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Interstitial Cajal-Like Cell: A New Player in Cholelithiasis?

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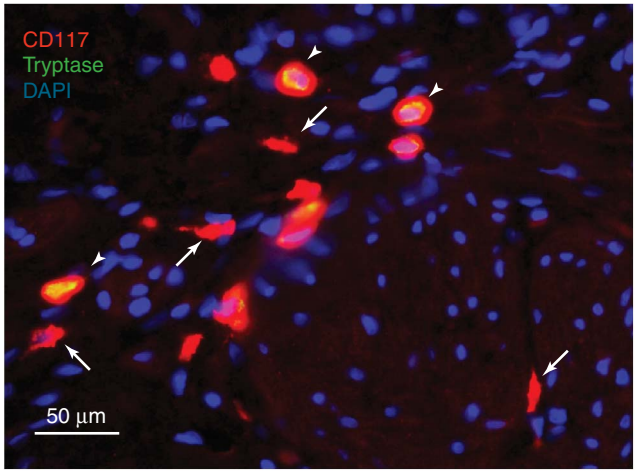

Figure 1. Cross-section through the muscularis propria of gallbladder stained for CD117 (red) and tryptase (green). The nuclei are counterstained with 4′,6-diamidino-2-phenylindole (DAPI, blue). CD117-positive/tryptase-negative interstitial Cajal-like cells (arrows) and CD117-positive/tryptase-positive mast cells (arrowheads).

To the Editor: The incidence of gallstones is relatively high in the developed countries, with ~10% of the whole population being affected. Even though there is a lack of clear hypothesis on gallstone formation, a few factors are proved to be responsible for this process: cholesterol supersaturation, hydrophobic bile salts, pronucleating proteins, mucus hypersecretion with gel formation in the gallbladder and disrupted gallbladder motility. The gallbladder dysmotility seems to be a "trigger" event in the pathogenesis of cholesterol gallstones, providing the time necessary for the precipitation of cholesterol microcrystals from bile supersaturated with cholesterol. Considering increasing knowledge of the role of interstitial cells of Cajal in the regulation of gastrointestinal tract (GI) motility as well as in the pathogenesis of multiple GI disorders, and the fact that these cells were recently described in human gallbladder and biliary tract, we wondered whether interstitial cells of Cajal (or interstitial Cajal-like cells—ICLCs—as they are called when localized in extraintestinal organs) are present in gallbladder wall in patients with cholelithiasis and whether their density decreases or perhaps remains intact.

We used indirect double immunofluorescence method to visualize ICLCs. A characteristic feature of ICLCs is the expression of transmembrane tyrosine kinase receptor proteins, including the c-Kit receptor (CD117), which enables the identification of ICLCs. Unfortunately, the CD117 is present in the mast cells as well, and for that reason we stained slides with anti-mast cell tryptase. ICLCs were defined as c-Kit-positive nucleated cells that lacked mast cell tryptase expression (**Figure 1**). ICLCs were observed throughout the gallbladder, including the fundus, body (corpus), and neck, although they were predominantly located in the corpus, almost exclusively within the muscularis propria. ICLCs had a centrally located nucleus and were mostly fusiform in shape; however, sparse, round tryptase/c-Kit-positive cells were also present (1).

In our study (2), we reported for the first time that interstitial Cajal-like cells are lost or damaged in patients suffering from cholelithiasis. We observed the cells positive for the c-Kit receptor (CD117) in the gallbladder wall in all cases examined. ICLCs were most frequently located in the muscularis propria. The density of ICLCs in the muscularis propria was significantly lower in the patients with gallstones than the density observed in the controls (26.24 ± 10.89 vs. 56.29 ± 13.35 cell mm^{-2} in the muscularis propria, $P<0.001$).

The published data on ICLCs in the human gallbladder are still very limited. ICLCs were described in the wall of the human gallbladder by Hinescu *et al.* (3) and in the bile ducts by Ahmadi *et al.* (4). Both teams reported that ICLCs in the gallbladder formed a cellular network that is likely involved in biliary tract motility. Consequently, animal studies suggested the potential role of ICLCs in functional disturbances of the gallbladder. So far, we have not found any works published on ICLCs in the context of pathogenesis of gallstone in humans. Our studies revealed that ICLCs play a role in the pathogenesis of gallstone disease. Furthermore, from the currently finished research (5) we conclude that bile content may influence these cells. It implies some possible future medical interventions.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Stress as a Risk Factor for Inflammatory Bowel Disease: More Evidence From Our OEF/OIF Veterans?

