Global Open Access Journal of Science

Open Access | Review Article | Neurology
1(2), 2025 | PP - 114 - 132

Multidisciplinary Journal ISSN - 3070-6173

Review Article

Neurology

A Keratan Sulfate: An Electroconductive Proton Capture Glycosaminoglycan Regulator of Neuronal Membrane Polarization, Ion Fluxes, Neuronal Activation and Neurotransduction

James Melrose[1,2*]

[1]Graduate School of Biomedical Engineering, University of New South Wales, Sydney 2052, NSW, Australia
[2]Raymond Purves Bone and Joint Research Laboratory, Kolling Institute of Medical Research, Northern Sydney Local Health District, University of Sydney at Royal North Shore Hospital, St. Leonards 2065, NSW, Australia

ABSTRACT

This study describes keratan sulfate (KS), a multifunctional electroconductive glycosaminoglycan, and it's participation in electrochemical processes that regulate neuronal activity. Neuronal cells are highly responsive to electrical stimulation and this is an intrinsic evolutionary property of this cell type. Tissue engineering protocols are being developed to produce scaffolds that provide electrical environments conducive to neuronal activity to improve neural repair and regenerative responses. Incorporation of KS in bioactive electroconductive hydrogels may enhance their therapeutic properties by improving their interactions with growth factors, structural and neuroregulatory glycoproteins and through the proton capture electroconductive properties of KS. Brain tissues are one of the richest sources of KS in the human body and it has diverse properties including roles in synaptic stabilization and plasticity essential for optimal neuronal activity. Electrical cues are important determinants of neurotransduction in neural networks and also regulate wound healing and neuro-regenerative processes. Novel bioelectronic neural therapeutics are being harnessed to promote repair of the CNS/PNS. KS has unique functional properties in cellular bioregulation, a greater understanding of these properties would be expected to improve the capability of biotherapeutic neural repair biology.

Keywords: Keratan Sulfate, Electrochemical Gradients, Proton Conductivity, Podocalyxin, Synaptic Plas-

Correspondence:

Professor James Melrose, Raymond Purves Bone and Joint Research Laboratories, The University of Sydney at Royal North Shore Hospital, Level 10, Kolling Institute of Medical Research, B6, St. Leonards, NSW 2065, Australia, ORCID: orcid.org/0000-0001-9237-0524;

Received Dates: October 19, 2025;
Accepted Date: October 27, 2025;
Published Date: October 30, 2025;

Cite this article as: Melrose J, Keratan Sulfate: An Electroconductive Proton Capture Glycosaminoglycan Regulator of Neuronal Membrane Polarization, Ion Fluxes, Neuronal Activation and Neurotransduction, Glob. Open Access J. Sci, 2025; 1(2):114-132..

GLOBAL OPEN ACCESS JOURNAL OF SCIENCE

ticity, Neural Tissue Repair

Abbreviations

BBB: Blood Brain Barrier; CNS: Central Nervous System; CS: Chondroitin Sulfate; DS: Dermatan Sulfate; DTHL: C-Terminal Amino Acid Asp-Thr-His-Leu motif; EB: Ezrin Inding Domain; ECM: Extracellular Matrix; ERM: Ezrin/Radixin/Moesin; FERM: F for protein 4.1, E for ezrin, R for radixin, and M for moesin; GAG: GAG; GPO: Glutathione Peroxidase; GSH: Glutathione; GTP: Guanosine Triphosphate; HA: Hyaluronan; HS: Heparan Sulfate; KS: Keratan Sulfate; NHERF-1/2 Sodium Hydrogen Exchanger Regulatory Factor-1 /2; PNS: Peripheral Nervous System; PDZ: Postsynaptic Density Protein (PSD95), Drosophila Disc Large Tumor Suppressor (DlgA), and Zonula Occludens-1 protein (Zo-1); PODXL: Podocalyxin; RhoA: Transforming Protein RhoA, Ras homolog; RhoGDI: Rho GDP-dissociation inhibitor 1; Robo: Roundabout receptor; SV2: Synaptic Vesicle Proteoglycan-2

INTRODUCTION

Keratan Sulfate (KS) is a Glycosaminoglycan (GAG) that is composed of D-galactose-N-acetyl glucosamine repeat disaccharides that are assembled into a sulfated poly-N-acetyl lactosamine chain which is sulfated in specific regions along the KS chain (Funderburgh, 2002). KS occurs as three forms, KSI, corneal KS; KSII, skeletal KS of cartilaginous tissues and KSIII which is found in brain tissues (Caterson, 2018). KS is O-6 sulfated in monosulfated and disulfated regions, the lactosamine region is non-sulfated. The monosulfated region is sulfated on N-acetylglucosamine while D-galactose and N-acetylglucosamine are both sulfated in the disulfated region. Each of these regions are of variable sizes leading to significant size and charge heterogeneity in KS chains in tissues which vary with tissue ageing and spatial location. KS has diverse interactive properties with growth factors, morphogens, and neuroregulatory proteins (Conrad, 2010; Weyers, 2013) and has proton capture electroconductive properties operative in neuronal cell signaling in neurotransductive processes (J. Melrose, 2024b, 2025a; J. Melrose, 2025; J. Melrose, 2025b) (Figure 1).

