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Review

Application of sialic acid/polysialic acid in the drug delivery systems

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ABSTRACT

The properties of modified biomaterial are gaining more and more importance in drug delivery systems. Sialic acid (SA) and polysialic acid (PSA) serve as endogenous substances, which are non-immunogenic and biodegradable. At the same time, SA modification of the drugs/carriers can enhance the uptake of tumor cell and retention in brain; PSA modification can reduce the immunogenicity of the proteins or polypeptides and increase circulation time of the modified drugs/carriers in the blood, thus achieving active targeting effect. These properties offer a variety of opportunities for applications in drug delivery systems. This article summarizes the biological functions of SA and PSA and presents the technologies of SA/PSA modified small molecule drugs, proteins and carriers in drug delivery systems.

1. Introduction

Nature sialic acid (SA) is constituted structurally by nine-carbons 3-deoxy-ulosonic acids. This saccharide moiety attached to carbohydrate chains of glycolipids and glycoproteins plays a crucial role in many important biological events [1]. Interestingly, it has been found that SA is a well-known ligand for selectin, which is known to have a close relationship with tumor metastases. Owing to its modulation of cell–cell interactions among leukocytes, platelets, endothelial cells and tumor cells, selectin is responsible for tumor metastasis [2–5]. SA serves as endogenous substances that can specifically bind to selectin [6–8]. Hence, the application of SA-modified carriers in cancer targeted therapy has a certain significance [9].

Polysialic acid (PSA) is a homopolymer of sialic acid in α-2,8 or α-2,9 linkages or a mixture of α-2,8 and α-2,9. PSA constituted of α-2,8 bond is non-immunogenic and biodegradable

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and then reduces the immunogenicity of the protein polypeptide. Likewise PSA shows the properties of escaping from phagocytes and presenting long circulation time *in vivo* [10,11]. This review summarizes the applications of SA/PSA in targeting carriers construction and briefly discusses their prospects in drug delivery systems.

2. Sialic acid, polysialic acid and derivatives

2.1. Sialic acid

In 1957, Blix [1] isolated a substance from the submandibular gland mucin via a hydrolysis method, which produced a purple color reaction with Bial's reagent. He named the substance as sialic acid (SA). Afterward, people got perfect crystalline SA from colostrum and bird's nest. With the progress of biological evolution, the amount of SA *in vivo* also increased, such as fish, amphibians, reptiles, birds and other vertebrates. In mammals, SA mainly distributed over the cerebrospinal fluid and mucus.

SA belongs to a family of neuraminic acid (5-amido-3,5-dideoxy-D-glycero-D-galacto-nonulosonic acid). In this family, there are three main SA derivatives, which are N-acetyl neuraminic acid (Neu5Ac), N-acetyl neuraminic acid hydroxyalkyl (Neu5Gc) and 3-deoxy-D-glycero-D-galacto-nonyl ketose (KDN) (Fig. 1). The other SA derivatives are further derived from these.

Each SA carries a unit negative charge, which generates repulsion or attraction between SA and plasma protein. Furthermore, the charge will modulate membrane surface charge density, while the carboxyl groups of SA can regulate its own pH. The surface charge density and pH coordinately regulate the transmembrane transport capacity of cell membrane [12].

SA spreads widely over mammalian cell surface, wherein the surfaces of red blood cells and endothelial cells are highly sialylated [13]. It has been found that after treated by sialidase, the lifetime of erythrocytes dropped from the initial 120 days to just a few hours [14]. In addition, many pathogens employ SA to camouflage themselves and mask their epitopes, which inhibits complement activation pathway to reduce immunogenicity and thus protect the pathogens from the attacks of host immune system [15–17].

2.2. Polysialic acid

Polysialic acid (PSA) was first found in *E. coli* (*Escherichia coli*) K-1 and K-235 by Barry [18]. Subsequent studies have discovered that PSA was one of the ingredients of bacterial capsular materials, such as *Neisseria miningitidis* B, *Salmonella toucra* 048 and *Citrobacter freundii* 05, etc. The structure of PSA was shown in Fig. 2.

In vertebrates, PSA can attach to the neural adhesion molecule (NCAM), with its fragments connecting to the asparagine at Ig5 of NCAM [19]. PSA can attenuate NCAM–NCAM interaction and facilitate cell migration and nerve regeneration. Accordingly, Polysialylated NCAM exists abundantly in the embryo brain. But for the brain tissue of adults, PSA only appears in the hippocampus and olfactory bulb with continuous growth ability [20].

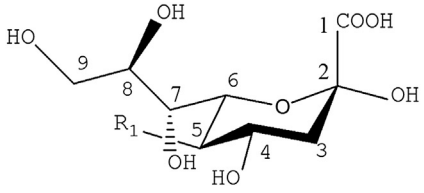
Polycondensation of SA occurs between hydroxyl groups at its 2 and 8 positions and makes the constructed PSA more stable [21]. The study also found that PSA showed excellent water solubility, low viscosity, good biocompatibility and degradation *in vivo* [22].

PSA has been found in various tumors including small cell and non-small cell lung carcinomas, rhabdomyosarcoma, multiple myeloma, neuroblastoma, and Wilms tumor etc [20]. Study [23] found patients with extensive rhabdomyosarcoma showed a high level of PSA-NCAM, while patients had a lesser amount after chemotherapy. They concluded that the presence of PSA on the tumor cells reduced adhesion of NCAM, and enhanced cell motility, thus allowing the tumor cells that expressed PSA to deviate from the primary tumor and format metastases. In another study [24], small cell lung carcinoma cells expressing different amounts of PSA were isolated from H69 cell line. After subcutaneous inoculation with nude mice, tumor cells that express PSA produced more intracutaneous metastasis than tumor cells poorly expressing PSA. Suzuki [20] et al. reported among 44 patients with astrocytoma examined, 30 cases were NCAM-positive, of which nine cases PSA were detected, interestingly the nine cases had strong diffusion ability, revealing that PSA closely correlated with tumor invasion. Therefore, PSA plays an important role in tumor invasion and recurrence.

2.3. Ganglioside

Ganglioside is widely used as a SA derivative, which is quite rich in the brain. It cannot only promotes nerve cell differentiation, growth and synaptic formation, but also takes part in regulation of neural plasticity and functional recovery after brain injury. Among gangliosides, monosialylganglioside (GM1) have drawn the most interest by far.

GM1 is mainly distributed over the central nervous system, which promotes the neuronal proliferation, neurotrophy, anti-excitatory nerve repair and other multiple effects. GM1 can be used clinically for the treatment of central nervous system injury diseases, such as stroke, traumatic brain injury,



Derivative		R_1 group
Neu	$-NH_2$	(amino)
Neu5Ac	$-NHCOCH_3$	(acylamino)
Neu5Gc	$-NHCOCH_2OH$	(glycolyl)
KDN	-OH	(hydroxyl)

Fig. 1 – The structure of sialic acid.