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Review article

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Glia of the heart's nervous system

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Abstract

The heart adapts to changing physiological demands through bidirectional interactions with the brain. These are mediated via extensive feedback loops of the cardiac autonomic nervous system, a complex network of neurons and glial cells. Although the presence of glia in the heart and its nervous system has been known for decades, only recently has an understanding of their contribution to cardiac physiology and pathophysiology emerged. As new types of cardiac glia are discovered, it becomes evident that they represent heterogeneous cell populations in distinct anatomical locations of the cardiac nervous system, contributing not only to autonomic control of the healthy heart but also to pathological changes in the diseased heart.

Sections

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Introduction

Initially introduced in the brain in the mid-nineteenth century by the pathologist Rudolf Virchow, the term 'glia' originates from the Greek word for 'glue'[1]. These cells are now accepted to be more than glue; the myelination of axons by glial cells in the peripheral nervous system (PNS) is considered one of the major steps in vertebrate evolution[2]. The term 'glia' is an umbrella term for numerous heterogeneous types of cell found all across the central, peripheral and enteric nervous systems[3–5]. Glia have long been renowned for their well-established core functions: supporting neuronal survival and homeostasis; contributing to nervous system development and synaptogenesis; providing energy support to axons[6]; and, importantly, supporting reinnervation after peripheral nerve injury[7,8]. However, recent studies have revealed new, organ-specific functions of peripheral glia, such as sensory processing of pain and touch in the skin[9–11], intestinal homeostasis and immune regulation in the enteric nervous system[12,13], and modulation of autonomic control of the heartbeat[14–16].

Glia in the heart were first described more than 50 years ago in electron microscopy studies in rodents[17,18] and humans[19–21], but characterization of the non-myocyte cardiac cell composition has long focused on its major populations, including fibroblasts, endothelial cells and immune cells[22,23]. Nowadays, state-of-the-art transcriptomic approaches allow us to explore the cellular landscape of the heart in greater detail, highlighting the presence of functionally important but rarer cell types such as neurons and glia, which are often found in close association with each other[24–27] (Fig. 1). Although the role of the autonomic nervous system for modulation of cardiac rhythm and function is well established and subject to investigation in health and disease[28,29], its neurons have traditionally been the focus rather than their glial counterparts. Recent studies are now providing more insights into glia of the heart and its nervous system, and specific functional roles are starting to emerge, such as regulation of cardiac nerve development[15,30], release of neurotrophic factors by glial cells upon neuronal injury in the heart[14], interaction with cardiac innervation to regulate the heart rate[16] and, potentially, even contribution to rhythmogenesis modulated via signalling molecules[17].

This Review explores the roles of different types of glial cell as an integral part of the cardiac nervous system and their physiological impact on cardiac autonomic control. We further discuss their involvement in cardiac arrhythmias, investigate potential clinical applications and assess open questions, such as the emerging role of glia in cardiac repair processes.

The intracardiac nervous system and its glial cells

The heart is a richly innervated organ that is connected to and interacts with the brain via sympathetic and parasympathetic efferents and

