

## Tubal telocytes: factor infertility reason?

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**Abstract:** Infertility is actually widespread pathological condition, which affected one in every four couples in developing countries. Approximately one third of all cases are connected with tubal factor infertility, often accompanies by endometriosis, acute salpingitis, urogenital infections etc. The newly identified telocytes (TCs) have multiple potential bio-functions and might participate in the fertility problems. They influence on structural and functional integrity of oviduct tissue. Despite recent discovery, TCs involvement in the majority of physiological and pathological processes is still unclear and require significant increasing of deep observations and data analysis. Focusing on female reproductive system help better understands the main reasons of infertility, while evaluation of TCs impact on Fallopian tube and uterus contractility might be a key point of its correction. The article summarizes the main features of telocytes in Fallopian tubes, emphasizing their involvement in pathophysiological processes and tubal factor infertility.

**Key words:** infertility, telocytes, ICLC instead ICLS, fibroblast-like cells, tubal peristalsis, Fallopian tube.

## Introduction: infertility in statistics

Infertility remains a highly prevalent condition worldwide. According to the Practice Committee of the American Society for Reproductive Medicine, infertility is a disease, defined by the failure to achieve a successful pregnancy after 12 months or more of appropriate, timed unprotected intercourse or therapeutic donor insemination [1]. Three surveys on the overall prevalence of infertility published in the new millennium (2004, 2007 and 2012) have very different results, between 48.5 million and 186 million. It is estimated that it may affect between 8 and 12% of couples at reproductive age, with a probable global incidence average of 9% [2]. Ombelet *et al.* published that worldwide more than 70 million couples suffer from infertility and bilateral tubal occlusion is the most common underlying cause [3].

## Telocytes: identification and main features

Telocytes, a novel type of interstitial cell population firstly described by Popescu group in 2005 and characterized by a small cell body and extremely long prolongations named telopodes (Tps) with alternating thin segments (podomers) and dilated segments (podoms) [4]. Currently these cells are identified by transmission electron microscopy (TEM), immunohistochemistry and immunofluorescence. TCs are widely distributed in vertebrate (fish, reptiles, birds, mammals, including humans) [5]. TCs have been described to possess different immunophenotype markers, such as the sialylated transmembrane glycoprotein CD34 and the tyrosine kinase receptor c-kit/CD117, among a variety of cavitory and non-cavitory organs: heart (endo-, myo-, epi- and pericardium, myocardial sleeves, heart valves); digestive tract and annex glands (esophagus, stomach, duodenum, jejunum, liver, gallbladder, salivary gland, exocrine pancreas); respiratory system (trachea and lungs); urinary system (kidney, renal pelvis, ureters, bladder, urethra); female reproductive system (uterus, Fallopian tube, placenta, mammary gland); vasculature (blood vessels, thoracic duct); serous membranes (mesentery and pleura); other organs (skeletal muscle, meninges and choroid plexus, neuromuscular spindles, fascia lata, skin, eye, prostate, bone marrow) [3–8]. They also have immunopositivity for numerous markers such as plated-derived growth factor receptor alpha and beta (PDGFR $\alpha$  and  $\beta$ ), VEGF, inducible nitric oxide synthase (iNOS), calveolin-1, vimentin, connexin 43, estrogen and progesterone receptors, CD44, desmin, nestin and cadherin-11 [4, 7, 9]. Important to note, that the most applicable method to identify TCs is immunohistochemistry combined with TEM. Despite the fact that has not yet been found a specific marker for TCs, usually for primary identification scientists use CD34 [9].

The TC interstitial system is composed of cells that by either homocellular or heterocellular contacts integrates the overall information from vascular, nervous and immune system, interstitium and stem cells [9]. In pathological condition, these cells

displayed ultrastructural change, significantly reduced and progressively disappeared [8, 10].

