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Telocytes in the reproductive organs: Current understanding and future challenges

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ABSTRACT

Over the past decades, we were witnessing spectacular molecular medicine advances. However, many of the reproductive medicine problems, such as fertility issues and premature birth still represent major challenges for obstetrics and gynecology worldwide. A new cell population – the telocytes (TCs) – were described in the interstitial space of many organs, and their possible implications in many important physiological and pathological processes should not be overlooked. In this article, we present a historical perspective outlining the landmarks in the discovery, evolution and achievements in the field of TCs over the last ten years. We focused on the potential roles of TCs in morphogenesis and maintenance of the normal three-dimensional architecture of tissues, in controlling of the stem cell microenvironment, as having anti-inflammatory and cancer-suppressing properties, participating in the immune surveillance, all mediated by direct homo- and heterocellular junctions or indirectly by extracellular vesicle release. Here, we overview the advances on TCs research in the reproductive organs (uterus and fallopian tube), accessory reproductive organs of female (mammary glands) and the temporary endocrine organ—placenta.

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1. Brief introduction in the history of telocytes

Telocytes (TCs) were recently identified as a distinct interstitial cell type with a wide distribution in reptile, bird and mammalian organs (for extensive details visit www.telocytes.com).

The discovery of TCs dates back in 2005 when our team in Bucharest, Romania conducted by Professor LM Popescu observed

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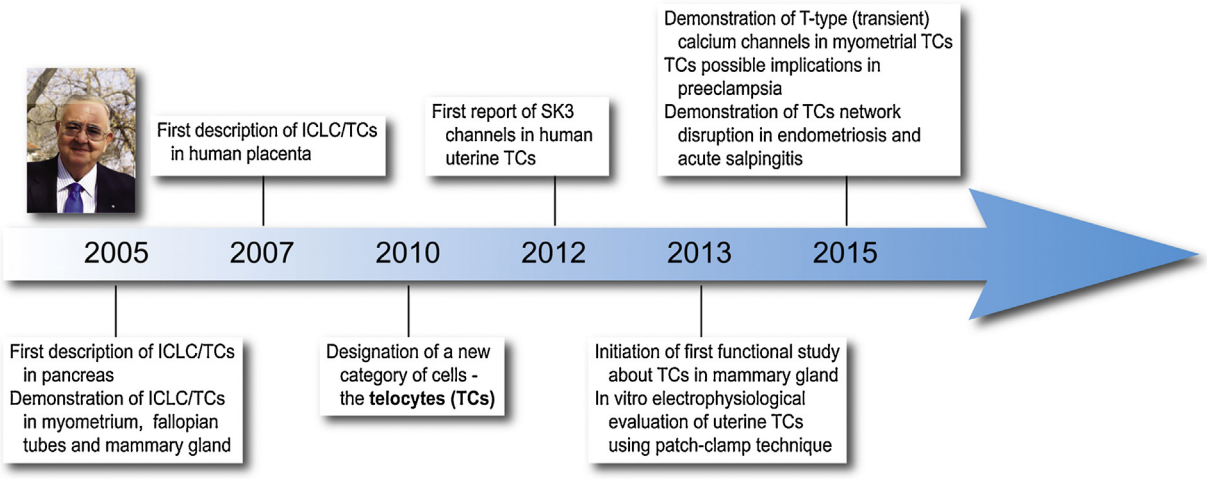

Fig. 1. A timeline of key discoveries and advances in telocytes research at the level of uterus, fallopian tube, mammary gland, placenta.