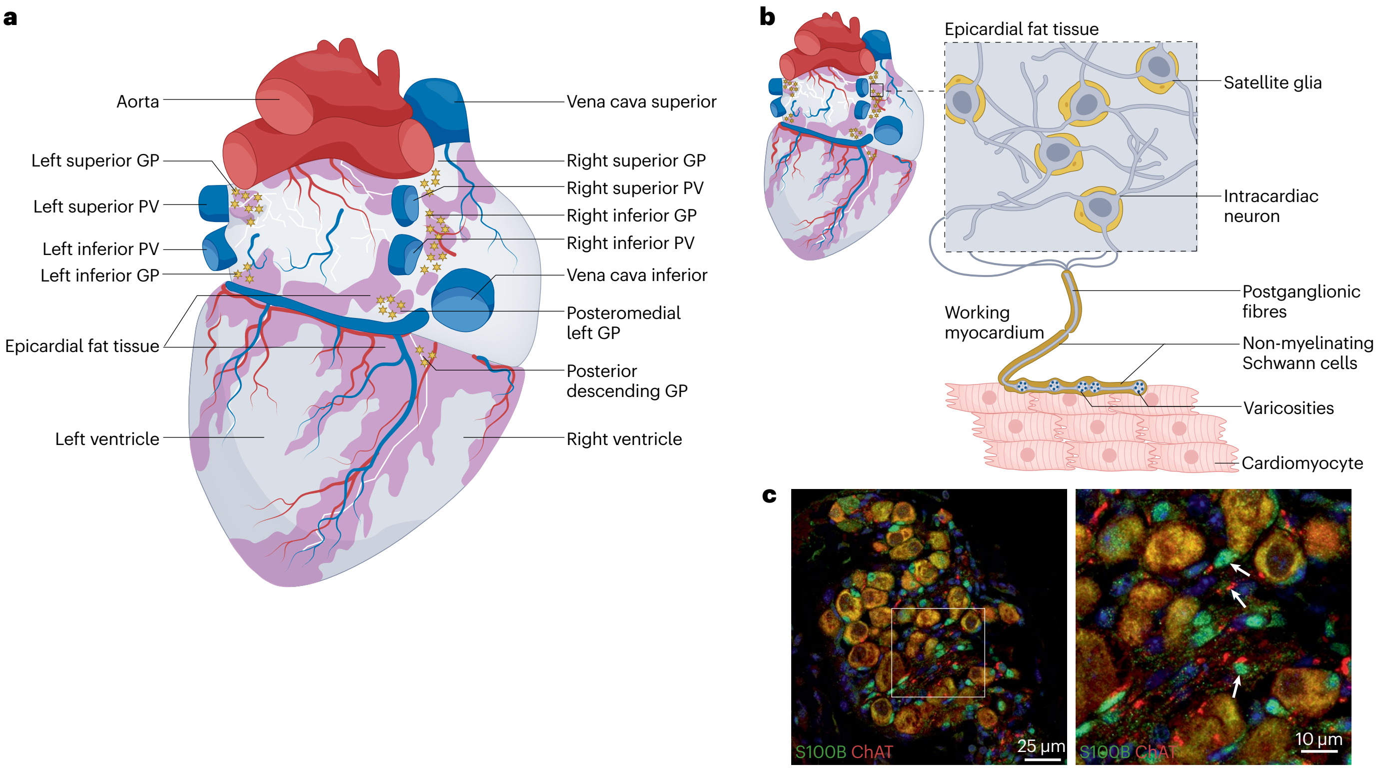


Fig. 1 | The 'little brain of the heart'. a, The intracardiac nervous system is composed of predominantly cholinergic ganglia organized into ganglionated plexi (GP). Most ganglionated plexi are located in the fat tissue surrounding the atria (epicardial fat) near the pulmonary veins (PV). The position of these central intracardiac relay stations on the posterior side of the heart is indicated (yellow asterisks). **b**, Different types of glial cells are associated with cardiac innervation – for example, satellite glia surrounding neuronal soma in an intracardiac ganglion (inset), and non-myelinating Schwann cells that ensheath intracardiac nerve fibres. These fibres provide postganglionic input to the working myocardium by releasing neurotransmitters from synapse-like varicosities. **c**, Immunohistological staining of a human intracardiac ganglion. Satellite glia, marked by expression of the glial marker S100 calcium-binding protein B (S100B) (green; labelled with white arrows in magnification (right panel)), surround cholinergic neuronal soma, marked by choline acetyltransferase (ChAT) (red). Part **c** modified with permission from ref. 14, AAAS.

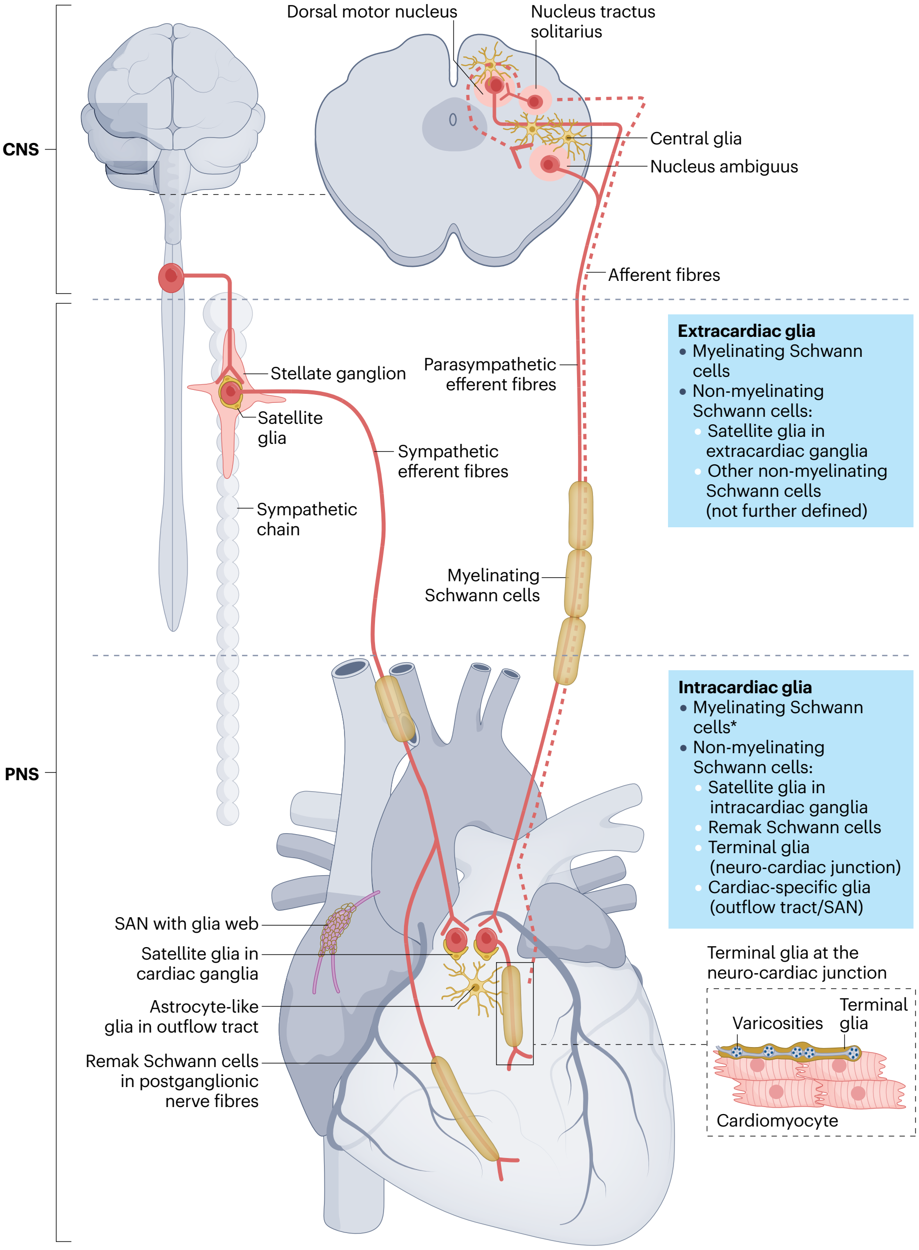


Fig. 2 | Glia of the cardiac autonomic nervous system. Different types of glial cell (yellow), associated with neuronal soma and nerve fibres (red), are present throughout the whole CNS and peripheral nervous system (PNS), including key regions for cardiac autonomic regulation. The dorsal motor nucleus and the nucleus ambiguus (the origin of parasympathetic preganglionic fibres) and the nucleus tractus solitarius (integration of afferent input) are located in the medulla oblongata of the brainstem (upper panel). The stellate ganglia are part of the sympathetic trunk and mediate sympathetic input to the heart (middle panel). Various non-myelinating Schwann cells have been found in specific cardiac locations: Remak glia along postganglionic fibres; satellite glia within intracardiac ganglia; terminal glia at the neuro-cardiac junction; and specialized, cardiac-specific glia such as astrocyte-like cells in the outflow tract (major vessels transporting blood to the pulmonary and systemic circulation) and an interstitial network between pacemaker cells of the sinoatrial node (SAN) (bottom panel). The SAN is located on the posterior side, as are most intracardiac ganglia. *The presence of myelinating Schwann cells has been demonstrated in the human but not the mouse heart[21,39].

sensory afferents[28,31] (Fig. 2). As is characteristic for the PNS, sympathetic neuronal soma are assorted into ganglia that are located away from the target organ within the sympathetic chain, whereas parasympathetic neuronal soma are located in ganglia in close proximity to the target organ. The number of these – predominantly, but not exclusively – cholinergic neurons in the adult human heart is only around 43,000 cells assorted into 700–1,500 ganglia[32]. Accumulations of these ganglia, so-called ganglionated plexi, are often described as the ‘little brain of the heart’ and located primarily within atrial epicardial fat tissue (Fig. 1a), whereas few are found on the ventricular level and in the myocardium[32,33]. In general, the autonomic nervous system is essential for maintaining physiological functions of the heart[31,34,35], whereas the intracardiac nervous system acts as a functional relay station to convey signals from the brain and via the large and small axons innervating the atrial and ventricular conduction system and working myocardium[31,36,37].