THE CHEMISTRY OF WATER AND EMERGENCE OF ELECTROCHEMICAL GRADIENTS IN THE EVOLUTION OF LIFE ON EARTH

The chemistry of water was one of the most crucial determinants that shaped the evolution of life on earth. An important chemical feature of water is its dissociation into protons and hydroxyl ions to provide relatively high proton concentrations in ambient solution. This resulted in the appearance of proton pumps in the deep ocean environments during the dawn of life and maintained a neutral pH inside the early cells that evolved (Lane, 2017). The generation of electrochemical proton gradients across membranes termed the proton-motive force was essential for the survival of the earliest unicellar organisms (Nelson, 1994). The emergence of membrane bioenergetics equipped membranes with ion transport properties essential to early cellular evolution (Wilson, 1980) providing a nutrient transport system for simple unicellular organisms (Daniel, 2006). With the evolution of the eukaryotes, the proton motive force generated by mitochondria evolved as a way to generate ATP (Mitchell, 1961). The evolution of GAGs (Yamada, 2011) served as a means of capturing and transporting protons in energy production and provided a cell instructive platform to control cellular behavior (Lafont, 1992). GAGs are the unsung heroes of biomolecular signaling (Gulati, 2016). GAGs regulate cell signaling interactions with growth factors and ECM components, control cellular adhesion, proliferation and differentiation and tissue development (Gandhi, 2008; Hayes AJ, 2018; Schwartz, 2023).

ELECTROCONDUCTIVE EVENTS IN TISSUES REGULATE CELL BEHAVIOR AND TISSUE DEVELOPMENT

Sulfation patterns on GAGs are important functional determinants which provide selectivity in interactions with growth factors, receptors and structural ECM proteins of importance in tissue development and stabilization of mature tissues (J. Melrose, 2025a; J. Melrose, 2025; Prydz, 2015). Sulfated GAGs regulate axonal migration and guidance for correct intercon-

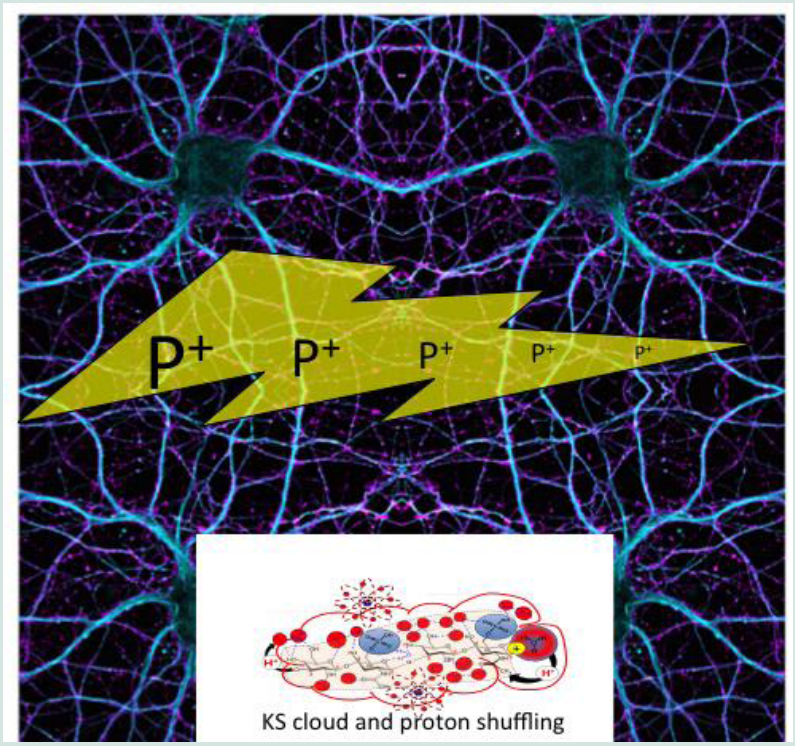

Figure 1: Cerebellar neuronal networks and signal carrying proton gradients. KS is a proton capture electroconductive GAG that may find application in the development of neural signaling platforms like electroconductive hydrogels being developed for neural repair.

nectivity of neural networks through interactions with neuroregulatory proteins such as Robo-Slit (Y. Chang, Dubnau, J. , 2025; Conrad, 2010; Schwend, 2012). The neuron is particularly sensitive to electrical stimulation and this is a central feature of its functional properties in neurotransduction in neural networks (Jones, 2023). Electroconductive events are intrinsic to many natural cellular phenomena (T. Decoursey, 2003; T. DeCoursey, Cherny, VV. , 2000) such as mitochondrial oxidative phosphorylation and energy production fundamental to life processes (Madeira, 2018; Mitchell, 1966, 1972, 2011; Nath, 2015), uncoupling of membrane potentials in membrane polarization and neuronal potentiation(Schoen, 2008; Shin, 2010; Ye, 2015) and the priming of cells undergoing cellular proliferation, apoptotic processes or cellular migration (Hodeify, 2018; Love, 2018; Valero, 2008). Electrochemical reactions are intrinsic to the control of cell and tissue polarity (Lafont, 1992; Viola, 2024) and regulation of cellular behaviour (F. Chang, Minc, N. , 2014; Mañes, 2000; Muthuswamy, 2012). All GAGs have electroconductive potential but to variable degree (Josberger, 2016), KS is the best electroconductive GAG and the most potent proton capture compound so far detected in nature (Selberg, 2019). The conduction of protons by KS occurs through H-bonding interactions (J. Melrose, 2024b) (Figure 2). Cell surface GAGs produce localized ion fluxes at the plasma membrane cell surface, and electrochemical gradients that contribute to cell polarization, migration, cellular division, proliferation and differentiation.

