REVIEW

Mucin-like glycopolymer gels in electrosensory tissues generate cues which direct electrolocation in amphibians and neuronal activation in mammals

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Abstract

Mucin-like glycoproteins have established roles in epithelial boundary protection and lubricative roles in some tissues. This mini-review illustrates alternative functional roles which rely on keratan sulphate and sialic acid modifications to mucin glycopolymers which convey charge properties suggestive of novel electroconductive properties not previously ascribed to these polymers. Many tumour cells express mucin-like glycopolymers modified with highly sulphated keratan sulphate and sialic which can be detected using diagnostic biosensors. The mucin-like keratan sulphate glycopolymer present in the ampullae of lorenzini is a remarkable sensory polymer which elasmobranch fish (sharks, rays, skate) use to detect weak electrical fields emitted through muscular activity of prey fish. Information on the proton gradients is conveyed to neuromast cells located at the base of the ampullae and mechanotransduced to neural networks. This ampullae keratan sulphate sensory gel is the most sensitive proton gradient detection polymer known in nature. This process is known as electrolocation, and allows the visualization of prey fish under conditions of low visibility. The bony fish have similar electroreceptors located along their lateral lines which consist of neuromast cells containing sensory hairs located within a cupula which contains a sensory gel polymer which detects distortions in fluid flow in channels within the lateral lines and signals are sent back to neural networks providing information on the environment around these fish. One species of dolphin, the Guiana dolphin, has electrosensory pits in its bill with similar roles to the ampullae but which have evolved from its vibrissal system. Only two terrestrial animals can undertake electrolocation, these are the Duck-billed platypus and long and short nosed Echidna. In this case the electrosensor is a highly evolved innervated mucous gland. The platypus has 40,000 electroreceptors around its bill through which it electrolocates food species. The platypus has poor eyesight, is a nocturnal feeder and closes its eyes, nostrils and ears when it hunts, so electrolocation is an essential sensory skill. Mammals also have sensory cells containing stereocilia which are important in audition in the organ of corti of the cochlea and in olfaction in the olfactory epithelium. The rods and cones of the retina also have an internal connecting cilium with roles in the transport of phototransduced chemical signals and activation of neurotransmitter release to the optic nerve. Mucin-like glycopolymer gels surround the stereocilia of these sensory hair cells but these are relatively poorly characterized however they deserve detailed characterization since they may have important functional attributes.

Key Words: *mucin glycopolymers; keratan sulfate; electrolocation; monosulphated keratan sulfate; neuroregulation; glycosaminoglycan; neurosensory hair cells; neurosensory proteoglycan*

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Introduction

A recent study has described a remarkable mucous keratan sulphate (KS) glycoconjugate with ultrasensitive proton gradient detection properties which elasmobranch sharks, skates and rays use to track the electric fields emitted by prey fish species (Zhang et al., 2018a). This glycopolymer is the most sensitive proton detection medium known in nature and this represents a remarkable, novel, electroconductive functional property of mucin glycoconjugates. This sensory capability is termed electro-location. Mucin-like glycopolymers normally have adhesive or anti-adhesive, boundary lubrication or barrier functions in epithelial tissues and electroresponsive capability has not previously been envoked for this class of biomolecule. However electroconductive properties in such glycopolymers are not so surprising features when the highly sulphated and sialic acid rich mucin-like glycoproteins produced by many epithelial tumours are considered. The electro-conductive properties of these tumour glycopolymers has facilitated the development of a number of biosensors for their diagnostic detection by analysis of tumour mass secretions (Ferreira et al., 2006; Cheng et al., 2009; Kim et al., 2009; Zhang et al., 2018b). Furthermore, while mammals (other than the Australian duck-billed platypus and echidna) no longer use electrolocation as a sensory medium through receptors and electro-sensory gels located in skin tissues such as found in amphibians, mammals nevertheless have remarkable features in their auditory, olfactory and visual sensory systems which resemble aspects of the sensory cilia and KS-glycoconjugate mucin-like glycoprotein gels found in The ampullae of lorenzini of elasmobranch fish and contained in the cupulla of lateral-line electroreceptors in bony fish. Sensory neurons in the mammalian auditory, olfactory and visual sensory systems contain stereocilia which are surrounded by a layer of mucin-like gel which may have a similar functional role to play as the ampullae KS-glycopolymers

in elasmobranch fish species. In the organ of corti of the cochlea these stereocilia are assembled into characteristic tiered stacks containing a single large cilium called a kinocilium. This contains internal axoneme (the fibrillar bundle of a flagellum or cilium that usually consists of nine pairs of microtubules arranged in a ring around a single central pair) microtubular arrangements and an anchoring basal body previously identified in motile cilia of other cell types and these have a similar morphology to the sensory hairs of piscine lateral line electroreceptors.