The importance of glia in the heart was recently highlighted by findings from the Human Heart Cell Atlas[25,26]. In this extensive single-cell transcriptomic analysis of human cardiac cell types, the first version annotated a cluster consisting of neuronal cells[26]. This interpretation was recently revised, finding that cells in this cluster lack core neuronal genes and instead express typical pan-glial genes[15,26]. The ‘neuronal cell cluster’ is now considered to represent exclusively different populations of glial cells[26], a finding consistent with the cardiac regions from which the samples were obtained, where glia would be expected but no neuronal soma: although glial cells can be found in cardiac ganglia (Figs. 1 and 2), they are mostly surrounding larger and smaller nerve fibres and bundles and are found between cardiomyocytes, where they are associated with the delicate autonomic nerve fibres that innervate the myocardium[14,18,38]. In the following sections, we summarize and examine the different glial cell types in the heart and its nervous system. These can be categorized by their anatomic location – central, peripheral and intrinsic cardiac components – as well as the specific type of glial cell, as visualized in Fig. 2.

Myelinating Schwann cells

Probably the best-known type of peripheral glial cell is the myelinating Schwann cell. These cells fill the niche of oligodendrocytes from the CNS, providing insulation of axons for improved electrical conduction – one of the key concepts in neurophysiology[2]. Myelinating Schwann cells are in constant communication with the axon they ensheath and are essential for axonal integrity[2]. Although they are highly relevant for proper electrical conduction in the large nerve fibres from the brain to the heart (Fig. 2), within the human heart itself myelinating Schwann cells are found only unevenly distributed within intracardiac nerves[21,39,40]. In general, cardiac nerve fascicles have been found to contain small unmyelinated (approximately 1.5 µm) and larger myelinated (approximately 2.6 µm) axons that are individually wrapped by Schwann cells separating them from neighbouring dendritic processes and surrounded by a collagen matrix[21]. Of note, in the mouse heart only non-myelinating Schwann cells have been described to date[18,38,41] (also see literature overview in Table 1), indicating potential species-related differences. Given that axon calibre is a primary determinant of myelination[42], the absence of myelinated axons in the mouse heart might be attributed to the size of the axons present. This differs in rats, where myelinating Schwann cells were shown to be present in the heart[43,44]. The ratio of myelinated to unmyelinated fibres in the epicardium is approximately 1:10 (ref. 43), but a recent transcriptomic study of the rat heart found that the majority of myelinating Schwann cells are actually located in the myocardial sleeves of the pulmonary veins and in sinus and atrioventricular nodes[44].

Non-myelinating Schwann cells

All other forms of peripheral glia are considered non-myelinating Schwann cells with functions far more diverse than those of their myelinating counterparts. Although often collectively only referred to as non-myelinating Schwann cells, these cells can be distinguished into several types that differ anatomically, morphologically and functionally, as recently summed up by Reed et al. for the whole PNS[45]. In the following sections, we will be focusing on those types of non-myelinating Schwann cells which have been observed in the heart and its nervous system. These include satellite glia, Remak Schwann cells, terminal (also perisynaptic) Schwann cells, which are depicted in Fig. 2, and cardiac-specific types addressed only in individual studies to date.

As in all other peripheral ganglia, satellite glia – a specialized subtype of glia wrapping around neuronal cell bodies – are present in the atrial intracardiac ganglia of mouse and human hearts[21,41] (as shown by the immunohistological staining in Fig. 1c). They are commonly marked by expression of anti-brain fatty acid-binding protein (B-FABP; also known as FABP7) (see Fig. 3 for an overview of commonly used markers). Satellite glia provide nutrients to 'their' neuron, but they also have specific roles depending on the need of the neurons they are associated with[4,46]. Although there is little information on the role of satellite glia, specifically in intracardiac ganglia, it has been suggested that they are important for establishing cholinergic innervation of the heart[41]. This is supported by the fact that parasympathetic neurons also derive from Schwann cell precursor cells during development[47,48], a phenomenon which has not been studied in the adult cardiac nervous system to date.

Remak Schwann cells are a type of non-myelinating Schwann cell of the PNS ensheathing small-calibre axons, such as slowly conducting group C-type fibre axons, including sensory and autonomic axons, forming so-called Remak fibres. They fulfil the role of myelinating Schwann cells in larger axons, and are in general smaller than their myelinating counterparts but make up a greater percentage[45,49]. Of note, they still share markers with Schwann cell precursor cells and, besides ensheathing axons in the healthy state, they have the ability to react to nerve injury by adaption to a repair phenotype, which is discussed below[49]. In the heart, data on these cells and their role are sparse, but genetic depletion of Remak cells (marked by periostin expression) during development was shown to lead to reduced sympathetic cardiac nerve fibre fasciculation (the process of bundling of axons from different neurons to form large nerves) in mice[30]. This indicates that cardiac Remak Schwann cells contribute to the maturation of cardiac innervation during development.

Terminal Schwann cells, also named perisynaptic glia[50], are very well studied at the neuromuscular junction of the skeletal muscle, where a large body of evidence points towards a role of these cells in synaptic transmission[50,51]. The concept of the tripartite synapse – the interaction of a presynaptic neuron, a postsynaptic target and a terminal glial cell – was initially used for astrocytes in the brain, later adapted to the neuromuscular junction and recently also proposed for the heart[52]. It is very likely that there are functional similarities between terminal glia at the neuro-cardiac junction (also called the cardiac neuroeffector junction[53]) and the neuromuscular junction, where their main function is to release chemicals and neurotrophic factors[3,54]. One specific example for a regulatory neuro-glial feedback loop that could also be relevant in the heart is the release of neuregulin 1 from axons of the neuromuscular junction upon release of the neurotrophic factors BDNF and GDNF by terminal Schwann cells[55]. Neuregulin 1 – originally termed 'glial growth factor' – is expressed by central and peripheral neurons and is key to Schwann cells and their precursors, as it promotes growth, survival, migration, differentiation and myelination[56]. Of note, neuregulin signalling is also important in heart development and cardiac remodelling[57,58].