KS HAS INSTRUCTIVE ROLES IN BRAIN DEVELOPMENT

KS has been proposed to form an instructive template that facilitates migration of neuroblasts during brain development and has been immunolocalised to radial and tangential neuroblast migratory pathways from subventricular zone to cortical plate as early as 9wk GA (H. Sarnat, Yu, W. , 2025). KS has also been prominently immunolocalised in the cytoplasm of astrocytes and extracellular parenchyma at 9wk in globus pallidus, at 15wk in the thalamus, at 18wk in the corpus striatum, at 22wk in the cortical plate, and in the hippocampus postnatally. KS has selective properties and repels glutamatergic axons but facilitates GABAergic axonal migration at sites of synapse formation (H. Sarnat, Flores-Sarnat, L. , 2024), consistent with proposed roles for

KS as an instructive GAG (J. Melrose, 2025a; J. Melrose, 2025; J. Melrose, 2025b, 2025c) and for KS-proteoglycans in axonal guidance roles during brain development (H. Sarnat, 2019; H. Sarnat, Yu, W, Flores-Sarnat, L. , 2021).

PROTONS, AN INTERCELLULAR MESSENGER WITH NEUROTRANSMITTER ACTIVITY

Protons act like a neurotransmitter, activating post-synaptic acid-sensing ion channels which act as proton receptors (Du, 2014). This property facilitates synaptic plasticity, and is an important requirement in cognitive learning and memory (Zeng, 2012). Protons and acid-sensing ion channels are both required for synaptic plasticity and neuronal signal transmission (Zeng, 2012). Protons in the absence of neurotransmitters can stimulate muscle contraction in C.elegans (Beg, 2008) acting as intercellular messengers with neurotransmitter activity (J. Kim, Zhen, M. , 2008). The transfer of protons by GAGs involves interactions with H bonds and water molecules and was proposed by Grotthus in 1806 (de Grotthuss, 1806) and reviewed on his 200th anniversary by Cukierman (Cukierman, 2006). Proton transfer has been described as "proton-hopping" where trains of protons tunnel across a series of hydrogen bonds between hydronium ions and water molecules in GAGs (Popov, 2023), this is termed Grotthuss shuttling (Knight, 2012). This transfer process facilitates nerve signal transmission (Kier, 2016). Proton shuttling also occurs in synthetic electroconductive hydrogels being developed in neural repair and regeneration strategies (Z. Liu, Lai, J, Kong, D, Zhao, Y, Zhao, J, Dai, J, Zhang, M. , 2024; Qin, 2023; Shahemi, 2023) suggesting that KS is a candidate that should be considered in such procedures. KS has the highest proton conductivity reported of any biological material (Josberger, 2016) and is an abundant GAG in the CNS/PNS (Caterson, 2018).

KS HAS ELECTROSENSORY PROPERTIES IN A RANGE OF TISSUES

Cartilaginous fish species such as the elasmobranch rays and sharks have gel-filled tubular sensory pits that interface with their neural systems, these are distributed primarily around the skin of their snouts (M. Phillips, Wheeler, AC, Robinson, MJ, Leppert, V, Jia, M,

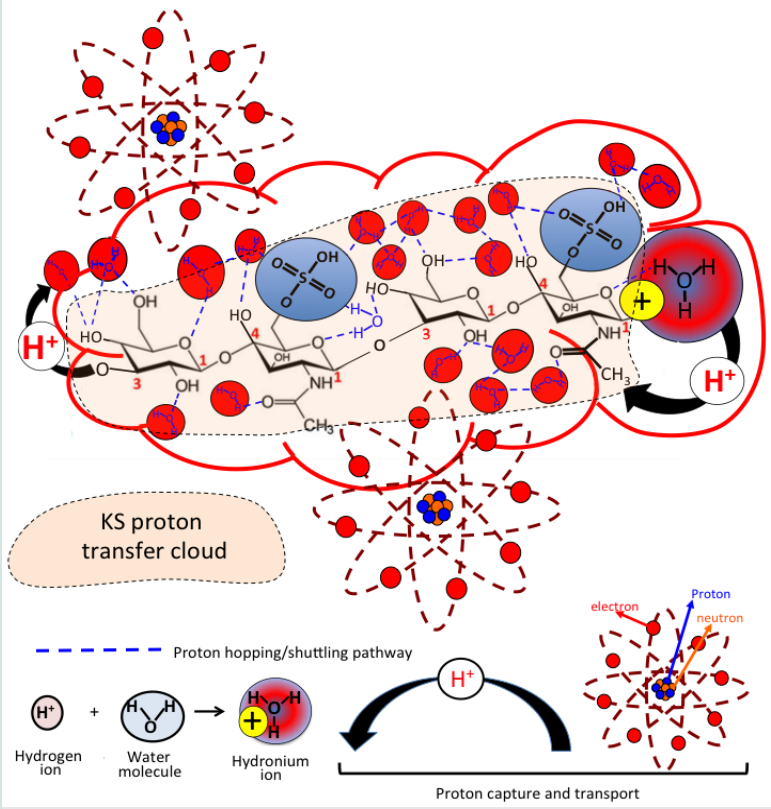

Figure 2: Schematic depiction of proton capture and transport by the KS hydronium ion co-operative network cloud formed through hydrogen bonding along the KS chain which facilitates hopping or shuttling interactions with protons in the internal structure of this GAG. This also involves interactions between hydronium ions and water molecules aided by the charge properties of the sulfate groups on KS. The bound proton does not remain with a single water molecule but cycles rapidly between many water molecules many times per second ensuring the proton remains entrapped in the KS hydrogen bonding cloud and also generates hydronium ions which are reactive species that attract further protons which furthers electroconductive processes.

