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## **Relevance of SARS-CoV-2 related factors ACE2 and TMPRSS2 expressions in gastrointestinal tissue with pathogenesis of digestive symptoms, diabetes-associated mortality, and disease recurrence in COVID-19 patients — [Source link](#)**

Ashutosh Kumar, Muneeb A. Faiq, Vikas Pareek, Khurshed Raza ...+10 more authors

**Institutions:** All India Institute of Medical Sciences, New York University, National Brain Research Centre, University of Pittsburgh ...+7 more institutions

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1 **Relevance of SARS-CoV-2 related factors ACE2 and TMPRSS2 expressions in**  
2 **gastrointestinal tissue with pathogenesis of digestive symptoms, diabetes-associated**  
3 **mortality, and disease recurrence in COVID-19 patients**

4 **Short title: Relevance of ACE2 and TMPRSS2 gastrointestinal expressions in COVID-**  
5 **19 pathogenesis**

6 \*Ashutosh Kumar<sup>1,2</sup>, Muneeb A. Faiq<sup>1,3</sup>, Vikas Pareek<sup>1,4</sup>, Khurshed Raza<sup>1,5</sup>, Ravi K.  
7 Narayan<sup>1,2</sup>, Pranav Prasoon<sup>1,6</sup>, Pavan Kumar<sup>1,7</sup>, Maheswari Kulandhasamy<sup>1,8</sup>, Chiman  
8 Kumari<sup>1,9</sup>, Kamla Kant<sup>1,10</sup>, Himanshu N. Singh<sup>1,11</sup>, Rizwana Qadri<sup>1,12</sup>, Sada N. Pandey<sup>1,13</sup>,  
9 Santosh Kumar<sup>1,14</sup>

- 10 1- Etiologically Elusive Disorders Research Network (EEDRN), New Delhi, India  
11 2- Department of Anatomy, All India Institute of Medical Sciences (AIIMS), Patna,  
12 India  
13 3- New York University (NYU) Langone Health Center, NYU Robert I Grossman  
14 School of Medicine, New York, New York, USA  
15 4- National Brain Research Center, Manesar, Haryana, India  
16 5- Department of Anatomy, All India Institute of Medical Sciences, Deoghar, India  
17 6- Pittsburgh Center for Pain Research, School of Medicine, University of Pittsburgh,  
18 Pittsburgh, Pennsylvania, USA  
19 7- Department of Pediatrics, Medical University of South Carolina, Charleston, USA  
20 8- Department of Biochemistry, Maulana Azad Medical College (MAMC), New Delhi,  
21 India  
22 9- Department of Anatomy, Postgraduate Institute of Medical Education and Research  
23 (PGIMER), Chandigarh, India  
24 10- Department of Microbiology, All India Institute of Medical Sciences (AIIMS),  
25 Bathinda, India  
26 11- TAGC-INSERM, U1090, Aix Marseille University, Marseille, France  
27 12- Neuro-oncology Laboratory, Rockefeller University, New York, New York, USA  
28 13- Department of Zoology, Banaras Hindu University (BHU), Varanasi, India  
29 14- Department of Anesthesiology and Critical Care Medicine, School of Medicine, Johns  
30 Hopkins University, Baltimore, USA  
31  
32  
33  
34  
35  
36

37 \*Corresponding author  
38 Ashutosh Kumar  
39 drashutoshkumar at aiimspatna.org

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## 44 **Abstract**

### 45 **Introduction**

46 COVID-19 is caused by a new strain of coronavirus called SARS-coronavirus-2 (SARS-  
47 CoV-2), which is a positive sense single strand RNA virus. In humans, it binds to angiotensin  
48 converting enzyme 2 (ACE2) with the help a structural protein on its surface called the S-  
49 spike. Further, cleavage of the viral spike protein (S) by the proteases like transmembrane  
50 serine protease 2 (TMPRSS2) or Cathepsin L (CTSL) is essential to effectuate host cell  
51 membrane fusion and virus infectivity. COVID-19 poses intriguing issues with imperative  
52 relevance to clinicians. The pathogenesis of GI symptoms, diabetes-associated mortality, and  
53 disease recurrence in COVID-19 are of particular relevance because they cannot be  
54 sufficiently explained from the existing knowledge of the viral diseases. Tissue specific  
55 variations of SARS-CoV-2 cell entry related receptors expression in healthy individuals can  
56 help in understanding the pathophysiological basis the aforementioned collection of  
57 symptoms.

