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Telocytes in the Submucosa of the Extrahepatic Bile Duct

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Authors' contributions

In this work, both authors contributed equally. Both authors read and approved the final manuscript.

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Commentary

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ABSTRACT

Hepatic ducts carry bile out of the liver and join together forming the common bile duct also known as extrahepatic bile duct. It then traverses the wall of the duodenum and deliver bile into its lumen. In species with a gallbladder, the extrahepatic duct flows into the cystic duct, which conveys bile to and from the gallbladder. In the extrahepatic duct, the submucosa layer forms the furthest internal lining, constituted by loose connective tissue that consist of several diffusing lymphatic aggregations, namely lamina propia. Telocytes (TCs) are special interstitial cells located in the lamina propia and in the connective tissue spaces between smooth muscle cell bundles. This cells were previously known as "interstitial Cajal like-cells (ICLC)" and they play multiple roles at different parts of physiological systems.

Keywords: Telocytes; telopodes; podomeres; common bile duct; gallstone disease and Crohn's disease.

1. INTRODUCTION

In a recent article communicated by Benias et al., 2018 [1], the authors proposed a novel expansion and specification of the concept 'interstitium' observed in the human submucosa of the bile duct wall.

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This paper shows the reticular pattern of the submucosa and demonstrate that the collagen bundles are asymmetrically lined on one side by thin, flat cells that have scant cytoplasm and an oblong nucleus. These cells were described by the authors as being fibroblast-like and also immunopositive for endothelial markers and vimentin. This allows us to think that these fibroblast-like cells could correspond to telocytes (TCs), first described by Popescu and his group in 2010 [2]. TCs were previously described by Popescu's team (between 2005 and 2009) using the acronym ICLC (interstitial Cajal-like cell) [2]. Our idea is also supported by the electron microscopy micrographs shown in the same article. We would also like to add that the ultrastructure of these interstitial cells, which presented thin and elongated extensions and the fact that they were positive for CD34 and vimentin, support our suggestion about their identity as TCs, based on the fact that they present the immunohistochemical and ultrastructural characteristics previously described for this type of cells by Cretoiu and Popescu [3]. This is further confirmed by the studies of Pasternak et al., [4] who stated that "in recent years, the physiology and regulatory mechanisms of smooth muscle tissue and the role of the interstitium has been enhanced by the study of a population of newly described cells, the so-called interstitial Cajal like cells "(ICLCs). This is consistent with the studies of Lavoie et al., [5] who described the presence of ICLCs in the gallbladder and extrahepatic biliary duct of the guinea-pig, concluding that ICLCs played a role in the generation and propagation of spontaneous rhythmicity, and hence, the excitability of gallbladder. It is also important to note that subsequently Huang et al., [6] using the same animal model, demonstrated that the ICLCs were distributed in the smooth muscle layers of the gallbladder and bile duct system. ICLCs gradually increased in number and formed a completed cellular network in the lower part of the common bile duct and ampulla, particularly in the sphincter of Oddi. The density of the ICLCs in the common bile duct was significantly higher than that of other bile ducts [7]. Finally these authors concluded that the increased number and density of the ICLCs in these organs strongly suggests that ICLCs could also contribute to the control of functions of the Sphincter of Oddi. ICLCs might also be involved in Sphincter of Oddi dysfunctions and disorders of the bile duct system, adding that Sphincter of Oddi dysfunction often causes a chronic biliary duct pain or recurrent pancreatitis. Hinescu et al., [8] and Ahmadi et al., [9] performed similar studies in humans and found that ICLCs in the extrahepatic bile duct mainly appeared beneath the epithelium in the lamina propia and in the connective tissue spaces between bundles of smooth muscle cells. These authors suggest that from "a physiological point of view, ICLCs might represent, through analogy to the gastrointestinal tract, an essential player in the physiology of a digestive cavitary organ such as gallbladder, imposing the rhythm of bile release (pace-maker cells)". They also concluded that these cells were "involved in gallbladder (dis)functions e.g. pace-making, secretion: auto- juxta- and/or paracrine, intercellular signaling, or stone formation".