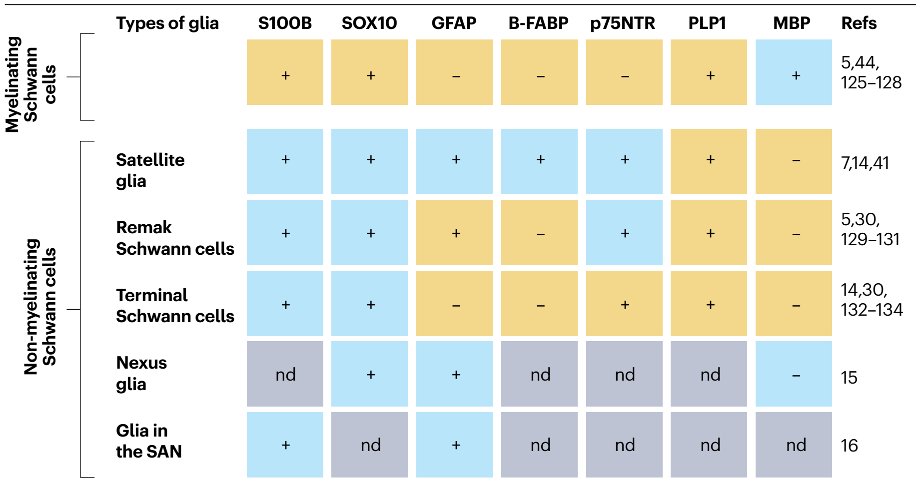
With organ-specific glia, for example in the skin and the gut[45], it is not surprising that new types of (non-myelinating) glia are also being discovered in the heart. Specifically, glia with a morphology resembling astrocytes (specific for the CNS) and expressing markers typically found in astrocytes (such as glial fibrillary acidic protein (GFAP)) were recently described for the first time[15]. These cells, termed nexus glia, were functionally characterized in the cardiac outflow tract, the region where blood leaves the ventricles, but transgenic evidence from this study suggests the presence of similar populations in other areas of the heart as well[15]. Experimental evidence in the zebrafish heart indicates that they delay axonal outgrowth in early developmental stages[15]. Additionally, they have been shown to regulate the heart rate by interacting with sympathetic and parasympathetic innervation, as their depletion in zebrafish abolishes the chronotropic effects of sympathetic and parasympathetic agonists[15]. Also recently, another new type of non-myelinating glial cell was discovered in the sinoatrial node (SAN), potentially contributing to the generation of every single heartbeat: an interstitial web of glia is located between pacemaker cells and was shown to interact with different cell types, including autonomic neurons and the conduction system, forming an anatomical unit[16].

Table 1 | Morphological, transcriptional and functional studies on intracardiac glia in mice and men

Year	Type of glial cell	Location in the heart	Main finding on glial cells	Type of study	Species	Ref.
1969	Non-myelinating Schwann cells	Atrial and ventricular myocardium	Nerve bundles of the atria and ventricles are partially ensheathed by non-myelinating Schwann cells	Morphological	Mouse	18
1970	Non-myelinating Schwann cells	Atrioventricular node	The atrioventricular node contains non-myelinating Schwann cells	Morphological	Mouse	38
1970	Schwann cells (not further classified)	Ventricular myocardium	The axonal varicosity is sheathed by a thin layer of Schwann cell cytoplasm	Morphological	Human	19
1997	Myelinating and non-myelinating Schwann cells	Atrial and ventricular intracardiac ganglia	In the human heart, myelinating and non-myelinating Schwann cells ensheath axons and satellite glia in cardiac ganglia	Morphological	Human	21
2000	Myelinating and non-myelinating Schwann cells	Atrial and ventricular epicardial nerve fibres	The authors characterize, in detail, nerve fibres and bundles of the heart and their association with myelinating and non-myelinating Schwann cells	Morphological	Human	39
2012	Satellite glia, Schwann cells (not further classified)	Intracardiac ganglia, atria, atrioventricular node, SAN, ventricles	Satellite glia and Schwann cells[a] in intracardiac ganglia are present in embryonic development, suggesting a role for development of cardiac innervation	Morphological	Mouse	41
2014	Non-myelinating Schwann cells	SAN	Non-myelinating Schwann cells incompletely envelop fibres in the SAN	Morphological	Mouse	123
2018	Schwann cells (not further classified)	Ventricular myocardium	The murine ventricles contain a relatively homogeneous population of Schwann cells[a]	Transcriptional	Mouse	24
2019	Cardiac glia (not further classified), intracardiac satellite glia	Whole hearts, intracardiac ganglia, atrial myocardium, intracardiac nerve fibres	Glia (satellite glia and Schwann cells) accompany every nervous structure in the heart, releasing neurotrophic factors upon myocardial neuronal damage, which modulates neuronal activity and outgrowth in vitro	Functional Morphological	Mouse Human	14
2020	Schwann cells (not further classified)	Right and left atrium, right and left ventricle, septum and apex	The authors used MBP, PRX and MPZ to define Schwann cells[a] within the neuronal subcluster	Transcriptional	Human	25
2021	Remak Schwann cells	Whole heart	Remak Schwann cells in the heart contribute to nerve fasciculation during postnatal development	Functional Morphological	Mouse	30
2021	Nexus glia (novel term)	Outflow tract, ventricular myocardium	A cardiac-specific astrocyte-like subtype (nexus glia) located in the outflow tract interacts with sympathetic and parasympathetic function	Functional Morphological	Mouse Human Zebrafish	15
2022	Glia (not further classified)	SAN	A cardiac-specific web of glial cells in the SAN contributes to calcium signalling and initiation of the heartbeat	Functional Morphological	Mouse	16
2023	Schwann cells	Right and left atrium, right and left ventricle, septum and apex, SAN, atrioventricular node	The neuronal subcluster from Litviňuková et al.[25] was revised as glial due to expression of pan-glial markers	Transcriptional	Human	26
2024	Schwann cells (not further classified)	Atrial and ventricular myocardium, conduction system	A reduction in the number of Schwann cells[a] (and nerve fibres) and a higher susceptibility to ventricular arrhythmias are detectable in ageing hearts	Functional Morphological	Mouse	93

MBP, myelin basic protein; SAN, sinoatrial node. [a]Not differentiated into myelinating and non-myelinating Schwann cells.

