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Review

Telocytes in their context with other intercellular communication agents

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ABSTRACT

The past decade has borne witness to an explosion in our understanding of the fundamental complexities of intercellular communication. Previously, the field was solely defined by the simple exchange of endocrine, autocrine and epicrine agents. Then it was discovered that cells possess an elaborate system of extracellular vesicles, including exosomes, which carry a vast array of small and large molecules (including many epigenetic agents such as a variety RNAs and DNA), as well as large organelles that modulate almost every aspect of cellular function. In addition, it was thought that electrical communication between cells was limited mainly to neurotransmitters and neuromodulators in the nervous system. Also within the past decade, it was found that – in addition to neurons – most cells (both mammalian and non-mammalian) communicate via elaborate bioelectric systems which modulate many fundamental cellular processes including growth, differentiation, morphogenesis and repair. In the nervous system, volume transmission via the extracellular matrix has been added to the list. Lastly, it was discovered that what had previously been regarded as simple connective cells in most tissues proved to be miniature communication devices now known as telocytes. These unusually long, tenuous and sinuous cells utilize elaborate electrical, chemical and epigenetic mechanisms, including the exchange of exosomes, to integrate many activities within and between nearly all types of cells in tissues and organs. Their interrelationship with neural stem cells and neurogenesis in the context of neurodegenerative disease is just beginning to be explored. This review presents an account of precisely how each of these varied mechanisms are relevant and critical to the understanding of what telocytes are and how they function.
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Contents

1. Introduction

Until recently the degree of communication recognized between cells was limited to simple endocrine, autocrine and epicrine mechanisms. The last few years has witnessed the explosive growth of our knowledge of other more complex forms of intercellular

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communication that includes microvesicles of various types, including exosomes, bioelectrical mechanisms, including local field potentials, volume transmission and special communication cells known as telocytes. This review contains an account of some aspects of the relationship between these different systems.

The essential feature of telocytes function is that they correlate the activity of a large number of different types of cell in a tissue, including blood vessels, nerves, immune cells, fibrocytes, stem cells, glandular cells and others, during normal and pathological activity, as well in morphogenesis and repair. This requires the dynamic synthesis, transport and exchange of numerous chemical and electrical signals. The process thus needs the modulation of the synthesis and transport of a number of different proteins. The following gives an example how telocyte and exosome function may be interconnected.

Telocytes contain only a small nucleus and very long and thin arms or podomeres. Along these are spaced enlargements (podoms), like boutons-en-passage, that contain the elements needed for protein synthesis. Given this structure we have suggested [14] that it is highly unlikely that this could all be done by the small nucleus, or that the skinny podomeres could handle the heavy intracellular traffic without monstrous traffic jams. Instead, we suggested that the telocytes is divided up into a large number of small functional units. At each telocyte contact with a tissue cell we propose that the telocytes and the target cell exchange exosomes. The exosomes from the target cell enter the telocyte and their epigenetic load reprograms the telocyte so that becomes able to interact with the target cell. For example, when the tissue cell is injured, it emits a chemical signal (e.g., hemoglobin in the case of a damaged blood vessel) that is taken up and recognized by the reprogrammed segment of the telocytes. In this way the local podom is now able to synthesize the appropriate proteins needed to repair that injury when transferred by exosomes from the podom to the target cell. Then, in the case where the target cell is a smooth muscle cell, and the telocyte modulates its frequency of contraction as in peristalsis, the machinery programmed by the target cell exosomes might relate to the generation of slow wave potentials. When the target cell is a macrophage or lymphocyte, the machinery set-up by exosome transfer to the telocyte would be specific to immune reactions. In this way, a very complex task is undertaken by a collection of simple mechanisms. Furthermore, specification of the various roles of different parts of the telocyte does not need any elaborate information-carrying mechanism within telocyte itself. All of this is supplied automatically from local target cell via exosomes.

This mechanism reduces the need for long distance and very slow information transfer in the T/C to a minimum. There is a precedent for this mechanism in the neural synapse. Smalheiser [50] has shown that exosomes from the postsynaptic neuron can carry epigenetic molecules that modulate the function of the presynaptic neuron. In essence, this is the mechanism that we propose, only operating at the telocyte-target cell contact.