Rolandi, M, Hirst, LS, Amemiya, CT. , 2021). These pits filled with a KS electro-sensory gel have been termed Ampullae of Lorenzini, this electrosensory gel allows fish to undertake electroreception (Crampton, 2019; J. Melrose, 2019a, 2025a; X. Zhang, Xia, K, Lin, L, Zhang, F, Yu, Y, St Ange, K, Han, X, Edsinger, E, Sohn, J, Linhardt, RJ. , 2018) where they detect electric fields through the proton conductivity properties of KS (Selberg, 2019; X. Zhang, Xia, K, Lin, L, Zhang, F, Yu, Y, St Ange, K, Han, X, Edsinger, E, Sohn, J, Linhardt, RJ. , 2018). Approximately 16% of fish species utilise electroreceptors to detect microvolt-range bioelectric fields generated by prey fish species. These electroreceptors can also be used for electrocommunication (Crampton, 2019). Fluorescent microscopy, small-angle Synchrotron X-ray scattering, atomic force microscopy and scanning electron microscopy has shown this sensory gel is a viscous dispersion of aggregating spherical microparticles within an aqueous medium (M. Phillips, Wheeler, AC, Robinson, MJ, Leppert, V, Jia, M, Rolandi, M, Hirst, LS, Amemiya, CT. , 2021). These particles are resistant to proteinase K digestion which decreased gel viscosity but did not diminish proton conductivity which was increased by protease treatment. Fluorescent microscopy with chitin binding bioprobes has identified chitin as a component of these microparticles (M. Phillips, Tang, WJ, Robinson, M, OcampoDaza, D, Hassan, K, Leppert, V, Hirst, LS, Amemiya, CT. , 2020) however the fine structure of the KS glycoconjugate in these electroconductive gels in fish awaits full clarification. Electroreceptors also detect water movement in fish, using an ancient subdivision of the lateral line sensory system which uses sensory hair cells in ampullary organs to detect water movement (Modrell, 2011; Solon, 2025). This is similar to how the sensory system of the cochlea in humans detect auditory signals through sound generated internal water displacements in the cochlea detected by sensory hair cells which interface with a neural system generating electrical signals that are transferred to the brain via the 8th cranial nerve (Goutman, 2015). KS-proteoglycans are also present on the tectorial membrane and sensory hair cells in the human cochlea (Thalmann, 1993) and these may have roles in auditory sensory transfer processes (J. Melrose, 2024b). This has parallels with the sensory hairs of the lateral line neuromast in fish which acts as a hydrodynamic sensory antenna (Chaumel, 2025).

GAGS HAVE ROLES IN CELL POLARIZATION AND TISSUE DEVELOPMENT

Cell polarization is a dynamic process equipping cells with plastic properties during cytoskeletal alterations in response to intrinsic and extrinsic ECM micromechanical instructive cues (F. Chang, Minc, N. , 2014; Muthuswamy, 2012) facilitating changes in cell shape during cell division, migration and tissue morphogenesis (Mañes, 2000). These cellular changes facilitate tissue development and ECM remodeling during tissue repair where cellular phenotypes and cellular behavior undergo alterations in structure and function. Mechanical directive environmental and electrochemical cues determine migratory, proliferative, and differentiative cellular responses (F. Chang, Minc, N. , 2014). Cell migration is guided by ECM components such as cell adhesive receptors and structural proteins conveying micromechanical cues that modify the cytoskeleton and alter cell shape. Axonal guidance cues are provided by the GAG side chains of a number of neural proteoglycans, CS-proteoglycans deliver inhibitory cues during neuritogenesis while HS-proteoglycans convey stimulatory effects promoting neural dendritic outgrowth (Ali, 2025; Maeda, 2015; J. Melrose, Hayes, AJ, Bix, G. , 2021; Schwartz, 2023; Yu, 2017). KS also regulates neuritogenesis through interactions with ECM neural guidance molecules such as Robo-Slit (Conrad, 2010; Schwend, 2012) ensuring correct assembly of functional neural networks (A. Hayes, Melrose, J. , 2021; Hayes AJ, 2018; J. Melrose, 2024a; Mitsunaga, Mikami, Mizumoto, Fukuda, & Sugahara, 2006; Saied-Santiago, 2018).

ELECTROCHEMICAL EVENTS IN BRAIN DEVELOPMENT

Neuron sensitivity to electrical stimulation from electrochemical environments directs brain development where the vast majority of neurons become polarized (Sakakibara, 2015b; T. Takano, Funahashi, Y, Kaibuchi, K. , 2019) making them responsive to the instructive ECM of niche environments through varied arrangements of HA and proteoglycans (J. Melrose, 2019a,

2019b, 2023, 2024a; J. Melrose, Hayes, AJ, Bix, G. , 2021). Neurons undergo extensive migration from neuroprogenitor sub-ventricular regions of the lateral ventricle and the subgranular zone of the hippocampal dentate gyrus which are known centres of neuroprogenitor cell production, to reach their final locations in the mature brain (Corbin, 2008). The internal connectivity of the CA3 (Cornu Ammonis region 3) subfield is more extensive than in other hippocampal regions and has been proposed to act as a "pacemaker" with directive properties that instruct the neuronal migration in the CA1 and CA2 regions (Cherubini, 2015; Jonas, 2014; Le Duigou, 2014). Phosphacan substituted with KS and splice variants of the transmembrane receptor protein tyrosine phosphatase β/ζ also have instructive guidance roles in the organization of mossy fibres in the hippocampus (Butler, 2004). The migrating neurons develop ion channels which allow them to respond to their ECM microenvironment during development (Isacoff, 2013; Smith, 2020) and adapt to their new microenvironments and can also modify local cellular niches through cell-cell interaction, release of secreted neuroregulatory factors and manipulation of ionic micro-environments affecting local electrical activity (Gu, 2023; Namba, 2015; Sakakibara, 2015a, 2015b; Schelski, 2017; Tahirovic, 2009; T. Takano, Funahashi, Y, Kaibuchi, K. , 2019; T. Takano, Xu, C, Funahashi, Y, Namba, T, Kaibuchi, K., 2015; Yoshimura, 2006). Migrating neurons are thus interconnected with the electrical properties of the cellular micro-environment they encounter(Medvedeva, 2020) and become uniquely interconnected with the ECM and resident neuronal cellular populations (Fritzsch, 2019). Recent progress in live cell imaging examines how neurons differentiate during development revealing the initial steps of formation of ion channels and cell polarization, where neurons establish an axon and shows how excitatory and inhibitory cortical neurons establish neuronal polarity (Sakakibara, 2015b). A developmentally regulated KS-proteoglycan has been shown to modulate neuronal cell adhesion during embryonic brain development (Cole, 1991). KS-proteoglycans modulate recovery of spinal cord injuries (Hilton, 2012; Imagama, 2011).

