Gineco.eu [14] 36-38 [2018]
DOI: 10.18643/gieu.2018.36

Morphology of telocytes from the mammary gland. A review

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Abstract

Telocytes are a novel type of cell, initially described by Popescu and Faussone Pellegrini. One of the first tissues in which telocytes, named first named as interstitial Cajal-like cells (ICLCs) were studies was the mammary gland. The purpose of this synthetic review is to summarize the main morphological characteristics of this cell type in the mammary gland. We interrogated the following databases: PubMed, Clarivate Web of Science, and Scopus, by using the following keywords: "breast," or "mammary," or "mamary" AND "telocyte," or "Cajal," or "ICLC." Breast telocytes respect the platinum ultrastructure standard for their identification. However, immunophenotypically, the results are less homogenous, with various studies showing different characteristics of these cells, which could be caused by the fact that there is more than one cell type with telocyte-like morphology in the breast, the fact that breast tissue can be caught in different stages activity, or simply due to issues generated by the detection technique. More studies should be performed to reveal the cause of this immune variability, and especially of the roles of these cellular types in the normal physiology and physiopathology of the mammary gland, maybe with an emphasis on breast cancer.

Keywords: *telocytes, breast, mammary, Cajal, ICLCs*

Introduction

Telocytes are a novel type of cell, initially described by Popescu and Faussone Pellegrini[1], mainly using electron microscopy criteria, replacing the older term interstitial Cajal-like cells (ICLCs). Recently, this cell type has been disputed by numerous groups, due to significant overlap with other cell types, such as fibroblasts[2,3], endothelial, pericytes[4], endothelial progenitor cells[5], or even endothelial lymphatic cells (our unpublished results). One of the first tissues in which telocytes/ICLCs were studied was the mammary gland. The purpose of this synthetic review is to summarize the main morphological characteristics of this cell type in the mammary gland.

We interrogated the following databases: PubMed, Clarivate Web of Science, and Scopus, by using the following keywords: "breast," or "mammary," or "mamary" AND "telocyte," or "Cajal," or "ICLC." After removing duplicates, we obtained 18 articles. We downloaded the articles and critically reviewed their contents.

A total number of 11 articles contained relevant data for our analysis, which were further analyzed.

Location of telocytes

ICLCs' long cellular processes form a mesh-like structure around capillaries and mammary gland ducts[6]. Petre et al. found fibroblastoid cells, with a telocyte-like appearance, in the intralobular and interlobular stromal components of normal breast tissue[7-11].

Received: *January 27, 2018*
Revised: *February 20, 2018*
Accepted: *March 05, 2018*

The involving of the immune markers

Radu et al. showed that cultured telocytes from the mammary gland stroma are positive for vimentin (in the cell body and prolongations), and CD117 (stronger in prolongations and weaker in the cell body)[7]. According to Faussone-Pellegrini and Popescu, the defining characteristic of telopodes is that they are thin from the emergence, this being used as a differential diagnosis with other stromal cell types, which have a thick emergence from the cell body, followed by a gradual thinning[1,8]. The telopodes presented in Figure 1 from their article revealed prolongations that have a slow decreasing diameter as departing from the cell body[7], suggesting that, at least some CD-117 or vimentin positive stromal cells with prolongations could be other cell types than telocytes/ICLCs. Popescu et al., in a study published in the same year, also presented a c-kit immunopositivity in mammary gland stromal cells, in which some cells have thin prolongations, while others had a gradual thinning[9], suggesting the presence of hybrid morphologies. Both articles[7,9] presented cells in methylene blue which had either prolongation with gradual thinning or abrupt thinning. Mou et al. used the following markers to detect telocytes in cultured mammary gland telocytes: c-kit, vimentin, CD34, alpha-SMA, and found these cells to be negative for CK-14, CK-18, and desmin[10]. Most cells identified in the immunohistochemistry/immunofluorescence figures had gradually thinning prolongations, but there were also exceptions. Petre et al. showed the presence, in the normal mammary stroma, of CD34+, vimentin+/c-kit-fibroblastoid cells, with long/extremely long processes serially linking them to collagen processes, and building up stromal networks, which could fulfill the morphological definition of telocytes. A subset of the intralobular fibroblastoid cells were also CD10+[11] (Figure 1).