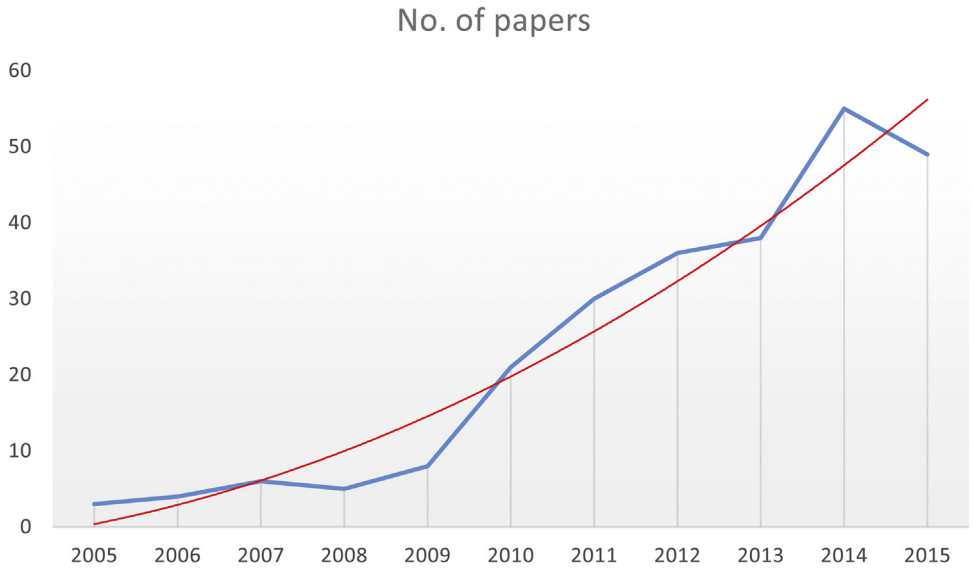

Fig. 2. The chart displays the evolution of the number of original papers (blue) dealing with ICLC or TCs (source: Thomson Reuters Web of Knowledge database). Other publications, such as conference proceedings are not accounted for in this statistics. The interest in telocytes is growing exponentially (logarithmic trendline in red).

them by serendipity while studying exocrine pancreas structure [1]. For a few years, the existence of these cells, initially called interstitial Cajal cells (ICLC) was embroiled in a controversy: are there any differences between ICLC and archetypal interstitial cells of Cajal (ICC), known as pacemakers of gastrointestinal rhythmicity? Soon enough, an affirmative response came from a well-recognized international scientist in the field of ICC—M.S. Faussone-Pellegrini. Her team from Florence, Italy described ICLC in the gut muscular layer, which were not at all similar to ICC [2]. Quickly after, in 2010, the two groups concluded that ICLC was, in fact, a brand new, undescribed cell type, which deserves a new appellation—telocytes [3]. Fig. 1 illustrates the main landmarks in the study of TCs located in uterus, fallopian tube, mammary gland and placenta. Since their discovery, many groups embraced the TC notion and the interest in TCs is growing exponentially (Fig. 2).

2. General morphologic profile of telocytes

Telocytes are best characterized by their unusually long prolongations measuring tens to hundreds of micrometers, called telopodes (Tps). Classically, Tps were described as having a moniliform aspect with dilated bead-like portions called podoms united through thread-like segments called podomers [3]. Tps spread over large distances and have a dichotomous branching pattern and are able to form three-dimensional networks being connected to each other by homocellular junctions [4]. Another remarkable aspect is the capacity of Tps to establish stromal synapses (planar or multicontact type) with immune cells such as plasma cells, eosinophils, mast cells, lymphocytes, macrophages, etc. [5,6]. By their Tps, TCs are often found in close proximity of nerve endings, blood vessels and contacting different types of progenitor cells, occupying a strategic position in relation to stem cell niches [7]. Recently, TCs were evaluated by FIB-SEM tomography and additional details were disclosed about Tps and their 3D special conformation: they can sometimes have the appearance of anfractuous, long and flattened veils (ribbon-like segments) with uneven surface due to the existence of numerous dilations corresponding to podoms, and other times they can take the classically described aspect of tubular structures (podomers) with an uneven caliber because of the podoms [8,9].

Telocytes are able to communicate with other cells at short and long distance through extracellular vesicles released both in tissue