KS-PROTEOGLYCANS EQUIP NEURONAL TISSUES WITH FUNCTIONAL PROPERTIES

KS is a multifunctional GAG (J. Melrose, 2019a, 2025a; J. Melrose, 2025; J. Melrose, 2025b) that equips a range of KS proteoglycans with important functional properties in the CNS/PNS functionalizing neuronal and astrocyte niche microenvironments optimizing cellular activity by preserving membrane polarization dynamics, ionic microenvironments, ion fluxes, neuronal activation, and network neurotransductive capacity (J. Melrose, 2024a). KS-proteoglycans have diverse interactive properties with growth factors, morphogens and neuroregulatory proteins of importance in neuronal regulation in tissue development and homeostasis in health and also in pathological processes in disease (J. Melrose, 2019b).

PODOCALYXIN IS AN IMPORTANT NEUROREGULATORY KS PROTEOGLYCAN

Neural development and synaptic plasticity are regulated by podocalyxin, a sialylated transmembrane KS-proteoglycan (N. e. a. Vitureira, 2010). Podocalyxin contains mucin-like core protein modules which are substituted with sialic acid, KS and N- and O-linked oligosaccharides (Figure 3). The transmembrane and phosphorylated cytoplasmic domains of podocalyxin have roles in cell signaling through interactions with ezrin and NHERF-1/2 (Sodium Hydrogen Exchanger Regulatory Factor-1 /2) cytoskeletal proteins. Podocalyxin's C-terminal amino acid Asp-Thr-His-Leu (DTHL) motif is required for recruitment of NHERF-1. The DTHL motif of podocalyxin interacts with the N-terminal FERM (F for protein 4.1, E for ezrin, R for radixin, and M for moesin) domain of ezrin. The FERM domain is a widespread 30 kDa protein module which aids in the localisation of cytoskeletal proteins to the plasma membrane. Ezrin interacts with podocalyxin via the C-terminal NHERF-1/2 motif following binding of DTHL to the PDZ2 domain of NHERF-1/2. The PDZ domain is a 80-90 amino acid module in multi domain scaffolding proteins with roles in cell signaling. PDZ stands for Postsynaptic density protein (PSD95), Drosophila disc large tumor suppressor (DlgA), and Zonula occludens-1 protein (zo-1). PDZ proteins are key organizers that control synaptic protein assembly and structural organization (E. Kim, Sheng, M. , 2004). Formation of PODXL-NHERF-1/2-ezrin complex promotes binding to

the actin cytoskeleton. Sequestration of RhoGDI (Rho GDP-dissociation inhibitor 1) a regulator of the Rho family GTPases (Dovas, 2005) by ezrin releases Rho-GDP, which upon its conversion to Rho-GTP enhances the activation of Rho-family GTPases which have axonal guidance, cell signaling roles and provide synaptic plasticity (Spillane, 2014). RhoA (Transforming protein RhoA, Ras homolog) promotes neuronal development (Govek, 2005) and assists in the functional recovery of spinal cord injury through promotion of synaptogenesis by Robo1. Roundabout (Robo) receptors expressed by various cell types in the CNS, mediate intracellular signal transduction pathways for Slit 2 (Li, 2017; Sanhueza, 2025). Slit 2 is a key regulator of axon regeneration and synapse formation and has been suggested as a therapeutic target in CNS disorders (Sherchan, 2020). Podocalyxin is an anti-adhesive transmembrane sialo-KS-proteoglycan with essential roles to play in neural development (N. Vitureira et al., 2010; N. Vitureira, McNagny, Soriano, & Burgaya, 2005) in health and ECM remodeling in disease (J. Nielsen, McNagny, KM. , 2009). Podocalyxin regulates neuronal migration and provides axonal guidance cues during development of the CNS. Podocalyxin has important functional properties in the CNS during neurotransductive processes, it co-localises with synapsin and synaptophysin in synaptic vesicles and preserves synaptic plasticity (N. Vitureira et al., 2010). The latter protein co-ordinates