### 58 **Materials and Methods**

59 The data were downloaded from the Human Protein Atlas available at  
60 (<https://www.proteinatlas.org/humanproteome/sars-cov-2>) and the tissue specific expressions  
61 (both mRNA and protein) of ACE2 and TMPRSS2 as yielded from the studies with RNA  
62 sequencing and immunohistochemistry (IHC) were analyzed as a function of the various  
63 components of the digestive tract. A digestive system specific functional enrichment map of  
64 ACE2 gene was created using g:profiler (<https://biit.cs.ut.ee/gprofiler/gost>) utility and the  
65 data were visualized using Cytoscape software, version 3.7.2 (<https://cytoscape.org/>).

### 66 **Results**

67 The correlated expression (transcriptomic and proteomic) of ACE2 (to which SARS-CoV-2  
68 binds through the S-spike) was found to be enriched in the lower gastrointestinal tract (GIT)  
69 (highest in small intestine, followed by colon and rectum), and was undetectable in the upper  
70 GIT components: mouth cavity (tongue, oral mucosa, and salivary glands), esophagus, and  
71 stomach. High expression of ACE2 was noted in the glandular cells as well as in the  
72 enterocytes in the lining epithelium (including brush border epithelium). Among other  
73 digestive system organs, Gall bladder (GB) showed high expression of ACE2 in glandular  
74 cells, while any protein expression was undetectable in liver and pancreas. TMPRSS2 was  
75 found enhanced in GIT and exocrine glands of pancreas, and co-localized with ACE2 in  
76 enterocytes.

### 77 **Conclusions**

78 Based on the findings of this study and supportive evidence from the literature we propose  
79 that a SARS-CoV-2 binding with ACE2 mediates dysregulation of the sodium dependent  
80 nutrient transporters and hence may be a plausible basis for the digestive symptoms in  
81 COVID-19 patients. ACE2 mediated dysregulation of sodium dependent glucose transporter  
82 (SGLT1 or SLC5A1) in the intestinal epithelium also links it to the pathogenesis of diabetes  
83 mellitus which can be a possible reason for the associated mortality in COVID-19 patients  
84 with diabetes. High expression of ACE2 in mucosal cells of the intestine and GB make these  
85 organs potential sites for the virus entry and replication. Continued replication of the virus at

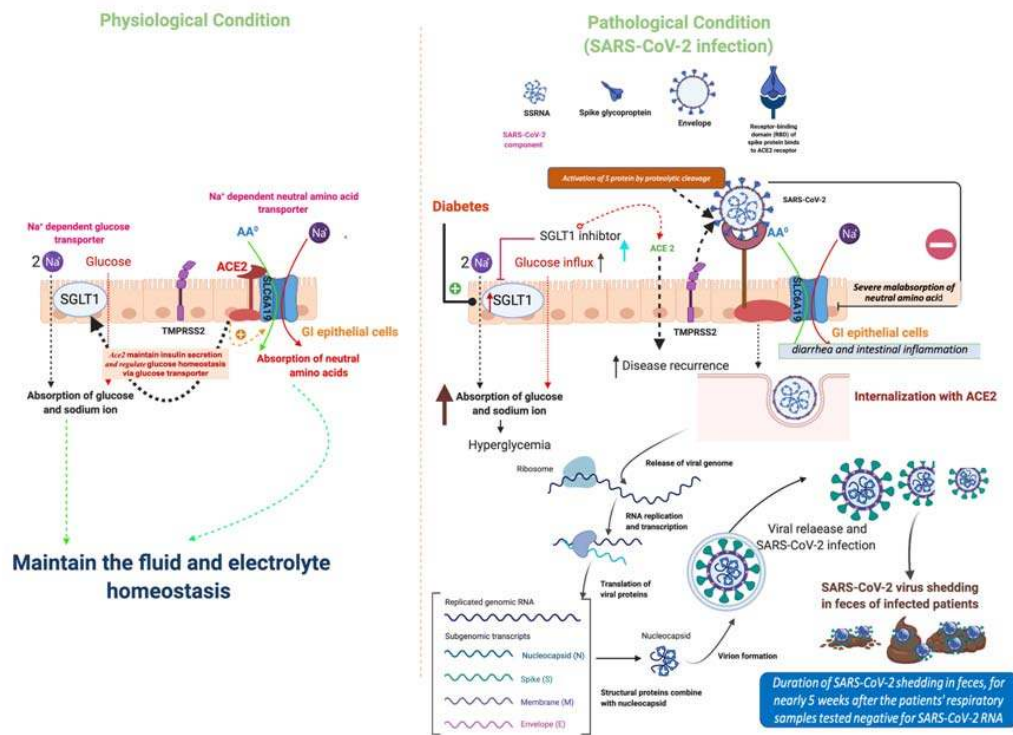
86 these ACE2 enriched sites may be a basis for the disease recurrence reported in some,  
87 thought to be cured, patients.