It is important to note that in the year 2010 these ICLCs or special interstitial cell type were named TC after Popescu and Faussone-Pellegrini argued for the necessity to unify criteria in its designation [2].

On the other hand, Pasternak et al., [10] demonstrated in humans that TCs were distributed in the smooth muscle layers of the gallbladder and bile duct, noting that gallbladder activity seemed to be dependent on the integrity of the TC network. This was supported by the fact that TCs are significantly decreased in the gallbladder wall in patients with gallstone disease, suggesting that the reduced density of TCs might affect gallbladder motility. This hypomotility would allow time for cholesterol microcrystals to precipitate from lithogenic bile that is supersaturated with cholesterol [11,12] Additionally, the studies of Matyja et al.,[13] concluded that bile composition may influence the TC network integrity: the supersaturated bile can decrease the number of TCs, while glycocholic and taurocholic acids have protective effects on TCs, and thus possibly influence the mechanisms regulating gallbladder and extrahepatic bile duct motility.

It is also important to note that TCs have been described in numerous other organs [2,3,4] performing functions such as repair and remodeling, angiogenesis, pacemaker, intercellular signals and establishing a relationship with the immune response, etc. Therefore, TCs are a peculiar stromal-cell type that play a role in tissue homeostasis and development, and it has also been implicated in the pathophysiology of several disorders [3]. Furthermore, in 2010 Popescu and Faussone-Pellegrini [2] described that TCs communicate

between themselves through their long slim cytoplasmic extensions called telopodes which can present wide endings or podomos or narrow endings denoted as podomeres. Caveolae, mitochondria and endoplasmic reticulum vesicles are accumulated inside podomos. These authors also proposed that “Telocyte communication established through telopodes is denominated homocellular junction. But if the communication is established with other cell types it is denoted as heterocellular junction. These junctions could be established either by direct communication (synapses stromal) or mediated via microvesicles or exosomes” [2,3].

Regarding TC participation in some other medical conditions or pathological disorders, a TC decrease in the stroma of the dermis and the gut has been described in patients with systemic sclerosis [14] and Crohn's disease [15]. In addition, Milia et al. [15] described in the normal gut that TCs form a network-like structure in all the ileal wall layers, from the mucosa to the subserosa. Also, in the gut of Crohn's disease patients, characterized by derangement of the normal disposition of the intestinal walls, these authors observed that TCs have disappeared. The authors stated that “due to the 3-D network of TCs and their strategic position between immune cells, smooth muscle cells, blood and lymphatic vessels, as well as nerve endings, the loss of TCs might have important pathophysiological implications, contributing to the disorder of the intestinal wall architecture, gut dysmotility, and impaired immune surveillance" [15]. It is important to note that in the gut, gallbladder and extrahepatic bile duct, a decrease in the number of TCs correlate with hypomotility effects [13].

Concerning the presence of TCs in other organs, Bosco et al., [16] described these cells showing elongated telopods in the pancreatic septa of the rodent Octodon degus. Further, they also observed that in this case TCs were located near blood and lymphatic capillaries as well as unmyelinated nerves. TCs have also been found in a non-innervated organ such as the placenta, and Suciu et al., [17] and Bosco and Díaz [18] postulated a pacemarker function in the chorionic villi of the organ. Additionally, Bosco and Díaz [18] have also proposed that TCs in the chorionic villi, situated between smooth muscle cells of fetal blood vessels and myofibroblasts, might act as a triad that coordinates the normal placental function.

According to the evidences mentioned above, TCs perform multiple important functions in different organs, and the work of Benias et al., 2018 [1] refers to them and highlights their functions in the extrahepatic biliary tree.

2. CONCLUSIONS

- Fibroblast-like cells reported in the submucosa of the extrahepatic bile duct correspond to TCs, a new cell type described among classical interstitial cells.
- TCs are a rather unique cell type with a particular ultrastructure, immunophenotype, and electrophysiology.
- The physiology and regulatory mechanisms of smooth muscle tissue and the role of the interstitium in different organs has been further understood by studies on TCs.
- Clinical studies have evidenced that a decrease in TC numbers is closely associated with some gastro-intestinal and gallbladder motility disorders.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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