2. Telocytes and volume transmission

2.1. Volume transmission

We now present data that ties the function of telocytes into the broader field of volume transmission. There exist widespread dopamine (DA), noradrenaline (NA) and serotonin (5-HT) nerve terminal networks in the CNS characterized by varicosities specialized for monoamine synthesis, storage and release [18,19]. VT is a major mode of intercellular communication that occurs in the extracellular fluid (ECF) and its pathways in the nervous system and in the cerebrospinal fluid (CSF) of the brain. The VT signals are represented by almost any soluble signaling molecule like transmitters, modulators, trophic factors, and ions. They move from source to target cells along energy gradients resulting in diffusion and flow [19]. The major decoding system in VT involving soluble signals are receptors which are located on all cells of the trophic units of the CNS which build up the neuro-glial networks (nerve and glial cells, pericytes, endothelial cells) [20]. The high afffinity G protein coupled receptors (GPCRs) are the major targets. However, also ion channels and enzymes can decode the VT signals.

Exosomes and microvesicles from neurons and glia contents can also be directly released into the extracellular matrix or ECM [56]. The ECM is produced by glia, neurons, and non-neural cells, and become linked with plasma membrane receptors to form protein assemblies that regulate cell structure and function. These ECM molecules include reelin, tenascins, chondroitin sulfate proteoglycans, laminins, and integrins, the transmembrane cell adhesion receptors that *inter alia* form ECM-cell bridges [54]. The width of the extracellular pathways is only about 20–60 nm [55] and changes in ECM composition can lead to marked increases in tortuosity with significant reductions in VT and disturbances in the information handling of the neuroglial networks [38,21,25].

2.2. Telocytes as sources of VT signals

It is of great interest that the thin and elongated processes of the telocytes possess varicosities, called podoms, along their route [52] as found along all monoamine nerve terminals in the CNS and in the autonomic nervous system. However, the podoms do not appear to form synapses. Instead wiring transmission is involved in telocyte communication through gap junctions with different types of cells including nerve terminals and neural stem cells [34] and with other telocytes to form syncytial extended networks of long distances along e.g. blood vessels.

Currently there is no evidence that soluble VT signals like transmitters are released into the ECF from the podoms via exocytosis. However, evidence exists that telocytes can operate via extracellular vesicle mediated VT along their extended processes, called telopodes [47,12,52]. It seems likely that such events take place both at the soma and at the podom level. Recent work has provided evidence that different types of extracellular vesicles can be released from the cardiac telocytes including not only exosomes and microvesicles but also vesicles with multiple vesicular cargos [15]. These results indicate that the extracellular vesicle mediated VT is a significant mode of communication used by telocytes in addition to gap junctions. These junctions within the extended telocyte network can contribute to the release of extracellular vesicles from multiple telocytes by allowing calcium ion gradients to pass between them. The extracellular vesicles operating through diffusion and flow in the ECF should have a major impact on cellular plasticity in the target area in view of their contents of proteins, especially receptors, mRNA, miRNA, mtDNA, and lipids.

2.3. Telocytes as contributors to building extracellular pathways for long distance VT

The distribution pattern of telocytes is unknown in the brain but they are present in the meninges and choroid plexus as well as in the subependymal layer of the brain surrounding the ventricles [46]. The proximity of telocytes to the neural stem cells was established. The telocytes have contacts also with capillaries and nerve fibers. In such positions in the brain, and also in the periphery, it is conceivable that telocytes, in view of their formation of "extremely" long thin processes or telopodes [47] that connect via gap junctions, can help form extracellular pathways for VT. It was proposed that such pathways exist along the blood vessels to assist in the migration of CSF VT signals and their clearance from the neural-glial networks [8,4,49,3,10]. It is therefore hypothesized that telocytes can help build these pathways in which pressure oscillations are driven by the arterial pulse. Based on the existence of telocytes in the subventricular zone, it is also postulated that telocytes can *inter alia* build-up extracellular pathways for the transport of neuronal precursor cells to the olfactory bulb and assist in their maturation. These concepts are strongly supported by the discovery of the glymphatic system by Nedergaard and colleagues that plays a major role in maintaining the internal milieu of the brain [24,37].

