Commentaries Article

TELOCYTES IN THE SUBMUCOSA OF THE EXTRAHEPATIC BILE DUCT

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Abstract

Bile flows out of the liver through hepatic ducts, which join and extend as the common bile duct also known as extrahepatic bile duct to traverse the wall of the duodenum and deliver bile into its lumen. In species with a gallbladder, this duct joins to 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 consists of several diffusing lymphatic aggregations, namely lamina propia. Telocytes (TC) are special interstitial cells located in the lamina propia and in the connective tissue spaces between bundles of smooth muscle cells layer. These cells were previously known as "interstitial Cajal like-cells (ICLC)" and they play multiple roles at different parts of physiological systems, widening-up the ways of researches to develop various fundamental ideas regarding it, along with its potentiality.

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

This paper shows the reticular pattern of this layer and the cells lining in a intermittently way the collagen bundles. These cells, described by the authors as fibroblast-like cells were immunopositive for endothelial markers and vimentin. These facts allow us to think that these fibroblast-like cells could correspond to telocytes (TC), which cells were first described by Popescu and his group in 2010 [2]. This is also supported by the electron microscopy micrographs showed in the same article. In addition TCs were previously described by Popescu's team (between 2005 and 2009) using the acronym ICLC (interstitial Cajal-like cells) [2]. 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 its identity as TC, 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 "(ICLC). The latter is consistent with the studies of Lavoie et al., [5] who described the presence of ICLC in the gallbladder and extrahepatic biliary duct of the guinea-pig, concluding that ICLC 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., [7] using the same animal model, demonstrated that the ICLCs were distributed in the smooth muscle layers of the gallbladder and bile duct system and that ICLC 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 ICLC in the common bile duct was significantly higher than that of other bile ducts. Finally these authors concluded that the increased number and density of the ICLC in the ampulla and the lower part of the common bile duct strongly suggests that the ICLC could also contribute to the control of functions of the sphincter of Oddi and might be involved in the pathophysiologies of sphincter of Oddi dysfunction 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 ICLC 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, ICLC 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 ICLC or special interstitial cell type was named TC after Popescu and Faussone-Pellegrini argumented the necessity to unify criteria in its designation [2].

On the other hand, Pasternak et al., [10] demonstrated in humans that TC were distributed in the smooth muscle layers of the gallbladder and bile duct, arguing that gallbladder activity seemed to be also dependent on the integrity of the TC network. This supported by the fact that TCs are significantly decreased in the gallbladder wall in patients with gallstone disease, suggesting that the reduced density of TC 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 the presence of TC has been described in numerous other organs [2, 3, 4], fulfilling perform functions: repair and remodeling, angiogenesis, pacemaker, intercellular signals, relationship with the immune response, etc. Therefore, TC is a peculiar stromal-cell type that plays a role in tissue homeostasis and development, and it has also been implicated in the pathophysiology of several disorders [3]. In order to complete the concept of TC, in 2010 Popescu and Faussone-Pellegrini [2] described that telocytes 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 "The telocyte communication established through telopodes is denominated homocellular junction, but if the communication is established with other cell type it is denoted as a 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 others 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 TC form a network-like structure in all the ileal wall layers, from the mucosa to the subserosa. On the other hand, in the gut from Crohn's disease patients, characterized by derangement of the normal disposition of the intestinal walls, these authors observed that TC have disappeared. The authors stated that “due to the 3-D network of TC and their strategic position between immune cells, smooth muscle cells, blood and lymphatic vessels, as well as nerve endings, the loss of TC 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 and in the gallbladder and extrahepatic bile duc, a decrease in the number of TCs correlate with hypomotility effects [13].

Concerning the presence of TC in other organs, Bosco et al., [16] described TC showing elongated telopods in the pancreatic septa of the rodent Octodon degus. Further, they also observed that in this case TC was located nearby blood and lymphatic capillaries as well as to unmyelinated nerves. TC have also been found in a not-innervated organ such as the placenta, and Suciu et al., [17] and Bosco and Díaz [18] postulated a pacemaker function in the chorionic villi of the organ. Additionally, Bosco and Díaz [18] have also proposed that TC in the chorionic villi, situated between smooth muscle cells of fetal blood vessels and myofibroblast, might acts as a triad that coordinates the normal placental function.

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

CONCLUSIONS:

- Fibroblast-like cells reported in the submucosa of the extrahepatic bile duct correspond to TC, 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 enhanced by studies on TC.

- Clinical studies have indicated that a reduction in the TCs is closely associated with some gastrointestinal and gallbladder motility disorders.

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