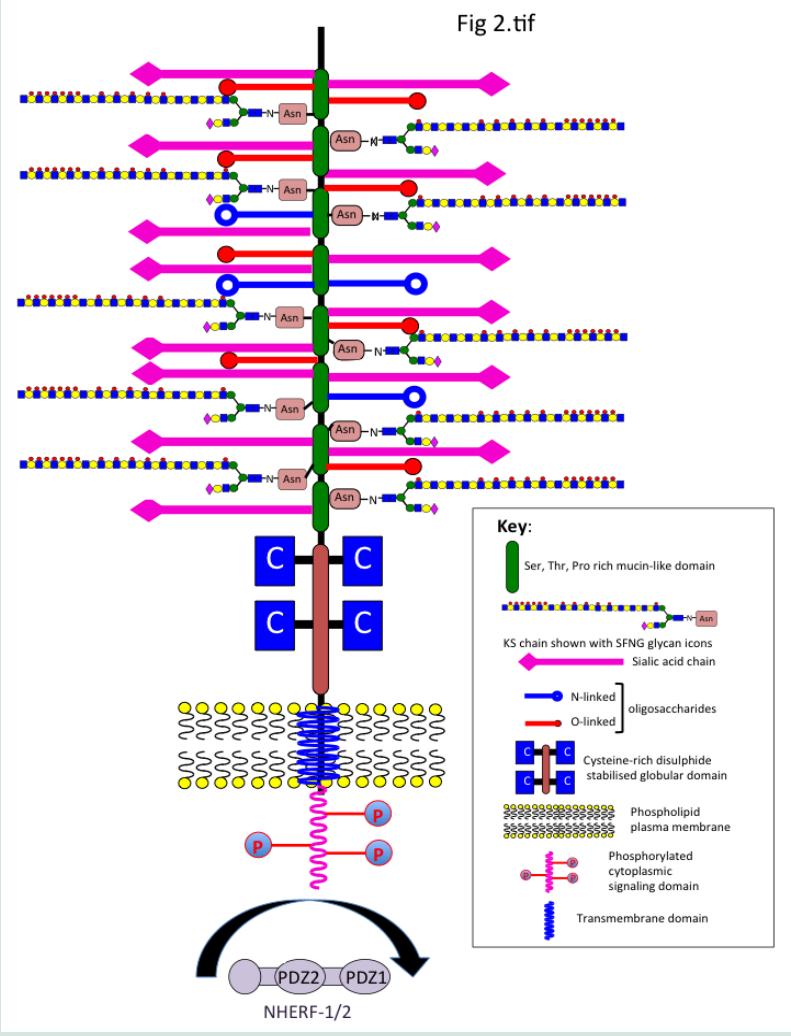

Figure 3: Schematic depiction of the structure of podocalyxin and some of the proteins it interacts with. Podocalyxin is a transmembrane cell regulatory sialo KS proteoglycan. The extracellular and intracellular domains of podocalyxin show its mucin-like core protein modules substituted with sialic acid, KS and *N*- and *O*-linked oligosaccharides, transmembrane and phosphorylated cytoplasmic domain which has roles in cell signaling through interactions with ezrin and NHERF-1/2. Podocalyxin's C-terminal amino acid Asp-Thr-His-Leu DTHL *motif* is required for recruitment of NHERF-1. The DTHL motif binds to the PDZ2 domain of NHERF-1/2. The PODXL-NHERF-1/2-ezrin complex promotes binding to the actin cytoskeleton and the activation of Rho-family GTPase cell signaling proteins. Abbreviations: DTHL, Asp-Thr-His-Leu *motif*; ERM, Ezrin/Radixin/Moesin; FERM, F for protein 4.1, E for ezrin, R for radixin, and M for moesin; NHERF, *Sodium Hydrogen Exchanger Regulatory Factor-1 /2; EB, Ezrin binding domain;* RhoGDI (Rho GDP-dissociation inhibitor 1).

the transport of synaptic vesicles to the synaptic gap during neural activation (Kwon & Chapman, 2011) , co-operating with another KS-proteoglycan, SV2, which is a synaptic vesicle neurotransmitter transporter proteoglycan (Bajjalieh 1992; Carlson, 1996; Nowack, 2010; Scranton, 1993; Wan, 2010). Synapsin tethers synaptic vesicles to cytoskeletal components preventing their premature release into the synaptic gap during neural activation (Bykhovskaia, 2011; Cesca, Baldelli, Valtorta, & Benfenati, 2010; Fornasiero, Bonanomi, Benfenati, & Valtorta, 2010; S. H. Song & Augustine, 2015). SV2 proteoglycan (Carlson, 1996; Scranton, 1993; Son, 2000; Wan, 2010) has roles in the storage and transport of neurotransmitters carried in neuronal synaptic vesicles which upon neural activation are transported in a co-ordinated manner to the synaptic gap where these vesicles fuse with the pre-synaptic membrane releasing vesicular neurotransmitters into the synaptic gap (J. Melrose, 2024b, 2025a; J. Melrose, 2025). These are then taken up by neurotransmitter receptors on the post-synaptic membrane of communicating neurons in the neurotransductive network.

