Commentaries/Opinion Article 1 2 TELOCYTES IN THE SUBMUCOSA OF THE 3 **EXTRAHEPATIC BILE DUCT?** 4 5 6 7 Abstract 8 Extra hepatic bile duct projects the bile inside the stomach so that the further process of 9 10 digestion can occur properly. Whereas, Sub mucosa layer inside forms the furthest internal lining of the duct and formed by loose connective tissue that consist of several diffusing 11 lymphatic aggregations, namely Lamina propria. Telocytes are the special interstitial cells 12 which are may be known as "interstitial neurones" that plays multiple roles at the different 13 parts of physiological system and also widen up the ways of researches to develop various 14 fundamental ideas regarding it, along with its potentiality. 15 16 Key words: telocytes, telopodes, podomeres, systemic sclerosis and Crohn's disease. 17 18 19 In a recent article communicated by Benias et al., 2018 [1], the authors propose a novel 20 expansion and specification of the concept 'interstitium' observed in the human submucosa 21 of the bile duct wall. 22 23 The article shows the reticular pattern of this layer and the cells lining in a intermittently 24 way the collagen bundles. These cells, described by the authors as fibroblast-like cells were 25 immunopositive for endothelial markers and vimentin. These facts allow us to think that 26 these fibroblast-like cells could correspond to telocytes (TC), cells first described by Popescu 27 and his group in 2010 [2]. This is also supported by the electron microscopy micrographs 28 showed in the same article. 29 We would also like to add that the ultrastructure of these interstitial cells, which presented 30 31 thin and elongated extensions and the fact that they were positive for CD34 and vimentin, 32 support our suggestion about its identity as TC. The presence of such cells has been described in numerous other organs [2-4], fulfilling different functions: repair and 33 34 remodeling, angiogenesis, pacemaker, intercellular signals, relationship with the immune 35 response, etc, [3-5]. In this regard, 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].

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39 In 2010 Popescu et al., [2] described that "telocytes communicate between themselves through their long, slim cytoplasmic extensions, called telopodes, which can present wide 40 41 endings, or podomos, or narrow endings denoted as podomeres. Caveolae, mitochondria 42 and endoplasmic reticulum vesicles are accumulated inside podomos". These authors also proposed that "The telocyte communication established through telopodes is denominated 43 44 homocellular junction, but if the communication is established with another cell type it is 45 denoted as heterocellular junction. These junctions could be established either by direct 46 communication (synapses stromal) or mediated via microvesicles or exosomes" [2, 6].

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Regarding TC participation in some medical conditions or pathological disorders, a TC 48 49 decrease in the stroma of the dermis and the gut has been described in patients with systemic sclerosis [7] and Crohn's disease [8]. In addition, Milia et al. [8] described in the 50 51 normal gut that TC form a network-like structure in all the ileal wall layers, from the mucosa 52 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 53 that TC have disappeared. The authors stated that "due to the 3-D network of TC and their 54 55 strategic position between immune cells, smooth muscle cells, blood and lymphatic vessels, 56 as well as nerve endings, the loss of TC might have important pathophysiological 57 implications, contributing to the disorder of the intestinal wall architecture, gut dysmotility, 58 and impaired immune surveillance" [8].

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60 Concerning the presence of TC in other organs, Bosco et al., [5] described TC showing 61 elongated telopods in the pancreatic septa of the rodent Octodon degus. Further, they also 62 observed that in this case TC were located nearby blood and lymphatic capillaries as well as to unmyelinated nerves. TC have been also found in a not-innervated organ such as the 63 64 placenta, and Suciu et al., [6] and Bosco and Díaz [4] postulated a pacemarker function in 65 the chorionic villi of the organ. Additionally, Bosco and Díaz [4] have also proposed that TC 66 in the chorionic villi, situated between smooth muscle cells of fetal blood vessels and 67 myofibroblast, might acts as a triad that coordinates the normal placental function.

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According to the above, the new evidence provided by Benias et al., [1], added to our interpretation of the identity of the fibroblast-like cells as TC widens the organological location of TC. It will be necessary to dilucidate the function of these interstitial cells in the

submucosa wall of the extrahepatic bile duct.

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