2.4. Telocytes as targets for VT signals

Little is known on the receptor populations that control the activity of the telocytes, including the organization of their cytoskeletal network and dynamic regulation of their calcium, potassium and chloride channels [51]. Therefore, it remains to be shown which soluble VT signals participate in the modulation of the telocytes. Furthermore, the possible involvement of extracellular vesicle mediated VT in their modulation is still unknown. However, it is of interest that PDGFR-alpha is expressed on telocytes of the gastrointestinal tract [57]. Thus, a trophic regulation of telocytes likely exists in this region and PDGF may be released from close by cells to reach the telocytes via VT. Such an activation of their PDGFR-alpha may have effects on their proliferation, trophism and structural and functional plasticity. Thus, a bidirectional communication may exist between telocytes and their target cells at least in the gastrointestinal tract. Nevertheless it is clear that this analysis of a bidirectional VT communication between telocytes and surrounding cells is only at its beginning.

The next section presents data on the bioelectric properties of telocytes in a wider framework of the widespread effects of bioelectricity in organ morphogenesis and tissue repair.

3. Bioelectricity beyond the brain: processing pattern memories

3.1. Ion channels, gap junctions, and neurotransmitters outside the brain

A primary goal of developmental biology, synthetic bioengineering, and regenerative medicine is to learn to understand and control patterning networks, for applications in birth defects, organ regeneration, and cancer reprogramming. A long history of work has implicated bioelectric events in patterning. However, recent advances in molecular physiology have revealed gap junctions, ion channels, and neurotransmitter pathway molecules ubiquitously expressed throughout the body, beginning prior to fertilization. Analogously to the brain, non-neural tissues continuously regulate resting potential (V_{mem}) and local field potentials (extracellular electric fields), as well as regulate the movement of neurotransmitters among cells [5,48]. Techniques have now been developed to detect these physiological parameters in vivo, using pharmacological and genetically-encoded voltage reporters and microelectrodes, and to manipulate them functionally using ion channel misexpression and drug blockers/activators [1,2]. As in the brain, there are basically 2 approaches: modulating synaptic plasticity by altering the way cells communicate electrically (target gap junctional connectivity and neurotransmitter exchange), or modulating intrinsic plasticity by directly changing V_{mem} in cells (by altering the expression or function of ion channels and pumps).

3.2. Bioelectric networks process information for pattern regulation

Recent work has shown that signaling mediated by bioelectric events plays a crucial, instructive role in pattern formation [29,17]. Ion channel-mediated changes in V_{mem} not only affects individual cell behaviors such as proliferation, differentiation, apoptosis, and migration [53], but also determines large-scale parameters such as organ size, shape, and axial patterning of the entire body [43,6]. In a range of model systems, we now know that V_{mem} regulates the formation of the brain, eye, wing, and face, and controls patterning along the anterior-posterior and left-right axes during embryonic development [31,13,41]. As in the brain, these elements often work together, such as the bioelectrically-controlled movement of 5HT through GJs during left-right patterning and control of nerve growth [9,32]. The molecular pieces are now being identified, but the idea of neurotransmitters being ancient "pre-nervous" developmental signaling molecules is an old one [11].

3.3. Bioelectric memories: rewriting the default genome pattern

The analogy between the brain and somatic pattern control makes several specific predictions. One is that ion channels, GJs, and neurotransmitters should play a role in development; this has been amply demonstrated by the identification of patterning channelopathies [28], functional experiments in regenerative and developmental biology [52], and the teratogenic effects of numerous psychoactive drugs [23]. Another key prediction concerns the encoding of instructive information. In the brain, genetics establish the hardware—genes encode the available components and thus define the limits of cellular activity. However, the information content of the brain is not directly encoded by the genome, but rather arises dynamically through environmental stimuli (learning) and self-organizing dynamics of the electrochemical circuitry (plasticity). Is this the case in pattern formation as well?

More impressive however would be the ability to rewrite pattern permanently; could "long term somatic memory" be edited, in the context of a wild-type genome, leading to a permanent change? A first example of this was shown in a different species of planaria [39], where targeting GJs for just 48 h in a chunk of tissue caused it to regenerate 2 heads—one at the former anterior end (normal), and one at the posterior-facing end (which would normally grow a tail). Remarkably, these 2-headed worms continue to regenerate as 2-headed when cut in subsequent rounds of regeneration, in plain water, months after the GJ blocking reagent is long gone from the tissue [40]. The target morphology – that is, the shape to which this animal regenerates upon damage – has been permanently re-written by temporarily editing the physiological network. This finding has clear similarity to plasticity (well-known to be exhibited by electrical synapses [44]: a brief induced change of GJ connectivity becomes stabilized to a long-term change [30]. This interaction between bioelectric activity and voltage-gated GJs makes developmental bioelectrical networks especially suitable as a labile yet stable memory medium [42]. Another brain-like property exhibited in this effect is its holographic nature: in each round of cutting, the ectopic head (perhaps "epigenetically reprogrammed") is removed,

and a middle fragment of the gut still knows it must make 2 heads if cut. The patterning information is distributed non-locally throughout the network.

