negatively charged sialic acids (monosaccharides), which are in turn bound to proteoglycans, glycolipids and endothelial cells, the glycocalyx converts mechanical into biomechanical signals, thus greatly affecting inter- and intracellular communication and vascular homeostasis. This barrier is also of importance in matters of material and substrate exchange, thereby affecting inflammatory processes as well as vascular permeability, coagulation, blood flow and the complement system [8][9][10][11][12][13]. Individual components of the glycocalyx e.g., heparan sulphate proteoglycans, sialic acids and hyaluronic acid glycosaminoglycans are able to

respond immediately to sensed shear stress, which is induced by the blood stream and affects the vessel's wall, by the physiological production of nitric oxide (NO). NO, known for its vasodilatory effect, consequently modulates the vascular tone [13][14].

2. Mammalian Neuraminidases

The polysaccharide-rich glycocalyx can be altered in terms of sialylation by enzymes which are able to recognize sialic acid glycosidic bonds and thus enzymatically remove sialic acids. In mammals, four endogenous NEU enzymes, belonging to the glycoside hydrolase family and also known as sialidases, have been identified to date, namely NEU1, NEU2, NEU3 and NEU4. The catalysed removal of these negatively charged 9-C-backbone sugars, which are terminally attached to glycolipids and glycoproteins on the cell surface, highly affects the cells' biophysical properties concerning protein-protein, cell-matrix and cell-cell interactions [1][6][15][16][17][18]. Most of the existing literature deals with desialylation by NEUs on the cell surface. However, due to localisation differences of the four NEU enzymes (**Table 1**), intracellular desialylation also takes place [19][20][21]. All four enzymes are encoded by different genes, own different enzymatic properties and prefer slightly different substrates. In addition, they can be distinguished by their different intracellular localisation [22].

Table 1. Overview of the four different mammalian NEUs and their isoform-specific properties.

Properties of the Four Mammalian NEU Enzymes				
	NEU1	**NEU2**	**NEU3**	**NEU4**
Human Gene Location	chromosome 6p21.3 [23]	chromosome 2q37 [24]	chromosome 11q13.5 [24]	chromosome 2q37.3 [24]
Murine Gene Location	chromosome 17 [25]	chromosome 1 [26]	chromosome 7 [24]	chromosome 10 [24]
Subcellular localisation	Lysosomal, translocation towards the plasma membrane upon different stimuli [7][27][28]	Cytosolic [24]	Associated with the plasma membrane [29]	Murine NEU4a and b, human NEU4S: ER membranes; human NEU4L: mitochondria, lysosomes [30][31]
Expression pattern	kidneys, skeletal muscle, lung, placenta, brain, pancreas, inflammatory cells and cardiomyocytes [7][27][32][33]	Muscle-specific isoform [7][34]	Adrenal glands, heart, thymus, skeletal muscle and testis [7]	Brain, heart, placenta, liver and skeletal muscle [31]
Substrate preferences	Oligosaccharides with an α2,3 linkage [24]	Oligosaccharides, gangliosides,	Gangliosides, most preferable	Oligosaccharides, gangliosides, glycoproteins [24]

Properties of the Four Mammalian NEU Enzymes				
	NEU1	NEU2	NEU3	NEU4
		glycoproteins [24][26][35]	with an α2,3 and α2,6 linkage [24]	
Physiological functions	Regulates exocytosis, modulator of inflammatory resposnse [27][36][37]	Myoblast and neuronal cell differentiation [38][39][40]	Neuronal cell differentitation, focal adhesion, cell invasion, cell survival, proliferation [41][42][43]	Neural differentiation, mitochondrial neuronal apoptosis [44][45]

eins [7], is required to form a multienzyme complex with β-Galactosidase (β-GAL) and protective-protein/cathepsin (PPC) A in order to be catalytically active and stable. NEU1 can also homodimerize via the binding site which is usually utilized for binding to PPCA, however, once PPCA is available, the affinity of NEU1 to bind to it instead of binding to another NEU1 is stronger [46]. Further, this conjunction not only protects NEU1 from lysosomal degradation but is required for its transport towards the plasma membrane upon e.g., inflammatory cell activation or differentiation but also for its activation [27][47][48][49]. The gene coding for human NEU1 is located on chromosome 6p21.3 while the single gene for murine NEU1 is located on chromosome 17. Both protein products are 83% identical [23][25][50][51][52]. A reduction in NEU1 usually leads to severe diseases such as sialidosis [53] whereas increased levels stimulate inflammation and phagocytosis [32][54]. Further, NEU1 is a negative regulator of exocytosis [36][37].