ROLES FOR KS IN THE TUMOUR ENVIRONMENT

High and low charge density forms of KS are expressed in the tumor environment (A. Hayes, Melrose, J. , 2020; J. Melrose, 2025b). Lung metastatic tumors show a higher-level expression of highly charged KS compared to primary tumors. Aberrant expression of KS is predictive of pancreatic cancer progression and metastasis and suggested as a novel prognostic biomarker for several cancers (Leiphrakpam, 2019; J. S. Nielsen & McNagny, 2009; Wang et al., 2017). KS is also associated with astrocytic tumors in glioma (Kato, 2008) and with their malignant status (N. Hayatsu, Kaneko, MK, Mishima, K, Nishikawa, R, Matsutani, M, Price, JE, Kato, Y. , 2008). Podocalyxin decorated with low-sulfation KS is preferentially expressed in human testicular endothelial cells (A. Muramoto, Hoshino, H, Inamura, S, Murahashi, M, Akama, TO, Terada, N, Kobayashi ,M. , 2024; A. Muramoto, Inamura, S, Hoshino, H, Terada, N, Kobayashi, M. , 2023) and in non mucinous ovarian cancer (Hoshino, 2024). KS contributes to the development of malignant phenotypes and the invasiveness of melanoma cells (Tachibana, 2022). Podocalyxin is produced by human embryonic neuroprogenitor and induced pluripotent stem cells (Toyoda, Nagai, Kojima, & Kinoshita-Toyoda, 2017) and is also upregulated in glioblastoma and in astrocytomas (Binder, 2013; N. Hayatsu, Kaneko, MK, Mishima, K, Nishikawa, R, Matsutani, M, Price, JE, Kato, Y. , 2008; N. Hayatsu, Ogasawara, S., Kaneko, M. K., Kato, Y. & Narimatsu, H. , 2008; He, 2010; Kato, 2008; B. Liu, Liu, Y, Jiang, Y. , 2015; Y. Liu, Yang, L, Liu, B, Jiang, YG. , 2014).

How proteoglycans substituted with these KS isoforms precisely promote tumor cell development has yet to be fully elucidated but the diverse interactivity of KS with a wide range of growth factors and morphogens likely contributes to these processes (Conrad, 2010) however other KS-proteoglycans such as lumican has MMP inhibitory and anti-angiogenic properties that inhibit tumor development (Niewiarowska, 2011; D. Nikitovic, Berdiaki, A, Zafiropoulos, A, Katonis, P, Tsatsakis, A, Karamanos, N, Tzanakakis, G. , 2007; D. Nikitovic, Chalkiadaki, G, Berdiaki, A, Aggelidakis, J, Katonis, P, Karamanos, NK, Tzanakakis, GN. , 2011; Pietraszek, 2014). The role of KS in tumor development is thus complex.

ESSENTIAL PROTECTIVE ROLES FOR PODOCALYXIN IN THE FILTRATIVE PROPERTIES OF THE BLOOD BRAIN BARRIER AND KIDNEY GLOMERULUS

Besides its roles in neuronal mediated assembly processes, neuroregulatory cell signaling and preservation of synaptic plasticity already described, podocalyxin also has important roles in the maintenance of blood-brain barrier integrity during acute inflammation (Cait, 2019). Podocalyxin promotes formation of tight junctions during endothelial cell morphogenesis forming functional barriers in blood vessels in the blood brain barrier (BBB). Endothelial podocalyxin expression is required for F-actin accumulation, association of β-catenin with cell junctions, and efficient formation of focal adhesion complexes essential for BBB integrity. Podcalyxcin also has essential roles in the development and function of the kidney glomerular filtration barrier. Ablation of podocalyxin in kidney tissues clearly shows a loss of filtrative properties compared to normal kidney tissues (Horrillo, 2016).

APPLICATION OF GAGS IN TISSUE ENGINEERING FOR TISSUE REPAIR

GAGs are an interesting class of functional biomolecules that modulate tissue repair processes (J. Melrose, 2016; Yang, 2024) through their charged sulfate and carboxyl groups which under physiological conditions are ionisable and can participate in interactions with cells to direct cellular behavior (Hayes AJ, 2018; J. Melrose, 2025; J. Melrose, 2025c; J. Melrose, Hayes, AJ, Bix, G. , 2021) and can influence tissue development through their ability to regulate tissue morphogenesis (A. Hayes, Sugahara, K, Farrugia, B, Whitelock, JM, Caterson, B, Melrose, J. , 2018). Biomimetic proteoglycans have been developed to repair the degenerate intervertebral disc in an attempt to promote tissue regeneration (Chopra, 2024).The therapeutic application of sulfated GAGs in tissue engineering applications demonstrates the cell directive capabilities of these molecules (Farrugia, 2018; Karumbaiah, 2015; Menezes, 2023; Sodhi, 2020; Uygun, 2009). GAGs incorporated into tissue engineering scaffolds and hydrogels can be used to direct stem cell differentiation to select for a specific cell lineage with tissue repair properties(Farrugia, 2018). In addition to enhancing neurite outgrowth, these GAG hydrogels recreate electrochemical environments that promote repair or regeneration of neural tissues, supporting endogenous cell signaling by delivery of exogenous electrical stimulation and neurotrophic factors. Schwann cells play a dominant role in nerve regeneration and development following peripheral injuries (Chitose, 2017; Ding, 2010; Li 2021; McMorrow, 2022; Pan, 2020). Neural injury and associated neurological diseases affect almost 1 billion people around the world so there is a clear need to develop effective methods that stimulate neural repair and regeneration (Evans, 2024; Gonsalves, 2024).

GAG-functionalized scaffolds are effective in modulating Schwann cell behavior (Idini, 2019) and can stimulate secretion of neutrophins such as brain-derived neurotrophic factor, neurotrophin 3 and nerve growth factor that aid in nerve repair (Taylor, 2004). These modulate the proliferation, differentiation, migration, or myelination of Schwann cells resulting in accelerated repair and regeneration of nerves and improved recovery of motor and sensory function in tissues (Alhamdi, 2025). An electroconductive self-healing hydrogel has been developed that stimulates the expression of genes and proteins that promote Schwann cell myelination by activating the interleukin 17 (IL-17) signaling pathway (Xuan, 2023). This hydrogel has been injected directly into rat sciatic nerve-crush injury sites and was highly effective in the promotion of nerve regeneration and functional recovery of neural activity (Xuan, 2023).