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Table 1. Demographic information and prevalence of different types of psychiatric disorders among cases and controls

	OEF/OIF with IBD cases	OEF/OIF without IBD control 1	Non-OEF/OIF with IBD control 2
n	202	426	6,808
Mean age in years (at diagnosis)	32.6[a]±9.0	35.2±9.4	58.2[a]±14.7
Mean BMI	28.2	29.4	28.6
Gender (% males)	177:26 (87%)	368:58 (86%)	6,358:449 (93%)
IBD type (CD/UC)	103/99 (51%/49%)	NA	3,127/3,681 (46%/54%)
Years to develop IBD after deployment (mean±s.d.)	4.5 ± 2.3 years. Range: 0.83-9.98	n/a	
Smoking	53 (26%) UC 63 (31%) CD	91 (21%)	2,518 (37%) UC 2,723 (40%) CD
Overall psychiatric disorders	*50%*	*32%* *OR=1.76* *95% CI 1.26, 2.48*	*36%* *OR=2.8* *95% CI: 2.15, 2.79*
Bipolar/manic disorder	3%	2% OR=1.41 95% CI: 0.50, 4.04	2.5% OR=1.15 95% CI: 0.50, 2.63
Major depressive/ mood disorder	11%	9% OR= 1.35 95% CI: 0.78, 2.34	10% OR=1.15 95% CI: 0.74, 1.78
Anxiety/panic disorder	28%	20% OR=1.53 95% CI: 1.04, 2.25	22% OR=1.41 95% CI: 1.04, 1.93
PTSD	32%	26% OR=1.31 95% CI: 0.91, 1.89	13% OR=3.03 95% CI: 2.27, 4.04

BMI, body mass index; CD, Crohn's Disease (ICD9 555.X); CI, confidence interval; IBD, inflammatory bowel disease; OEF, Operation Iraqi Freedom; OIF, Operation Enduring Freedom; OR, odds ratio; PTSD, post-traumatic stress disorder; UC, Ulcerative Colitis (ICD9 556.X).
[a]Age at diagnosis.

To the Editor: With a growing number of veterans returning from military engagements abroad, a new focus is being placed upon the psychological effects of experiencing combat. Depression, post-traumatic stress disorder (PTSD), and other psychiatric diseases are common diagnoses in veterans of wars such as Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) (1). With a plausible link between psychological stress and inflammatory bowel disease (IBD) (2–4), we hypothesized that exposure to combat and the subsequent presence of psychiatric disorders is related to the development of IBD. More specifically, we expected that veterans of OEF and OIF (post-combat veterans) with IBD would have a higher prevalence of psychiatric disorders than either non-OEF/OIF deployed veterans (non-combat veterans) with IBD or post-combat veterans without IBD.

In this pilot study, we used a two-to-one case–control analysis utilizing psychiatric and drug history data from the South Central VA Health Care Network VISN 16 medical database. The sample included data from 202 combat veterans with IBD (case group, ICD-9 codes 555-556-x) diagnosed between January 1996 and May 2012 following their initial deployment date, 426 non-matched randomly selected combat veterans without IBD (control group 1), and 6,808 veterans with IBD who were not deployed to OEF or OIF but developed IBD during the same time period (control group 2) (**Table 1**). The psychiatric disorders studied were bipolar/manic disorders, major depression/mood disorders, anxiety/panic disorders, and PTSD. Odds ratios were used to quantify and compare risks between the case group and control groups. Data was excluded from analysis if the patient had an IBD diagnosis before the deployment, a psychiatric disorder diagnosed after the IBD diagnosis or before the deployment to OEF/OIF, or a diagnosis of non-infectious or non-specified colitis (ICD 558.x).

We discovered that more post-combat veterans with IBD were diagnosed with psychiatric disorders when compared with post-