There is only little known about the soluble protein NEU2 which is located in the cytosol and able to hydrolyse different glycoproteins, oligosaccharides and gangliosides [24][35]. The gene coding for human NEU2 is located on chromosome 2q37 [24] while its murine counterpart is located on chromosome 1 [26]. The exact role of NEU2 does not seem to be discovered yet. One reason might be lacking evidence which clearly demonstrates glycosidically bound sialic acids in the cytosol or on the inside of the plasma membrane [55], albeit, one study reports complex-type free sialylated N-glycans in the cytosol that were in turn degraded, likely due to the interaction of NEU2 and the cytosolic β-glycosidase (GBA) 3. NEU2 was stabilised by the latter one and both seem to be involved in a non-lysosomal catabolic degradation process [56]. In the physiological context, NEU2 seems to play a role in myoblast differentiation as an increased expression was observed during the differentiation of murine myoblasts. In this regard, experiments using NEU2 overexpressing clones which spontaneously underwent myoblast differentiation, showed that an upregulation of NEU2 per se sufficiently induces differentiation of myoblasts [38][39]. In addition to its role in myoblast differentiation, NEU2 also seems to be involved in the differentiation of neuronal cells derived from a tumour located in the adrenal medulla [40].

NEU3, per se associated with the plasma membrane, has additionally been reported to be translocated towards the plasma membrane in response to different stimuli, e.g., activation and differentiation of immune cells [29][57][58]. The gene coding for human NEU3 is located on chromosome 11q13.5 while its murine counterpart is located on chromosome 7 [24]. Like NEU2, NEU3 is also assigned a role in neuronal differentiation. However, for NEU3, a decreased expression and activity was shown to negatively interfere with cell proliferation while on the other hand promoting neurite extension, thereby inducing a shift towards cells with a differentiated phenotype [41]. In addition, NEU3 was shown to affect cell invasion and focal adhesion of glioblastoma cells, the former one though the

regulation of calcium-dependent calpain [42]. Besides, the activation of the enzyme was shown to protect cultured skeletal muscle cells from hypoxia-induced apoptosis through the induction of the EGF receptor signalling pathway and thus, hypoxia inducible factor (HIF) 1α [43].

The gene encoding for human NEU4 is located on chromosome 2q37.3 and its murine counterpart on chromosome 10 [24]. The gene encodes for two different isoforms which holds true for both organisms. These isoforms are NEU4a and b in mice and NEU4L and S in humans, they differ in their first 12 N-terminal amino acids. Murine NEU4a and b have been reported to localize to endoplasmic reticulum (ER) membranes which are calnexin positive. NEU4L and S differ in their subcellular localization with NEU4L being present in mitochondria and lysosomes and NEU4S being present in membranes of the ER. The isoforms differ not only with regard to their localization but also in terms of their sialidase activity with NEU4b displaying a higher activity compared with the shorter isoform NEU4a [24][30][31][58][59]. Under certain conditions, a translocation of NEU4 towards the surface of cells has also been observed, however, the mechanisms behind that movement are not yet understood [24]. It has been proposed that NEU4 is, in connection with NEU3, involved in neural differentiation [60]. NEU4L, expressed in mitochondria as mentioned earlier, seems to be involved in the mitochondrial apoptotic pathway in neuronal cells [44][61].

Human NEU1 bears only a minor resemblance of approximately 19–24% to the other three NEUs with regard to its DNA sequence whereas these exhibit a similarity of 34–40% to each other. In line with this, the binding pocket of NEU1 is also distinct from the one of the other NEU enzymes [24]. However, for an optimal activity, all four human NEU enzymes need an ideal pH environment which is defined between acidic 3.5 and 5.5 [18].

In summary, the four endogenous mammalian NEU enzymes, each encoded by a different gene, exhibit different enzymatic characteristics which subsequently result in partly different substrate specificities as well as different intracellular localization.

4. Occurrence and Substrate Specificity of Neuraminidases

All 4 NEUs differ with regard to their expression pattern. NEU1 is ubiquitously expressed and most abundant in kidneys, skeletal muscle, lung, placenta, brain, pancreas, inflammatory cells and cardiomyocytes whereas NEU2 depicts a muscle-specific isoform. NEU3 on the other hand is mostly expressed in the adrenal glands, heart, thymus, skeletal muscle and testis, and NEU4 in the brain, heart, placenta, liver and skeletal muscle [7][27][32][33][52][62]. In mammals, among all 4 NEU enzymes, NEU1 is the most abundant one [15].

The enzymatic removal of sialic acids represents a regulatory function of NEU enzymes through which they highly affect intra- and intercellular communication. The entirety of sialic acid types and underlying connections is versatile due to the fact that these α-keto acids occur in different forms and with different underlying linkages [6][63][64]. Due to these varieties, it is no surprise that the NEU enzymes differ from each other in terms of substrate preferences. Even though NEU1, 2 and 4 share oligosaccharides as substrates, NEU1 prefers those joined with an α2,3 linkage. Sialic acid containing glycosphingolipids, so called gangliosides, belong to the substrate group of all

NEU enzymes except for NEU1. Eventually, gangliosides seem to be the only substrates of NEU3, most preferable those with an α2,3 and α2,6 binding. NEU2 and NEU4 share the feature of a broad substrate specificity including, next to already mentioned oligosaccharides, glycoproteins and gangliosides [24][35][58].

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