What is the Functional Significance of Monosulphated Keratan Sulphate in Electrosensory Tissue

It is noteworthy that a single glycosaminoglycan (GAG) species (KS) occurs as a component of the glyco-sensory gel found in the ampullae of elasmobranch fish. This is the purest form of KS found in any tissue so far identified and along with sialic acid substitution provides ion exchange and electroconductive properties to this gel. Mucin gels can bind a number of growth factors, cytokines and morphogens which can regulate cellular activity through cell signalling so they have a functional capability far beyond simple boundary protection or lubrication (Lillehoj et al., 2013). High charge density KS glycoforms in particular have also been shown to bind a number of neuroregulatory proteins (Conrad et al., 2010). The binding characteristics of low sulphation KS glycoforms still have to be established and it cannot be assumed that these KS glycoforms will bind the same repertoire of high charge density KS ligands. While historically the emphasis on KS pathobiology has been on high charge density mediated KS interactions, such interactions with low charge density KS glycoforms may offer improved sensitivity and more subtle and physiologically relevant levels of control over KS interactions at the cellular level. Furthermore, networking of these responses from electroreceptor networks involving many thousand receptors may still provide a signal of sufficient intensity to overcome any responsive thresholds inherent in neural networks to effect a positive response. This may explain the exquisite detection limits of the ampullae KS glycoconjugates as a proton gradient detection system (Josberger et al., 2016; Zhang et al., 2018a). These possibilities need to be experimentally verified but may demonstrate a novel aspect of the biology of KS requiring further exploration and has the potential to provide useful insights into the design of therapeutic GAG mimetic molecules. Corneal KS binds growth factors and morphogens including fibroblast growth factor 1 and 2 and sonic hedgehog (Weyers et al., 2013). KS interactions with insulin-like growth factor binding protein-2 (Russo et al., 1997), sonic hedgehog and fibroblast growth factor 1 and fibroblast growth factor 2 (Weyers et al., 2013) regulate tissue homeostasis. KS binding to sonic hedgehog also regulates murine embryonic spinal development (Hashimoto et al., 2016) acting as a morphogenetic switch to regulate the generation of oligodendrocyte progenitor cells (Hashimoto et al., 2016). A proteomics study demonstrated corneal KS interactions with a range of nerve regulatory proteins (Conrad et al., 2010). Use of customized 8268 protein microarrays demonstrated interactivity with 217 proteins including 75 kinases, membrane/secreted, cytoskeletal, and nerve functional proteins (Conrad et al., 2010). A secondary screen of 85 nerve-related epitopes, showed KS bound 40 of these including Slit-2, two Robbo's, nine Ephrin receptors, eight Ephrins, eight semaphorins, and two nerve growth factor receptors (Conrad et al., 2010).

Electroconductive Biopolymers

Conductive hydrogels combine the hydrophilic characteristics of hydrogels and the electrical properties of conductive media. These polymers have been applied in the development of supercapacitors, fuel cells, rechargeable lithium batteries, chemical/biosensors and biomedical devices (Wu et al., 2013; Kumar et al., 2014; Li et al., 2015; Li et al., 2016). Conductive macroporous hydrogels have even been developed for nerve regeneration applications (Guarino et al., 2013) and for tumour detection in immunosensors/biosensors (Hamd-Ghadareh et al., 2018; Hasanzadeh et al., 2018).