These cells express GFAP, but also S100 calcium-binding protein B (S100B), a common – but not exclusive – marker for central and peripheral glial cells[59]. Of note, different kinds of glia also release S100B, which has various functions such as neurotrophic activity[14], modulation of neuronal activity[14,60] and calcium-binding properties[59,61]. The latter might be the reason why the glial network in the SAN generates and processes calcium oscillations, leading to increases in variability of the heart rate and cycle length upon treatment with S100B. Even though



	Types of glia	S100B	SOX10	GFAP	B-FABP	p75NTR	PLP1	MBP	Refs
Myelinating Schwann cells		🟧 +	🟧 +	🟧 –	🟧 –	🟧 –	🟧 +	🟦 +	5,44,125–128
Non-myelinating Schwann cells	Satellite glia	🟦 +	🟦 +	🟦 +	🟦 +	🟦 +	🟧 +	🟧 –	7,14,41
	Remak Schwann cells	🟦 +	🟦 +	🟧 +	🟧 –	🟦 +	🟧 +	🟧 –	5,30,129–131
	Terminal Schwann cells	🟦 +	🟦 +	🟧 –	🟧 –	🟧 +	🟧 +	🟧 –	14,30,132–134
	Nexus glia	nd	🟦 +	🟦 +	nd	nd	nd	🟦 –	15
	Glia in the SAN	🟦 +	nd	🟦 +	nd	nd	nd	nd	16

Fig. 3 | Established subtypes of intracardiac glia and commonly used markers. Overview of commonly used markers for different subtypes of intracardiac glia. Data derived from studies on cardiac glia (blue) and from studies on (non-cardiac) peripheral glia (orange)[5,7,14–16,30,41,44,126–135], or study data are not available (grey). +, marker is expressed; –, marker is not expressed. B-FABP, anti-brain fatty acid-binding protein (also known as FABP7); GFAP, glial fibrillary acidic protein; MBP, myelin basic protein; nd, no data; $p75^{NTR}$, p75 neurotrophin receptor; PLP1, proteolipid protein 1; SAN, sinoatrial node; SOX10, SRY-box transcription factor 10; S100B, S100 calcium-binding protein B.

the underlying mechanisms are still unresolved, this study indicates that a specific type of glial cells in the sinus node might contribute to the local calcium oscillations that initiate each heartbeat, potentially contributing to stability of the heart rhythm[16]. Of note, the authors also discovered a different 'glia-like' cell population in the SAN associated with pacemaker cells and other cell types. These cells express S100B, but not GFAP, and some of them appear to have vesicles which are secreted into the interstitial space[16], again indicating a modulation of SAN function.

These findings underscore the existence of diverse intracardiac glial subtypes with distinct functions, many of which remain to be fully characterized. Table 1 sums up all studies since their first description 55 years ago. It becomes evident that there is a focus on morphological studies in the healthy heart, and functional data indicate that glia have a role in nerve development and neuronal–myocardial signal processing. Figure 4 sums up the current understanding of functional insights into intracardiac glia and their interaction with cardiac neurons. The underlying mechanisms and pathways, but also functions specific to certain subtypes, need further study. However, there are technical limitations when studying cardiac glia: they make up only a small proportion of the cells in the heart and to date there are no markers to distinguish intracardiac glial cells from other peripheral glia.

Physiological roles of peripheral (extracardiac) glia in the heart

Heart rate, rhythm and function are constantly modulated by the different branches of the autonomic nervous system: sympathetic and parasympathetic efferents and sensory afferents transmit communication between the brain and the heart[31,62] (Fig. 2). In general, functions of satellite glia in sympathetic and sensory ganglia are better studied than in parasympathetic ganglia and include contributions to pain sensation, synaptic transmission and metabolism[4,63]. They provide metabolic and trophic support for neurons, buffer extracellular fluid via expression of potassium channels, control the microenvironment of the associated neuron, promote synapse formation and influence neurotransmitter synthesis[64–66]. As one of the key centres for mediating sympathetic input to the heart, there is now also growing evidence that satellite glia in the stellate ganglia (Fig. 2) can also modulate cardiovascular function. Notably, these glia are not homogeneous but, rather, consist of several different subpopulations with the potential for dynamic adaptations to changes in the neuronal requirements[67]. Two of these populations, described by van Weperen et al., make up more than half of the cells and express genes associated with mature astrocytes such as GFAP[67]. Interestingly, a study in rodents has shown that increased activity of GFAP-expressing glia in sympathetic ganglia leads to subsequent increases in the heart rate and left ventricular contractility (ejection fraction and fraction shortening)[68]. This indicates a potential function for these cells in cardiac control, but it must be considered that the authors used DREADD (designer receptor exclusively activated by designer drugs) technology, resulting in a non-physiological depolarization of glia in response to a designer drug to increase their activity[68]. The authors hypothesize that the subsequent effects are mediated by sympathetic neurons, as they are accompanied by an increased release of norepinephrine from cardiac sympathetic fibres and subsequent β_1-adrenergic receptor activation in the heart[68]. This might indicate that glia are acting hand in hand with their neuronal teammates. Mechanistically, there are also growing data that satellite glia contribute to local cholinergic regulatory circuits within sympathetic ganglia[69] and regulate firing rates of sympathetic neurons[66]. As autonomic neurons of the different branches of the autonomic nervous system differ regarding neurotransmitters and protein expression[53], the same can be expected for glial cells, especially given their high level of heterogeneity. Importantly, although satellite glia are present in all peripheral ganglia, gene expression patterns of sensory ganglia-specific and sympathetic ganglia-specific satellite glia have been reported to differ according to the needs of their respective neurons[63]. Also, the constitution of glia differs: Schwann cells are scarce in sympathetic ganglia compared with sensory ganglia[63].

Taken together, these findings show that glia of the extracardiac autonomic nervous system do not represent one unique population but show different phenotypes depending on the neurons they are associated with, and have the potential to modulate cardiac function.

