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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.

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