3.4. Where do we go from here?

Thus, neuroscience offers developmental bioelectricity more than just tools and molecular mechanisms: it offers a unique paradigm, otherwise unavailable to molecular and cell biologists, of the emergence of higher levels of organization that have both causal potency and experimental tractability. Neuroscience teaches us that we must look upward as well as downward, for emergent levels with their own rules and advantages [16]. And we now know that beneficial changes at the genetic and chemical levels can be induced by cognitive therapies – top-down control of tissue structure and function by thoughts and experiences. If patterning tissues are "primitive cognitive agents", in the sense that they can be profitably understood as memory-bearing, information processing, goal-directed cybernetic systems [45], then a whole new set of approaches becomes available for regenerative medicine. If we understood the bioelectric code, we could interact with it at these higher levels of organization, taking advantage of endogenous modularity and perhaps rationally controlling anatomical outcomes without having to micromanage molecular networks. However, the knowledge flow is likely not all in one direction: cracking the bioelectric code in patterning tissues is likely to in turn benefit fundamental neuroscience by showing, in perhaps a simpler context how to extract semantic content from bioelectrical cell states in the brain.

The many cell types mediating bioelectric signaling in vivo, especially in mammals, are not fully characterized. Telocytes are an ideal candidate for this role. Lastly we review our developing understanding of the clinical role of telocytes in neurodegenerative disease.

4. Telocytes and neurodegenerative disease

The number of patients affected by neurodegenerative diseases increases continuously, probably due to different factors, the simplest one being extended life span [58]. Unfortunately, there is no intervention to date to cure or stop progression in any of these diseases. Interestingly, there are a few common pathogenic mechanisms, encountered in most, if not all neurodegenerative disorders, such as accumulation/aggregation of abnormal proteins (within or outside the cells), mitochondrial dysfunction and oxidative stress, intracellular calcium dyshomeostasis, loss of synapses and disorganization of neural-glial networks, abnormal cell death usually with features of apoptosis, inflammation, small vessel abnormalities, brain barriers dysfunction and others [26]. In our view it is difficult to identify one of these multiple pathogenic events as cause of all others, but most of the experts currently design the therapeutic solutions mainly against the protein aggregation (i.e. β-amyloid, hyperphosphorylated tau, α-synuclein, etc.; [22]). However, one of the current approaches to develop new interventions in neurodegeneration relates to neural stem cells (NCSs), classically located in the subventricular zone (SVZ) of the anterolateral ventricle and the subgranular zone of the hippocampus [7]. In more recent works, NCSs were identified in other locations as well, such as meninges [36] and choroid plexus [35], and in different experimental models of injury NCSs from these locations were capable to multiply, differentiate and migrate to the injury area. We demonstrated that both leptomeninges and choroid plexus host telocytes, which are in contact with putative stem cells, as shown by electron microscopy and immunohistochemistry [46].

As mentioned already, telocytes are part of a network intercellular communication, which might interfere as well with the fate of NCSs in brains with neurodegeneration. Considering that at the level of choroid plexus passage of cells from the blood to the brain and vice versa is possible and that SVZ itself is close to ependymal layer, it is also possible that circulating stem cells might be in contact with the NCSs pool. Telocytes might guide the cellular blood-brain exchange at this level as well. Moreover, taking into account the recent identification of the meningeal lymphatic system (the glymphatic system) [33] and a more consistent analysis of the clearance role of the choroid plexus [27], it seems like both these tissues are gate keepers of physiological abnormal protein extrusion (such as of β-amyloid peptide), property in which telocytes might also play a role. Thus, considering that telocytes are specialized in transmitting integrated signals to different neighboring cells in the tissue, they might be an interesting therapy target in the future for both regulating neurogenesis and abnormal protein clearance.

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