Physiological effects of central glia on the heart

Key centres for central regulation of cardiac autonomic control are located in the brainstem (pons, medulla oblongata)[62]. In particular, the role of motor neurons of the nucleus tractus solitarii (NTS), an afferent integration station for cardiovascular reflexes, is well established. But the CNS consists in equal proportions of neurons and glia[6,70], the latter presenting not one but several different types of cell such as, in decreasing order, astrocytes, oligodendrocytes and microglia making up the biggest populations[6,70]. Astrocytes have been shown to contribute to numerous functions in the brain from metabolic support to altering neuronal activity[6]. Thus, it is not unexpected that there is evidence that astrocytes in the NTS contribute to cardio-neuronal reflex control[71,72]. Damage of NTS astrocytes – with intact neurons – was shown to lead to an attenuation of key elements of haemodynamic homeostasis such as the baroreflex, chemoreflex and von Bezold–Jarisch reflex[73]. The extent of these effects is comparable with the results of damage to neurons of the NTS themselves, demonstrating an important role of central glia in the physiology of cardiac autonomic control. This is further strengthened by the fact that astrocytes of the NTS also react to changes in autonomic input. Dissection of the vagal nerve and subsequent removal of afferent input leads to differences in not only astrocyte morphology but also microglial morphology, number and activation[74]. Vice versa, stimulation of the vagal nerve to increase its activity induces the release of adenosine triphosphate from NTS astrocytes, which then subsequently modulates sensitivity of the baroreflex via purinergic receptor signalling[75]. These data show that glial cells of the CNS contribute to cardiac reflex control and react to autonomic stimulation.

Glia in pathophysiology

Cardiac arrhythmias are associated with remodelling of the autonomic nervous system, such as an increase in sympathetic tone and a decrease in parasympathetic tone, induced by physiological (for example, ageing[76]) and pathophysiological (for example, hypertension[77], heart failure[34,78], myocardial infarction[79], diabetes[80,81]) changes. Neuronal remodelling is well known to take place on all levels of cardiac autonomic innervation but, more recently, similar findings have been elucidating glial cells in the context of arrhythmias, which will be discussed in the following.

In the CNS, astrocytes have been described to undergo morphological and molecular remodelling, a process called 'reactive astrogliosis', in response to pathological conditions[82]. This process includes changes in shape, size (hypertrophy) or number of glial cells and, interestingly, upregulation of GFAP expression is its most widely used marker[82]. Astrocytes lose some functions (for example, for homeostasis) and gain others (for example, neuroprotective), which can be beneficial or harmful for the specific disease depending on the specific changes[82]. Although acutely neuroprotective, this state might also negatively regulate neuronal plasticity[83,84]. In the PNS, glial remodelling and increased glial activity can also be induced by pathophysiological changes. Astrogliosis has been shown to be pro-arrhythmic in several studies: in autonomic control centres in the CNS, damage of NTS astrocytes without neuronal damage leads to various rhythm disorders; ventricular arrhythmias (extrasystoles and runs), but also bradycardia, asystole and sudden death[73]. Increased glial activity in the paraventricular nucleus of the hypothalamus – one of the central control regions for sympathetic activity – has been shown to accompany an increase in ventricular arrhythmias after myocardial infarction[85]. Chemical inhibition of glial activity in this region also reduces arrhythmias and improves ventricular electrical stability[85]. This indicates that increased glial activity contributes to the pathological increase in sympathetic tone that contributes to the generation of arrhythmias.

Activation of satellite glial cells, along with increases in GFAP expression, inflammation and oxidative stress, is present in the stellate ganglia – one of the key relay stations of the sympathetic nervous system – of patients with ventricular arrhythmias compared with individuals with healthy hearts[86]. This reactive state was also inducible by myocardial infarction in the stellate ganglia and dorsal root ganglia in experimental models[87]. Interestingly, this can be counteracted by chronic vagal stimulation. This not only stabilizes electrical heterogeneity in vivo by normalizing myocardial repolarization, and reduces the potential for ventricular arrhythmias, but also suppresses satellite glial activation[87]. As mentioned earlier, the DREADD-mediated increase in activity of GFAP-expressing satellite glia in genetically modified mice leads to an increased noradrenaline release in the heart[68]. Importantly, this study indicates that the increased activity of these specific glial population is not only a reaction to the pathophysiological processes in the heart, but actively contributes to them by increasing sympathetic tone.

Other typical cardiac comorbidities that are associated with increased sympathetic tone, such as diabetes, are also often found to accompany pathological changes in satellite glial cells of the stellate ganglia[88,89]. Indeed, experimental studies have shown increased expression and activity of purinergic receptors in diabetic rats[88,89]. Although the role of purinergic receptors in this context still has to be studied in detail, reducing their expression leads to decreases in blood

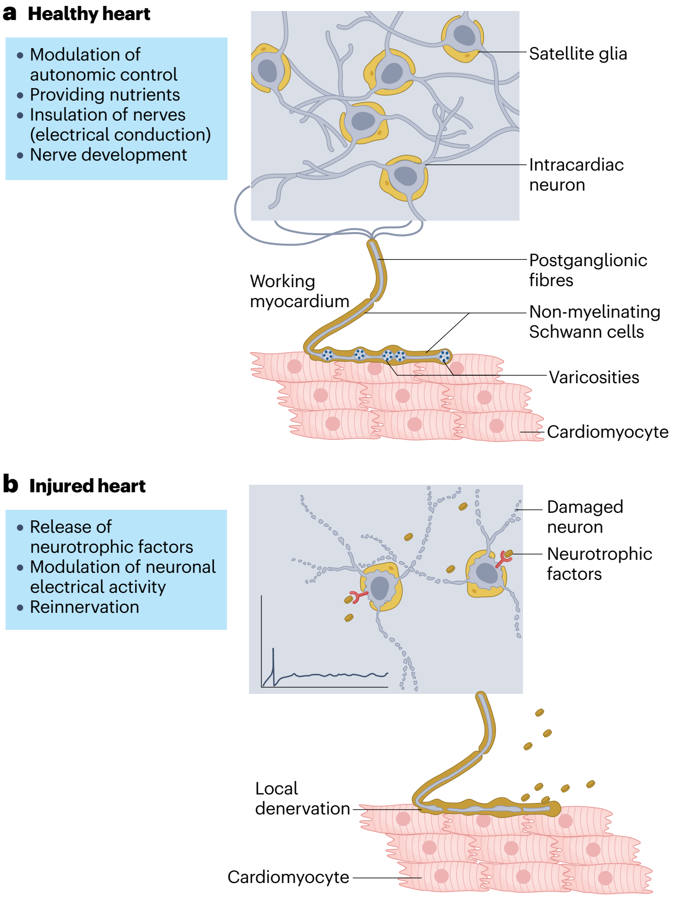


Fig. 4 | Current understanding of the functional roles of intracardiac glial cells and their interactions with neurons. a, In the healthy heart, different types of glial cell interact with neuronal soma and fibres and contribute to various functions. **b**, In the injured heart, intracardiac neuronal damage (for example, due to local denervation) leads to the release of neurotrophic factors from intracardiac glia (probably satellite glia and terminal glia).

pressure, heart rate and heart rate variability as well as sympathetic nerve activity[88,89], again connecting glial activity and a pathological increase in sympathetic tone.