All cells are responsive to electrical stimulation to some degree and this can also be incorporated into tissue repair strategies (Dai, 2021; A. Hayes, Melrose, J., 2020; Hoare, 2016). Neural cells are highly responsive to electrical stimulation, development of electrochemical hydrogels in tissue engineering of neural tissues has shown that these stimulate neural outgrowth aiding in the repair or regeneration of neural tissues (Xu, 2018).

The positive stimulatory response elicited by electrical potentials on bone cells in repair processes is a particularly well known example of such electrical phenomena in action. Bone tissue consists of apatite crystals embedded in an organic matrix, which upon compression exhibits piezoelectric properties [Greek piezein, “to squeeze or press”, and piezo, which means “push”]. Like many other multicrystalline structures, upon mechanical loading this generates an electrical potential which acts as a driving force stimulating bone cell metabolic activity, bone remodeling and repair processes (Fukada, 1957; Marino, 1970; Shamos, 1963). Electrical signals represent an essential form of cellular communication and for decades electrical stimulation has been used effectively in clinical practice to enhance bone healing (Baek, 2022; Guillot-Ferriols, 2022).

THE POTENTIAL OF KS TO IMPROVE THE PROPERTIES OF ELECTROCONDUCTIVE HYDROGEL COMPOSITES FOR REPAIR OF NEURONAL TISSUES

Cells communicate with each other, and with their surrounding ECM using metabolically driven electrochemical signals (Koo, 2023). Cell-ECM communication provides guidance cues to neurons during the development of neural networks (J. Melrose, Hayes, AJ, Bix, G. , 2021). These signals are generated by ions passing back and forth through cell membranes and these play a key role in the regulation of cellular functions during tissue

development, ECM remodeling during healing responses, and in tissue regeneration. CNS/PNS proteoglycans have important electronic roles in tissue development and homeostasis (J. Melrose, 2024a). KS-proteoglycans have particularly important roles to play in such processes (J. Melrose, 2025a). The KS component of these proteoglycans conveys cell regulatory activity and synaptic neuronal control of cellular interactions and synaptic plasticity (J. Melrose, 2024b; J. Melrose, 2025).

Mesenchymal stem cells have long been known to have tissue reparative and regenerative potential (Barry, 2004; Caplan, 2007). Stem cells are also responsive to electrical stimulation (Heng, 2020) and this has been investigated as a means of guiding these to a neuronal phenotype appropriate for the repair or regeneration of neuronal tissues (Eftekhari, 2023; Esmaeili, 2022). Electrical stimulation within a conductive scaffold promotes the differentiation of stem cells toward a neuronal phenotype leading to improved stem cell-based regenerative therapies and functional recovery of peripheral nerves (S. Song, McConnell, KW, Amores, D, Levinson, A, Vogel, H, Quarta, M, Rando, TA, George, PM. , 2021). Electrical stimulation has also been used therapeutically to directly stimulate tissues (A. Hayes, Melrose, J., 2020) and the central nervous system to promote repair responses (Benabid, 2005).

The development of high-resolution neuroprosthetics has led to the development of electroconductive polymer hydrogel composites for therapeutic electrostimulation of target cells (Mario Cheong, 2014). However, these composites are largely composed of synthetic polymers that have limited biorecognition properties for ECM and cellular components limiting their biointegration in repair tissues and thus repair capability to some degree. Incorporation of bioactive cell-recognition molecules in electroconductive hydrogels has been proposed as a means of improving these biomatrices. KS may be useful in the enhancement of the repair properties of such synthetic electroconductive hydrogels by providing better biorecognition properties. KS is a highly interactive GAG with ECM components and bioactive growth factors and neuroregulatory proteins and through these it also has cell instructive properties (J. Melrose, 2019b, 2024b; J. Melrose, 2025). Variably sulfated regions in KS define its interactive properties with ligands such as growth factors, morphogens and cytokines which determine the instructive properties conveyed by KS-proteoglycans (J. Melrose, 2019a, 2025a).

CONCLUSIONS

KS is a multifunctional cell instructive electroconductive GAG which can participate in electrochemical stimulation of cells and has directive roles not only in tissue development but also in ECM remodeling in tissue repair responses. KS is abundant in brain tissues and has important roles in the electrochemical regulation of neuronal activity in neurotransductive events that regulate tissue functional properties. Bioelectricity is a universal signaling cue in living organisms (G. Zhang, Levin, M. , 2025) and has roles in wound healing and regenerative processes (Tyler, 2017) and may be useful in bioelectronic therapeutics in health care (Garg, 2025). A greater understanding of how KS acts as the “vital-spark” in bioelectric cell regulatory phenomena may be insightful into how strategies in tissue repair may be improved.

ACKNOWLEDGEMENTS

This study was funded by The Melrose Personal Research Fund, Sydney, Australia. Previous collaborations with Prof B. Caterson and Dr AJ Hayes, University of Cardiff, UK were highly constructive and aided significantly in the development of background material that initiated this review. The Queensland brain institute, Brisbane, Australia are thanked for kindly supplying the neural network image used in the graphics abstract.

FINANCIAL DISCLOSURE

JM has received consultancy fees from Arthropharm-Fidia Pharmaceutics, Sydney. This company had no input into the content or interpretation of data presented in this review or the reason to publish.

CONFLICT STATEMENT

The author has no competing interests to declare that are relevant to the content of this article.

DATA AVAILABILITY

All data supporting the findings of this study are available within the cited papers of the bibliography.

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Cite this article as: Melrose J, Keratan Sulfate: An Electroconductive Proton Capture Glycosaminoglycan Regulator of Neuronal Membrane Polarization, Ion Fluxes, Neuronal Activation and Neurotransduction, Glob. Open Access J. Sci, 2025; 1(2):114-132..