88 **Keywords:** SARS-CoV2, digestive symptoms, recurrence, amino acid  
89 transporter, glucose transporter

90

## 91 Graphical Abstract

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93

94

## 95 Introduction

96 The world is currently reeling in an alarming outbreak of novel coronavirus disease 2019  
97 referred to as COVID-19. COVID-19 is caused by a new coronavirus strain severe acute  
98 respiratory syndrome coronavirus 2 (SARS CoV-2)—a positive sense single strand RNA  
99 virus. Recent studies which decoded structure of the virus showed binding of its S-spike  
100 protein to a human protein- angiotensin converting enzyme 2 (ACE2) (1-3). Following ACE2  
101 binding, cleavage of the viral spike protein (S) by the serine proteases like transmembrane  
102 serine protease 2 (TMPRSS2) or Cathepsin L (CTSL) is essential to effectuate host cell  
103 membrane fusion and virus infectivity (4). Clinical presentation in COVID-19 patients is  
104 highly diverse and majority of them primarily presents with pulmonary symptoms (cough,  
105 fever, shortness of breath) (5). In addition, some of the patients present with digestive  
106 symptoms like diarrhea, nausea, vomiting and abdominal pain (data ranges from 3.8% to  
107 50.5%) (6). Digestive symptoms have been the only presentations in some of the patients  
108 (8,9). Digestive symptoms are not unique to the COVID-19 and usually present in the  
109 gastroenteritis caused by many other respiratory syndrome viruses like SARS-CoV-1 and  
110 influenza A and B (10,11). However, how SARS-CoV-2 makes entry into the gastrointestinal  
111 (GI) tissue leading to gastroenteritis-like features, does not imbibe sufficient and coherent  
112 explanation in the light of the existing literature. Some investigators have speculated a fecal-  
113 oral route of transmission based on fecal shedding of viral proteins and infectious virus in  
114 some COVID-19 patients (12,13).

115 Knowing the expression pattern of ACE2 and one of the proteases, TMPRSS2 in  
116 gastrointestinal tract (GIT) may explicate the pathogenesis of digestive symptoms in COVID-  
117 19. Digestive juices and enzymes secreted from the liver, gall bladder (GB) and pancreas play  
118 an important role in maintenance of the secretions and absorption of nutrients across  
119 intestinal epithelium. Hence their possible dysfunction in COVID-19 patients needs to be  
120 examined in order to understand pathogenesis of the digestive symptoms which, in turn,  
121 prevent some COVID-19 associated mortality.

122 Existing literature on the role of ACE2 in regulation of the ion transporters which maintain  
123 secretion/absorption across intestinal epithelium provide a clue that digestive symptoms in  
124 COVID-19 may have an ACE2 based etiogenesis (11,14-16). Investigating the ACE2  
125 expression pattern of digestive system components may also help to explain exacerbated  
126 diabetic complications and mortality in COVID-19 patients. Diabetes has been noted as a co-  
127 morbidity (16.2%) in COVID-19 and has contributed to increased mortality (22%) (17)  
128 Existing literature implicates ACE2 mediated dysregulation of sodium dependent glucose  
129 transporter (SGLT1 or SLC5A1) at intestinal epithelium in the pathogenesis of the diabetes  
130 mellitus (18,19).

131 In this study, we aim at examining the plausibility (based on the tissue specific expression of  
132 ACE2) whether any of the digestive system components can be involved in the continued  
133 replication of the SARS-CoV-2 after pulmonary symptoms are relieved. Many incidences of  
134 disease recurrence have been reported in COVID-19 patients even after being discharged  
135 from the hospital. Studies have reported continued shedding of SARS-CoV-2 in the feces of  
136 COVID-19 patients up to five weeks after disappearance of the pulmonary symptoms  
137 bolstering the indication that a residual persisting of virus inside the digestive system  
138 components may be a reason for the disease recurrence (20).

139 We aimed to validate transcriptomic and proteomic expression of ACE2 and TMPRSS2 in  
140 the components of human digestive system (including liver, GB, and pancreas) in tissues

141 derived from the healthy individuals to understand pathophysiological basis of the digestive  
142 symptoms in COVID-19 patients.

## 143 **Materials and Methods**

144 We analyzed the tissue specific distribution of ACE2 and TMPRSS2 (mRNA and protein) in  
145 digestive system components (GIT, liver & GB, and pancreas) using RNA sequencing and  
146 immunohistochemistry (IHC) data available in Human Protein Atlas  
147 (<https://www.proteinatlas.org/humanproteome/sars-cov-2>). A digestive system specific  
148 functional enrichment map of ACE2 gene was constructed using g:profiler  
149 (<https://biit.cs.ut.ee/gprofiler/gost>) utility and viewed with Cytoscape software, version 3.7.2  
150 (<https://cytoscape.org/>). Since no direct subject or patient data were used in this study,  
151 clearance from the Institutional Ethics Committee was precluded.