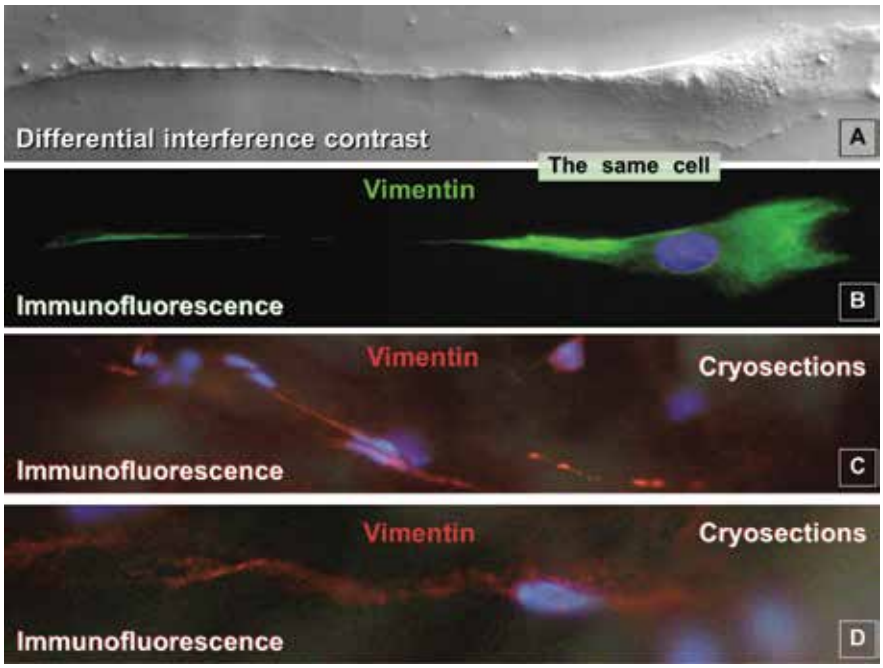

Figure 1. *Human inactive mammary gland: the same Cajal-like cell in vitro (A and B), primary cell culture, day 6. Differential interference contrast microscopy (A, original magnification: 60x) shows a typical Cajal-like cell with a slender prolongation. IF analysis (B, original magnification: 60x) shows vimentin positivity – green (primary antibodies: monoclonal mouse anti-vimentin, clone V9, DakoCytomation, Glostrup, Denmark; secondary antibodies: FITC-conjugated goat anti-mouse - BD Pharmingen, San Jose, CA, USA). Cajal-like cells in situ (C and D, IF on cryosections). Specimens were cryosectioned, fixed, and immunostained for vimentin. IF revealed vimentin immunopositive ICC-LC (red), with long processes that contact the vicinal cells (C, original magnification 40x). At higher magnification (D, 60x), the heterochromatic nuclei and branching prolongations are visible. Primary antibodies were detected using biotinylated polyclonal anti-mouse antibodies and streptavidin-AlexaFluor 546. Nuclear counterstaining (blue) with Hoechst 33342 (B) or DAPI (C and D). From Radu E, Regalia T, Ceafalan L, Andrei F, Cretoiu D, Popescu LM. Cajal-type cells from human mammary gland stroma: phenotype characteristics in cell culture. Journal of cellular and molecular medicine. 2005;9(3):748–752., with permission from Wiley and sons, Order No. 4301751470555*

Electron microscopy analysis

The main ultrastructural features of mammary gland telocytes weree: location in non-epithelial spaces, caveolae representing around 2-4% of all cytoplasmic volume, mitochondria (5-10% of all cytoplasmic volume), the presence of small quantities of smooth and rough endoplasmic reticulum, intermediate and thin fragments, gap junctions with other telocytes or with smooth muscle cells, close apposition to target cells/structures, no myosin, inconstant basal lamina, and characteristic cytoplasmic processes (i.e. telopodes):1-5, tens-hundreds of micrometers, with dilations, uneven caliber, dichotomous branching pattern, with Ca^{2+} releasing units, and organized in a labyrinthic system[6].

Compared to fibroblasts, telocytes have a larger nucleus with more heterochromatin, mitochondria and smooth endoplasmic reticulum are in larger quantities, while rough endoplasmic reticulum is less dense, and they do present caveolae[6].

Mihalcea et al. described telocytes associated with mammary gland tumors, in which they were detected in close vicinity to blood capillaries, or other stromal cells but not in direct contact with endothelial cells or pericytes[12].

Again Mihalcea et al., in a later study on breast cancer tissues, depicted some telocytes that realize the so-called plug&socket synapses[13], and, unlike those from normal tissue, with a decreased density of mitochondria.

Telocytes (or similar cell types, as the naming of this particular type of stromal cell, is still disputed), have been suggested to play important roles in mammary gland homeostasis[7], connecting immune cells into a network[6], cellular signaling[6], immunomodulatory functions[6], lactation[9], tumorigenesis[7,10,12,13], apoptosis[10] or could be important players in the mammary stem niche[11,14].

Their ultrastructural appearance is established, based on the so-called "platinum standard" of

telocytes, namely: characteristic cell processes (coined telopodes), numerous mitochondria, intermediate filaments without thick filaments, surface caveolae, variable basal lamina, contacts with nerve bundles, smooth and rough endoplasmic reticulum, close apposition with target cells, and specific targets in a particular organ[15].

Their immune phenotype is however more disputed, with various studies showing different characteristics of these cells, which could be caused by the fact that there is more than one cell type with telocyte-like morphology in the breast, the fact that breast tissue can be caught in different stages activity, or simply due to issues generated by the detection technique.

Conclusions

More studies should be performed to reveal the cause of this immune variability, and especially of the roles of these cell types in the normal physiology and physiopathology of the mammary gland, maybe with an emphasis on breast cancer. ■

Conflict of interests: The authors declare no conflict of interests.

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