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Editorial

Telocytes, what are they doing in the Female Reproductive System?

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Telocytes (TCs) are interstitial cell type. The history of TCs has started since 1889 when the Spanish neuroanatomist and Nobel Prize winner Santiago Ramon y Cajal demonstrated a new type of cells located within the muscle layer of the intestine, between nerve ganglia and smooth muscle cells and named them as interstitial neurons [1]. By the 1960s, Taxi., *et al.* firstly described the interstitial cells of Cajal (ICC) as a new cell type which was distinguished from other types of cells [2]. ICC were continually detected outside the gastrointestinal musculature after the year 2000. As for the similar morphology and immunohistochemical features, these cells were renamed as "Interstitial Cajal-like cells (ICLC)". The presence of ICLC has been reported in the interstitium of several organs [3]. Kostin and Popescu (2009) confirmed that the ICLC was a distinct cell type from the classic ICC in the myocardium and uterus, respectively [3]. It was necessary to give a new name for ICLC to avoid confusion from ICC because ICLC is a peculiar and independent cell type. Popescu and Faussone-Pellegrini (2010) proposed to name ICLC as "telocyte" for the first time [3].

Telocytes (TCs) can be detected by Toluidine or Methylene Blue stains. They have small spindle-shaped or pyriform body containing oval to flat nucleus and a small amount of cytoplasm. TCs have extremely long, thin cytoplasmic extensions called telopodes (Tps) [4]. There are many markers used to detect TCs that vary in their reactivity according to their sites suggesting the presence of various subtypes. The most common markers used for the identification of TCs, CD34, α -SMA, CD44, vimentin, Sca-1 and c-Kit (CD117). The gold standard for the identification of TCs is the transmission electron microscopy [5]. The cell body of TCs contains a nucleus which occupies about 25% of the cell volume. There is a small quantity of cytoplasm containing mitochondria, small Golgi complex, rough and smooth endoplasmic reticulum and cytoskeletal elements. The number of their Tps varies from 1 to 5 for [6]. TPs' length ranges from tens to hundreds of micrometers and their thickness is below 0.2 micrometer. The main characteristic of Tps is the moniliform aspect due to the presence of thin portions called podomers alternating with dilated portions called podoms [7].

The function of TCs in different tissues and organs is a subject of research. Their heterocellular junctions provide a visible direct structural support for the maintenance of cellular stability, tissue repair, remodeling, regulation of blood flow and intercellular signaling [8]. TCs have been identified in many organs either cavitary organs like the Heart (endo, myo and pericardium), stomach, intestine, gall bladder, uterus and fallopian tubes or non-cavitary organs like, lungs, pleura, pancreas, mammary gland and placenta [7]. In the gastrointestinal tract, they were considered as the pacemaker for regulation of peristaltic movement [5], in the gastric lamina propria, they are considered as regulators to other cell type regeneration. In the human skeletal muscles they are said to have proliferative and supporting abilities [3]. The intercellular junctions of telocytes with the surrounding cells across their telopodes also suggest a potential functional relationship in the development of various abnormalities [9]. It is conceivable that progressive local loss of TCs might contribute to altered intercellular communication or disrupted immune homeostasis, chronic inflammatory and fibrotic disorders [10].

In the female reproductive system telocytes were demonstrated in the ovary, fallopian tubes, uterus, vagina, mammary glands and placenta [11].

Vagra and Urban (2016) demonstrated TCs within the smooth muscles of the vagina suggesting that they initiate the contractility of the vaginal smooth muscle cells [12].

In the fallopian tubes TCs form junctions with the smooth muscles, mast cells, plasma cells and nerves. It was stated that in salpingitis, tubal endometriosis and tubal pregnancy the number of TCs was reduced with altered morphology [13].

In the animal ovary, TCs were seen within the stroma and their number greatly decreased in ovulation failure suggesting that they may play a role in ovarian microenvironment regulation [14].

In the uterus TCs were demonstrated in the endometrium and myometrium. In the former they locate around the endometrial glands. In the myometrium TCs form a highly intermingled 3-D network with the smooth muscles. Their number varies according to the physiological state of the uterus. They are more numerous in the non-pregnant compared to the pregnant suggesting that they may prevent premature labor. Furthermore, in post-partum uterus, there are plentiful number of TCs suggesting their role in uterine involution [15-17]. Tcs form communications with other cells rather than smooth muscles like macrophages and may cause their activation with a rise in the interleukin level suggesting that they may play a role in abnormal implantation, abortion or endometriosis [18].

The presence of TCs in mammary glands was confirmed by previous studies. They are located within the stroma in the inter lobar and interlobular areas. They form junctions with the stromal cells like plasma cells, macrophages, fibroblasts and mast cells. Their function suggested to be immune regulation of the microenvironment [19]. *In vitro* study of Mou., *et al.* (2013) showed that TCs form junctions with breast cancer cells increasing their proliferation forming clusters of neoplastic cells [6].

Placental TCs were demonstrated in the stem, mature intermediate and terminal villi underlying the trophoblast cell layer and around the blood vessels. They form junctions with the stromal cells like; plasma and mast cells, myofibroblasts and Hofbauer cells suggesting their role in immune surveillance [20]. The presence of TCs forming multiple junctions with the smooth muscles around the blood vessels of the chorionic villi together with the fact that the placenta is a non -innervated organ suppose that they have a key role in regulating the fetal blood flow [21].

In conclusion, TCs are a connecting interstitial cells present in many tissues and organs. They characteristically have long slender multiple processes that form junctions with most of the surrounding cells suggesting their role in immune surveillance, maintenance of cellular stability, tissue repair, remodeling, regulation of blood flow and intercellular signaling. Electron microscopy is the gold standard for TC detection and could be detected by many antibodies immune histochemically. In female reproductive system, TCs have been detected in the ovary, tubes, uterus, vagina, mammary glands and placenta. It is stated that TCs have a role in follicular maturation, ectopic pregnancy, premature labor and pre-eclampsia. Further researches needed to clarify the exact mechanism that TC act in pathogenesis of various abnormalities in female reproductive system that help in development of curative strategies.

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