The Mucin Glycoprotein Family

The Mucins are a diverse family of 5–50 MDa heavily glycosylated glycoproteins which occur as secreted and cell membrane bound forms with established roles in boundary lubrication and protection in epithelial tissues but are also synthesized by other cell types and are located in tissue niches other than the epithelium. A total of six secreted mucins (MUC2, MUC5AC, MUC5B, MUC6, MUC19, MUC7) and 12 cell associated mucins (MUC-1, MUC3A, MUC 3B, MUC 4, MUC 12–17, MUC 21, MUC 22) have been identified (Dhanisha et al., 2018). All of the secreted mucins except MUC7 are gel forming mucins. The gelation properties of mucins with cations such as Ca^{2+} provide an anti-convective medium which limits the diffusion of ionic species bound by the mucin conjugates. The Mucin glycoproteins typically contain 80% N-acetylchondrosamine, N-acetyl-D-glucosamine, galactose, fucose, neuraminic acid (NeuA), Lewis-X-antigen (Le^X) as O- and N-linked oligosaccharide chains. The O-linked oligosaccharides on mucous glycoproteins consist of highly sialylated core 1 and 2 structures with a smaller amount of sulphate core 2 structures. These glycan structures can be further extended into small low sulfation KS-type oligosaccharides of up to four N-acetyllactosamine units or extended to longer chain highly sulphate KS chains (Aplin et al., 1998). Le^X epitopes can also participate as ligands for the Selectin family but may deleteriously impact on neuroinflammation. A family of glycosyl transferases have been identified which sulphate the galactose and N-acetyl-D-glucosamine epitopes in mucin type glycoproteins. These include KS galactose 6-O-sulphotransferase (GST-1), the ubiquitously expressed GlcNAc 6-O-sulphotransferase (GST-2), high endothelial cell N-acetyl-D-glucosamine 6-O-sulphotransferase (GST-3), and intestinal GlcNAc 6-O-sulphotransferase (GST-4). A form of GST-4 is also expressed in the cornea and brain named C-GlcNAc6ST (GST-4beta). C-GlcNAc6ST catalyzes 6-O-sulfation of N-acetyl-D-glucosamine in KS, null-mutations in its encoding gene cause human macular corneal dystrophy (Bartes et al., 2001). GST-5 is the newest member of this emerging family of carbohydrate 6-O-sulphotransferases to be identified, chondroitin 6-sulphotransferase (GST-0) is also a sulphotransferase family member.

High and Low Sulfation Keratan Sulphate Mucin Glycoforms

Small monosulphated KS chains in mucin-like glycopolymers are not detected by the commonly used KS antibodies such as 5-D-4 and MZ-15 which identify highly sulphate hexa saccha-

ride and larger KS glycoforms (Caterson and Melrose, 2018). However an antibody has also now been developed to these small low sulphation KS chains (Kawabe et al., 2013; Nakao et al., 2017). Monoclonal antibody R-10G was developed against the podocalyxcin transmembrane KS-proteoglycan expressed by pluripotent progenitor stem cells and alternative functional roles for these monosulphated KS chains on glycopolymers are now emerging (Kawabe et al., 2013). MUC1 containing high charge density glycoforms of 5-D-4 +ve and sialylated KS have been identified in the endometrial epithelium at the luminal epithelial surface until the implantation phase, thereafter its expression ceases (Aplin et al., 1998). 5-D-4 positive KS is also produced by microglial cells in normal neural tissues (Bertolotto et al., 1998) and in amyotrophic lateral sclerosis, Alzheimer's disease, malignant astrocytic tumours (Kato et al., 2008), glioblastoma and in papillary thyroid carcinoma (Magro et al., 2003). Moreover, deficiency of the KS biosynthetic enzyme GlcNAc6STI in J20/GlcNAc6STI$^{-/-}$ mutant mice results in a complete absence of sialylated KS thus GlcNAc6STI has been suggested as a potential therapeutic target for the treatment of AD (Zhang et al., 2017, 2018a).

Human MUC1 substituted with highly sulphated 5-D-4 +ve KS chains has also been identified in the surface regions of the corneal epithelium (Kurpakus Wheater et al., 1999), tectorial membrane and stereocilia of the sensory hair cells of the organ of corti (Katori et al., 1996). The interphotoreceptor pericellular matrix of the eye also contains a 320 kDa KS-mucin whose function has yet to be fully defined (Plantner, 1992) and full characterisation of the KS glycoforms associated with these tissue structures need to be undertaken. MAb 5-D-4 localises to the surface of the tectorial membrane but not the main substance of the membrane where a monosulphated KS is found (Killick and Richardson, 1997). The tips of the stereo cilia in sensory hair cells in the organ of corti also contain 5-D-4 KS epitopes (Katori et al., 1996).

MUC2 was the first human secretory mucin to be fully sequenced and like the other five secreted mucin proteins, MUC2 is characterised by tandem irregular repeat sequences rich in threonine and serine which are also sites of O-glycosylation. MUC2 is polymerised end to end through disulphide bridges to form large secreted polymeric gel-forming mucins (Mr ~10^7) with glycosylation representing ~80% of the mass of the mucin molecule (Dhanisha et al., 2018).