### Fallopian tubes as a point of infertility

Fallopian tube is a central organ of human reproduction as plays an essential role in transport of both gametes and embryos and in early embryogenesis [11]. The length of each oviduct ranges from 15 to 20 cm, while tubal lumen can be from tenths of a millimeter to several millimeters depending on the anatomical part. It is lined by simple cuboidal or columnar epithelium containing secretory and ciliated cells, which produce tubular fluid and facilitate transport of gametes, respectively [12]. Ciliated cells are found predominantly on the apex of the mucosal folds. Their reactivity is affected by a variety of hormonal and neuronal stimuli. Many pathological conditions associated with infertility and ectopic pregnancies have been shown either to destroy cilia or to reduce ciliary motion or both. [11]. Also, Fallopian tube consists of smooth muscle cells (SMC), immunocompetent cells such as leukocytes, and blood vessel cells [13, 14]. The first description of a distinct oviductal cycle in women was made in 1928 [11].

Tubal factor infertility is the most common cause of female infertility and diagnosed in approximately 30% to 35% of younger and older infertile women. The main causes of tubal factor infertility are congenital bilateral agenesis and full oviduct blockage, inflammation of the pelvic organs (in the majority caused by infections), endometriosis, former surgical treatment lead to adhesive disease, polyps and diverticula of Fallopian tubes, hydrosalpinx [15].

The most prevalent cause of tubal factor infertility is pelvic inflammatory disease (PID) and acute salpingitis. Tubal damage from PID causes inflammation and long-term tubal changes, such as fimbrial agglutination, fimbrial phimosis, tubal obstruction, hydrosalpinx, and nodular thickening of the muscularis layer of the isthmic portion of the fallopian tube called salpingitis isthmica nodosa. The risk of ectopic pregnancy can increase sixfold to sevenfold after an episode of PID [14].

Endometriosis affects over 70 million women worldwide and pathophysiological is associated with inflammation and elevated cytokine levels [12]. Among women with tubal factor infertility, endometriosis accounts for 7% to 14% [16]. The expression of progesterone receptors A and B types (PR-A and PR-B) is altered in endometriotic lesion stromal cells. Attia *et al.* showed that PR-A was reduced while PR-B was absent compare with eutopic endometrium [17]. Macrophage migration inhibitory factor (MIF) is a potent mitogenic factor for human endothelial cells *in vitro* and tumor angiogenesis *in vivo*. Endometriosis leads to increasing of its expression in ectopic and eutopic endometrium. Moreover, MIF has been shown to stimulate prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), cyclooxygenase-2 (COX-2), vascular endothelial growth factor (VEGF), interleukin-8 (IL-8), and monocyte chemotactic protein-1 (MCP-1) expression. Yang

*et al.* emphasizes that endometriosis-associated infertility seems to be multifactorial, involving mechanical, molecular, and genetic mechanisms [18, 19].

### Possible role of telocytes in tubal infertility

Telocytes are often observed between smooth muscle bundles and make contacts with smooth muscle cells. They are located around capillaries and make junctions with fibrocytes and pericytes. Urban *et al.* observed that TCs were localized mainly in tunica muscularis externa [20]. Likewise, TCs form heterocellular synapse to mast cells (MCs) with their Tps and potentially participated in immunoreactions [21, 22]. The last experiments have shown that TCs also contains in the fimbriae of Fallopian tubes [6, 23–26]. Although, its spatial distribution gradient decreases from the subepithelial area toward serosa measured in the relative numeric density (percentage of TCs out of all cells found in that area) (Table 1).

**Table 1.** Distribution of telocytes in Fallopian tube stratum.

Area of the human Fallopian tube	Density of TCs (%)
The border epithelium/lamina propria, a 'belt' 10 $\mu\text{m}$ thick underneath the basement membrane of the endosalpinx epithelium	18 $\pm$ 2
The subepithelial portion of lamina propria (~20 $\mu\text{m}$ thick)	11.7 $\pm$ 0.9
Area, containing the whole lamina propria thickness	9
Tunica muscularis	7.8 $\pm$ 1.2
Remaining zone beneath serosa	not assessed

As TCs make heterocellular contacts with various oviduct interstitium components, they might be involved in intercellular information exchange between various stromal cells, or represent a "functional unit" by participating in making a primitive nervous system through telocytes-exosomes gap junctions-cytoskeleton [18, 22].