Even though intracardiac glia have been studied to a lesser extent, it has been shown that removing the astrocyte-like glia from the heart leads to ventricular tachycardia and ventricular fibrillation in zebrafish, suggesting that their disruption is pro-arrhythmic. This effect is potentially mediated via their interaction with sympathetic and parasympathetic autonomic innervation[15]. But it should also be noted that the cardiac outflow tract, where these cells are located, is a clinically relevant origin for cardiac arrhythmias in the structurally healthy heart[90] and that neural crest-derived cells play an essential role in the formation of the outflow tract during embryonic development[91], potentially contributing to the predisposition to arrhythmias[92].

In the ageing heart, an increase in susceptibility to ventricular arrhythmias in vitro was observed together with a reduced number of Schwann cells and decreased autonomic innervation[93]. Interestingly, the restoration of intracardiac innervation with senolytics abolishes ventricular arrhythmias in aged mice[76]. Glia were not analysed in this study, so it remains unclear whether glial and nerve reduction go hand in hand or one entails the other, but as the role of peripheral glia in nerve regeneration has long been known[94], their function in ageing is also starting to emerge[95].

In addition, it was shown that cardiac glia release the neurotrophic factor S100B upon damage of intracardiac innervation in patients with atrial arrhythmias[14]. S100B is taken up by intracardiac neurons in vitro, probably via the receptor of advanced glycosylation end products (RAGE), and increases neurite growth[14]. Whether this uptake mechanism and its effects on neurite growth are definitively mediated by RAGE in this context remains an area for further investigation. Also, whether this potentially contributes to an increase in axonal sprouting in vivo, which is a pro-arrhythmic substrate[96], still needs to be determined. Of note, S100B also functionally modulates electrophysiological properties of parasympathetic neurons and the sinus node itself, but not the atrial working myocardium[14,16]. Another study has shown directly that glial cells can modulate the density of cardiac innervation and arrhythmia susceptibility: transplantation of Schwann cells isolated from the sciatic nerve led to an increase in the intracardiac parasympathetic/sympathetic nerve fibre ratio in a rat model of myocardial infarction[97]. This was accompanied by changes in functional parameters of cardiac innervation (heart rate variability) and a decrease in susceptibility to ventricular arrhythmias. Even though it remains unclear to what extent Schwann cells from the sciatic nerve resemble intracardiac glia, this indicates that glial cells could be a potential therapeutic target for treatment of cardiac arrhythmias.

Clinical applications for cardiac glia

The intracardiac nervous system is clinically highly relevant and addressed in translational and clinical approaches to treat atrial fibrillation, vasovagal syncope and other entities[98]. The fact that intracardiac glia act as a first responder to intracardiac nerve damage with the acute release of S100B, which can be measured in the blood[14,99], gives rise to diagnostic applications of glial cells. In patients undergoing catheter-based interventions for the treatment of atrial fibrillation, S100B was recently established as a surrogate marker for neuro-cardiac damage[14,99,100]. Several groups have compared the extent of neuro-cardiac damage with thermal and novel non-thermal energy forms that are used for the treatment of atrial fibrillation (see Table 2 for an overview of clinical studies)[101–103]. Even though glia in the heart clearly express and release S100B[14], astrocytes in the brain are one of its largest sources and S100B has also been used as a surrogate for the detection of central neuronal damage[104–106]. As a consequence, the application of glial blood-based measurements should be accompanied by appropriate controls and functional testing.

Interestingly, the glial growth factor neuregulin 1 has been tested for patients with heart failure in several clinical trials (phases I–III; see Table 2 for details)[107,108]. Intravenous treatment with different recombinant forms of neuregulin 1 was found to improve left ventricular function. Although a temporary reduction of nearly 50% in serum noradrenaline was found in one study[108], the impact of glia and cardiac innervation has unfortunately not been studied in this context.

Currently, clinical translation is still limited, but these studies highlight that there might be a future diagnostic and therapeutic potential for glial cells in cardiovascular disease. Whether or how glia can be used for autonomic neuromodulation in cardiac pathologies remains a subject for further studies.

Future directions — repair glia?

One of the most notable facts on the PNS is its intrinsic ability for regeneration after nerve injury, which is assisted by glial cells[109]. In the heart, reinnervation after injury (also known as nerve sprouting) has been a well-established phenomenon for decades, which is clinically highly important as it is a potential pro-arrhythmic mechanism[96,110,111]. The presence of Schwann cells together with sprouting nerve fibres has been described in human hearts from patients with arrhythmias[112]. Of note, GAP43, a protein which is upregulated in Schwann cells in the absence of axons, has been used in several studies to characterize the sprouting of nerves in the canine heart, indicating that glia might be present in cardiac nerve regeneration[110,113,114]. The release of neurotrophic factors by glial cells is probably an important underlying mechanism for this[14]. Open questions are currently remaining, such as whether repair Schwann cells (a repair phenotype that myelinating as well non-myelinating Schwann cells can redifferentiate into[45,49,115]) play a role in the heart. As terminal glia in the neuromuscular junction are also able to assume this repair phenotype[12,116,117], the same could hold true for glia at the neuro-cardiac junction, but the role of repair glia in the heart after injury, such as myocardial infarction, remains unclear to date and warrants further exploration.