The Electrosensory Gel of the Ampullae of Lorenzini

The electrosensory ampullae of lorenzini were first described by Marcello Malpighi in 1663 and described in detail by Stephano Lorenzini in 1678. More recently further information on the molecular structure of the ampullae electrosensory gel and its physicochemical properties have been uncovered (Josberger et al., 2016; Zhang et al., 2018b). The sensory gel contained within the ampullae of lorenzini of the elasmobranch sharks, skates and rays is the most thoroughly examined mucin-like electrosensory gel, displaying an exquisite level of sensitivity for the detection of proton gradients generated by the weak electric fields emanating from the muscular activity in preyfish species (Zhang et al., 2018a). KS is the only GAG detected in this glycoconjugate and it is present as a monosulphated form. The ampullae electrosensory gel has conductive properties rivalling the Nafion electrocytes of fuel cells and is the most sensitive proton gradient detection system known in nature (Zhang et al., 2018a). Nafion is a synthetic highly conductive sulfonated tetrafluoroethylene based polymeric fluoro ionomer which is used in fuel cell technology (Mileo et al., 2018). The room temperature proton conductivity of the ampullae electrosensory gel is very high at 2 ± 1 ms/cm which is only 40-fold lower than the current state-of-the-art proton-conducting polymer Nafion, and the highest reported for a biological material. The KS and sialic acid components of ampullae sensory gel may contribute to its high proton conductivity through their ionisable COO^- and SO_4^{2-} groups and associated counterions (Josberger et al., 2016).

Like the mucin glycoproteins, the ampullae of lorenzini KS-mucin monomer is assembled end to end to form a dimer which is further stabilised by disulphide bonding at its N- and C- termini and these dimers are then assembled to form a large aggregated complex bearing KS and sialic acid charged groups. The KS chains are mainly N-linked to the mucin core and are monosulphated with a molecular weight of 20–30 kDa (Zhang et al., 2018a). The ampullae gel macrostructure is further stabilised by extracellular actin-myosin microfilamentous fibres while other proteins interactive with the KS mucin component including serotransferrin and keratin provide further stabilisation. Additional proteins such as parvalbumin-like protein and calreticulin regulate calcium and potassium channels involved in the transduction of the electrosensory signal detected by the KS sensory gel.

Electrolocation in the Duck Billed Platypus, Echidna and Guiana Dolphin

Electrolocation is a sense mainly found in amphibian species however two species of terrestrial animals also display this detection system and one species of dolphin. The monotreme duck billed platypus and long and short nosed echidna electroreceptors are evolved mucous glands with a bulbous region containing the sensory cells leading to a stalk filled with a mucous detection gel leading to an external pore on the skin. The platypus is a nocturnal feeder, has poor eyesight and when foraging for food closes its eyes, ears and nose but opens the skin pores leading to its electrolocation receptors. This is an important sensory feature of the platypus which ensures success during food collection and is used in combination with tactile properties conveyed by adjacent mechanoreceptors also located on the bill of the platypus. The Guiana dolphin also has a collection of vibrissal electroreceptors located on its bill. These pore like structures are also filled with a fibrous gel matrix which apparently has similar sensory properties as the sensory gel of the ampullae of lorenzini in elasmobranch fish but awaits detailed characterisation.

A series of electroreceptors are also located along the lateral-line of bony fish, the ampullae receptors are believed to have evolved from these over 500 million years ago. The lateral line electroreceptors are located in a surface canal in which sea water circulates and are not exposed directly to sea-water. Furthermore, the sensory hair cells are encapsulated by a cupula which contains a sensory gel which conveys movements of the cupula due to external water flow to the stereocilia of the neuromast sensory hair cells contained within the cupula then transduced to interconnected neural cells. The glycoconjugates

which convey these sensory properties in these electroreceptor systems in the above species await to be fully characterised but would be expected to be mucin-like glycopolymers similar to those present in the ampullae of lorenzini.