Yang *et al.* reported that in acute salpingitis-affected oviduct tissues, TCs was obviously decreased or lost, severely damaged/degenerated with multiple ultrastructural abnormalities, such as loss of organelles, numerous swollen nucleus, mitochondria and rough endoplasmic reticulum dilatation, cytoplasmic vacuolization, discontinue or dissolution of Tps, swollen or loss of intercellular junction [21].

Endometriosis is estrogen-dependent disease and might leads to local damage of TCs. Massive neutrophils infiltration and overproduced inducible nitric oxide synthase (iNOS), COX-2, oxidative stressor (lipid peroxide, LPO) and estradiol in oviduct tissue suggested mechanism of inflammatory-induced TCs damage [21, 22]. On the other hand, he also proposed that TCs damage might contribute to structural abnormalities of oviduct [18, 22].

The morphology and functional integrity of the Fallopian tube are estrogen dependent [13]. Biological activity of  $17\beta$ -estradiol (E2) is linked to both inhibition and stimulation of the interactions between progesterone (P4) and progesterone receptor (PR) in the female reproductive tract. Oviduct TCs express estrogen/progesterone receptors, and thus might act as “hormonal sensors” [4, 5, 27–29].

Kissler *et al.* observed dysperistalsis of utero-tubal smooth muscle and Yang *et al.*, taking into account his results, suggested a possible role of “tubal motility disorder” in contribution to endometriosis-associated tubal factor infertility [18, 29]. Combination of estrogen and progesterone is necessary for normal contractility of smooth muscle cells in oviduct. Adrenomedullin (ADM) is expressed in epithelial cells of the human and rat Fallopian tube. There is evidence suggesting that circulating ADM levels increase and decrease along with circulating  $17\beta$ -estradiol levels in humans during the menstrual cycle. Studies have shown that ADM increases ciliary beat frequency and decreases smooth muscle contractility. Estrogens impact on tubal peristalsis. Telocytes express both types of hormonal receptors (estrogen and progesterone) and might be involved in tubal contractility and dysperistalsis. They form heterocellular contacts with smooth muscle cells and have both types of hormonal receptors. Tubal telocytes generates slow waves within oviduct smooth muscle and has been recognized as oviduct pacemaker cells [18, 22, 23].

TCs involved in organization of 3-D extracellular matrix. They can regulate the activity of neighboring cells (stem cells, immunocytes, smooth muscle cells etc.), with intercellular different signaling mechanisms. TCs damage and 3-D interstitial architectural derangement leads to abnormal tissue homeostasis and angiogenesis, interstitial fibrosis and consequent reproductive problems [9, 21, 30].

Secretion of epidermal growth factor and insulin-like growth factors is significantly important for normal fertilization and embryo development, but it is changed in endometriosis affected tissue. Others involved in fibrosis and neo-angiogenesis. TCs are positive for growth factors receptors (VEGF, PDGFR $\alpha$  and  $-\beta$ ). Numerous experiments have shown involvement of vessels in endometriosis and adenomyosis pathogenesis. Likewise normal microenvironment and the inflammation disease are based on blood circulation in capillaries of the uterus and oviduct. Neo-angiogenesis is the main in pathogenesis of tubal ectopic pregnancy. TCs not only located around capillaries and make junctions with fibrocytes and pericytes, they also express growth factors receptors involved in neo-angiogenesis [9, 31–33].

Telocytes also surrounded stem cell niches with telopodes and heterocellular contacts. They may participate in oviduct tissue repair/regeneration processes. Damage or loss of TCs will change the activity of telocytes-stem cells and decrease tissue reparation or renewal capacity, subsequently inducing development of tissue fibrosis. As a result — oviduct dysfunction and infertility. TCs-mediated function-specific intercellular signaling contributes to regulate activity of neighboring cells,

including involvement in neurotransmission by spreading the slow waves generated by the pacemaker interstitial cells of Cajal (ICCs) in the gut, modulating tissue development/remodeling/metabolism, immunoregulation/immunosurveillance and maintaining homeostasis of the gastrointestinal tube [9, 31, 34, 35]. We postulate that similar mechanisms concerning telocytes in fallopian tube might be involved in the pathological processes, leading to infertility of oviductal origin.

### Conflict of interest

Authors declare no conflict of interest.

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