The heart and its glia — methodological challenges and gaps in knowledge

Cardiac autonomic innervation is affected in many cardiac pathologies[118], as well in physiological processes such as ageing[76]. With current knowledge, it remains unclear whether glial cells play an active role in these conditions or are just passive bystanders. To elucidate this, a deepened knowledge of intracardiac and extracardiac glia is needed. State-of-the-art techniques such as single-cell RNA sequencing have been performed on extracardiac glia in the stellate ganglia[67,119], but not on intracardiac glia specifically. Although glia have been detected from cardiac tissue in RNA sequencing studies in mouse and men[24–26], they do make up a very small population of the total cell composition, which may result in their overall transcriptome not being fully captured. Enrichment of cells via cell sorting would therefore be recommended. Chemogenetic approaches such as DREADD technology[68,120] and optogenetic modulation[121] of cardiac autonomic innervation have already been shown to be helpful in uncovering first autonomic neuro(-glial) pathways and mechanisms in cardiac control. But they are currently limited by a lack of specificity for cardiac glia, as

Table 2 | Diagnostic and therapeutic clinical studies on glial cell and glial-derived factors

Application	Type of study	Study identifier	Condition	Study treatment	Patients	End-points	Publication year (ref.)
Diagnostic	Observational	NCT03388333	Arrhythmias	NA	*n* = 153 patients undergoing ablation of atrial fibrillation	S100B release for intracardiac neuronal damage, heart rate, arrhythmias	2019 (14)
	Observational	NCT03388333	Arrhythmias	NA	*n* = 73 patients undergoing ablation of atrial fibrillation (sub-analysis from ref. 14)	S100B release for intracardiac neuronal damage, heart rate, arrhythmias	2020 (99)
	Observational	NA	Arrhythmias	NA	*n* = 18 patients undergoing ablation of atrial fibrillation	S100B, GFAP, B-FABP, neurofilament light chain for intracardiac neuronal damage	2022 (102)
	Observational	NCT05521451	Arrhythmias	NA	*n* = 91 patients undergoing ablation of atrial fibrillation	S100B release for intracardiac neuronal damage, heart rate, arrhythmias	2023 (101)
	Observational	NA	Arrhythmias	NA	*n* = 97 patients undergoing ablation of atrial fibrillation	S100 [*sic*] release for intracardiac neuronal damage, silent cerebral emboli	2023 (103)
	Observational	NA	Arrhythmias	NA	*n* = 40 patients undergoing ablation of atrial fibrillation	S100 [*sic*] release for intracardiac neuronal damage, biomarkers for haemolysis, myocardial injury and renal function	2025 (124)
Therapeutic	Open label, not randomized, first in man	ACTRN12607000330448	Heart failure	Intravenous infusion with 1.2 μg kg^{-1} per day neuregulin 1β2 (Neucardin) daily for 11 days in ascending doses	*n* = 15 patients with chronic heart failure, NYHA II and III	Change in haemodynamics (acute and sustained; LVEF, left ventricular end systolic and diastolic volume), neurohormonal and immunological serum markers, safety and tolerability	2011 (108)
	Phase II, randomized, placebo controlled	NA	Heart failure	Intravenous infusion with 0.3, 0.6 and 1.2 μg kg^{-1} per day neuregulin 1β2 (Neucardin) peptide over 10 days	*n* = 44 patients with chronic heart failure, NYHA II and III	Change in haemodynamics (LVEF, left ventricular end systolic and diastolic volume) at baseline and days 11, 30 and 90	2010 (125)
	Phase I, randomized, placebo controlled	NCT01258387	Heart failure	Intravenous infusion with full-length neuregulin 1β3 (Cimaglermin alfa) in ascending doses	*n* = 40 patients with chronic heart failure, NYHA II and III	Safety; LVEF	2016 (107)
	Phase III, randomized, placebo controlled (status: ongoing)	NCT05949801, study completed October 2024	Heart failure	Intravenous infusion with 0.6 μg kg^{-1} per day neuregulin 1β2 (Neucardin) for 10 days	*n* = 198 patients with NYHA II–III chronic systolic heart failure (male: NT-proBNP ≤1,700 pg ml^{-1}; female: NT-proBNP ≤4,000 pg ml^{-1})	Change in haemodynamics (simultaneous reduction of left ventricular end systolic and diastolic volume) after 35 days	https://clinicaltrials.gov

B-FABP, anti-brain fatty acid-binding protein (also known as FABP7); GFAP, glial fibrillary acidic protein; LVEF, left ventricular ejection fraction; NA, not applicable; NYHA, classification of heart failure according the score of the New York Heart Association (I–IV); S100B, S100 calcium-binding protein B.

they express typical markers for peripheral glial cells (see Fig. 3), and specific targeting of cardiac glia is not yet possible.

To advance our understanding of cardiac glial cells, their developmental origin also needs to be clarified. In the PNS in general, non-myelinating Schwann cells originate from Schwann cell precursors which are largely derived from the neural crest, a common developmental origin they also share with myelinating Schwann cells[5,45]. In the heart, however, experimental evidence is limited and originates primarily from single studies. Nexus glia have been shown to originate from the neural crest[15], as well as the non-neuronal cells – presumably satellite glia – within intracardiac ganglia[122]. But Schwann cells expressing proteolipid protein (PLP), a marker for Schwann cell precursors, immature and myelinating Schwann cells[5], appear not to share this origin[30]. In contrast, cardiac Remak cells have partially been traced to the neural crest[30]. This shows that systematic lineage tracing is needed to define the origins and to understand the diversity of cardiac glial populations.

Conclusions

Central and peripheral glia are emerging as integral players in the regulation of cardiac neural control. Future studies will need to determine cellular interactions and molecular pathways by which the heterogeneous glia of the cardiac nervous system contribute to the modulation of rhythm and function in the healthy heart and the diseased heart. Individual findings indicate that glia have the potential to modulate cardiac innervation and electrophysiology after injury, yet the role of the repair glia in this context remains to be elucidated. A deeper understanding of the underlying mechanisms is required to establish a clear roadmap for translation into clinical applications. Initial clinical evidence indicates that glia could serve as therapeutic targets in the pharmacological and interventional treatment of cardiovascular diseases. That being said, further research is needed to better characterize glial involvement in pathophysiological processes and to develop targeted therapeutic strategies. In summary, it is essential to recognize the role of cardiac glia in the exploration of cardiac autonomic control, in arrhythmia mechanisms and in potential patient-specific diagnostic and therapeutic applications.

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