Common Functional Features of Keratan Sulphate in the Amphibian Electrosensory and Human Sensory Tissues

The organ of corti of the cochlea of the inner ear in humans has sensory hair cells very similar to the neuromast hair cells of fish lateral line electroreceptors. These both contain tiered stacks of stereo cilia which detect movements of the sensory gel filled cupula or fluid filled tectorial membrane respectively where an efflux of endolymph K^+ occurs in response to auditory signals. This depolarises the sensory hair cell and results in transduction of the auditory signal by mobilisation of synaptic neurotransmitters to the synaptic gap and transmission of these to interconnected neurons. The tectorial membrane contains 5-D-4 +ve KS on its surface but monosulphated KS on tectorin, a KS-proteoglycan within the tectorial membrane. KS has also been immunolocalised to interconnections between individual stereo cilia and in their tip regions. A large 320 kDa KS substituted mucin is also present in the interphotoreceptor matrix around the rods and cones which undertake phototransductive processes and transmission of visual signals to the optic nerve and brain stem for interpretation. Monosulphated KS is a key component of the electrosensory glycoconjugate of the ampullae of lorenzini (Zhang et al., 2018a). The human neuron contains two intracellular KS-proteoglycans with neuroregulatory properties. MAP1B associates with microtubules and the cytoskeleton and may regulate neuritogenesis while SV2 is a 12 span transmembrane KS-proteoglycan which provides a smart gel storage medium for neurotransmitters in synaptic vesicles and may co-ordinate their release from synaptic storage in response to membrane depolarisation events initiated in response to sensory input signals. Determination of the specific roles KS plays in these sensory and neuroregulatory processes may be highly instructive and of therapeutic application.

Future Research Applications With Glycosaminoglycan Gels

An electroconductive capability is a useful functional attribute in a biopolymer particularly in neural systems which are known to be sensitive to electrostimulation. GAG emulsions are receiving increasing levels of attention in the development of artificial neural networks and in biomedical applications (Abiodun et al., 2018; Aregueta-Robles et al., 2018; Guha Roy et al., 2018; Seo et al., 2018). Nanotechnology is also being applied in the synthesis of single neurons (Fabbro et al., 2012). GAGs may be of application as conduits for the synaptic interface to such developed neural networks. Neurons are an electrically excitable cell type and this forms the basis of their participation in electrocommunication in neural networks. Innovative developments in smart biopolymer and electroconductive material design and monitoring systems suitable for application in neural repair studies may facilitate a better understanding of the effector molecules operative in neural repair and the role of KS in these processes. Biocompatible, polymer, microelectrode arrays for the capture of cardiac and neuronal signals has facilitated the monitoring of events occurring in neural repair in heart cell preparations, retinal whole mounts, and in cortico-hippocampal co-cultures (Blau et al., 2011). Spinal neurons grown in electroconductive carbon nanotube bioscaffolds generate voltage dependent currents or action potentials, microarray studies have also identified markers of cell differentiation and neural regeneration (Fabbro et al., 2013). Nanopatterned cell-seeded cardiac patches of electroconductive biomaterials prevent electro-uncoupling which improves cardiac repair (Lin et al., 2014). Thermosensitive, electrically conductive gold-chitosan nanoparticle hydrogels, have also been applied in cardiac tissue engineering (Baei et al., 2016). Cytocompatible, injectable, electroconductive hydrogels with free radical scavenging properties have also been used to encapsulate cardiac cells and fibroblasts sparing them from oxidative stress, and may also be applicable to neural cultures (Komeri and Muthu, 2017). Electrically conductive, HA hydrogels, containing single-walled carbon nanotubes and/or polypyrrole have been applied to promote differentiation of human neural stem/progenitor cells (Shin et al., 2017). Electroconductive hydrogels have also been developed through the functionalization of non-conductive polymers with a conductive choline-based bio-ionic liquid. Bio-ionic liquid conjugated hydrogels exhibit a wide range of highly tunable physical properties, remarkable *in-vitro* and *in-vivo* biocompatibility, and high electrical conductivity without the use of additional conductive components (Noshadi et al., 2017). Bio-ionic liquid conjugated hydrogels have been used to culture cardiomyocytes and are compatible with implantation procedures into heart defects but also display properties which might be harnessed in neural repair strategies. Knowledge is still wanting of the molecular interactions occurring at the biological interface of these implant materials facilitating bio-integration and repair. KS may facilitate such processes a thorough knowledge of these processes may outline roles for KS-proteoglycans in neural development and remodeling and provide intuitive clues applicable to improved neural repair strategies.

Conclusions

An open mind needs to be kept as to what constitutes a functional proteoglycan. Low sulphation KS glycoconjugates represent a new development in KS functional glycobiology and deserve further investigation. Mucin glycoconjugates have not previously been ascribed electro-sensory roles in neurosensory tissues or in neural regulation.

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