### 152 **Human Protein Atlas methods**

153 Estimation of mRNA expression and localization of human proteins were performed by the  
154 source laboratory using deep sequencing of RNA (RNA-seq) and IHC in normal tissue.

### 155 **IHC**

156 As described by the source labs, specimens containing normal tissue were collected and  
157 sampled from anonymized paraffin embedded material of surgical specimens, in accordance  
158 with approval from the local ethics committee. The specimens were derived from surgical  
159 material, normal was defined by morphological parameters and absence of neoplasia. IHC  
160 staining was performed using a standard protocol on normal tissue microarray  
161 ([https://www.proteinatlas.org/download/IHC\\_protocol.pdf](https://www.proteinatlas.org/download/IHC_protocol.pdf)). Antibodies against human ACE2  
162 (HPA000288, CAB026174) and TMPRSS2 (HPA035787) were labeled with DAB (3, 3'-  
163 diaminobenzidine) stain. Protein expression score was done based on the staining intensity  
164 (negative, weak, moderate or strong) and fraction of stained cells (<25%, 25-75% or >75%).  
165 For each protein, the IHC staining profile was matched with mRNA expression data and  
166 gene/protein characterization data to yield an 'annotated protein expression' profile.

### 167 **Transcriptomics**

168 The Human Protein Atlas collects transcriptomic data from the three databases (HPA, GTEx  
169 and FANTOM5). HPA RNAseq was performed on human tissue samples from healthy  
170 individuals (Accession no: PRJEB4337, Ensembl: ENSG00000130234 (version 92.38). Total  
171 RNA was extracted from the tissue samples using the RNeasy Mini Kit (Qiagen, Hilden,  
172 Germany) according to the manufacturer's instructions. The extracted RNA samples were  
173 analyzed using either an Experion automated electrophoresis system (Bio-Rad Laboratories,  
174 Hercules, CA, USA) with the standard-sensitivity RNA chip or an Agilent 2100 Bioanalyzer  
175 system (Agilent Biotechnologies, Palo Alto, USA) with the RNA 6000 Nano Labchip Kit.  
176 Only samples of high-quality RNA (RNA Integrity Number 7.5) were used for the mRNA  
177 sample preparation for sequencing. mRNA sequencing was performed on Illumina  
178 HiSeq2000 and 2500 machines (Illumina, San Diego, CA, USA) using the standard Illumina  
179 RNA-seq protocol with a read length of 2x100 bases. Transcript abundance estimation was  
180 performed using Kallisto v0.43.1 (<https://pachterlab.github.io/kallisto/about>). The normalized  
181 Tags Per Million (TPM) for each gene from the three databases were calculated and included  
182 in the Human Protein Atlas. Each tissue was categorized for the intensity of gene expression  
183 using a cutoff value of 1 NX as a limit for detection across all tissues. A tissue was  
184 categorized (i) enriched if it had NX level at least four times higher than other tissues, (ii) low  
185 specificity if  $NX \geq 1$  in at least one tissue, (iii) Not detected if  $NX < 1$  in all tissues. Further

186 details of the assays and annotation used by the Human Protein Atlas can be accessed at:  
187 <https://www.proteinatlas.org/about/assays+annotation#ihk>.

### 188 **Gene enrichment analysis and visualization**

189 Functional enrichment analysis of the ACE2 gene was performed with g: profiler web server  
190 (<https://biit.cs.ut.ee/gprofiler/gost>) and p-value computed using a Fisher's exact test with  
191 multiple-test correction. Enrichment map visualization was done with the help of Cytoscape  
192 software, version 3.7.2 (<https://cytoscape.org/>).

### 193 **Results** (Fig. 1-3, S1-3, Table 1, S1-2)

194 The transcriptomic and proteomic expression of ACE2 displayed high enrichment in the  
195 lower GIT (small intestine, colon, and rectum) (Fig. 1, 2e-h, Table 1). It was highest in the  
196 parts of small intestine followed by the colon and the rectum, and nearly absent  
197 (negligible/low mRNA expression and undetectable protein expression) in the upper GIT  
198 components: mouth cavity (including tongue, oral mucosa, and salivary glands), esophagus,  
199 and stomach (Fig. 1, 2a-d). GB showed high glandular expression of ACE2, while any  
200 protein expression was undetectable in appendix, liver (hepatocytes and bile duct), and  
201 pancreas (exocrine and endocrine glandular tissue) (though minimal mRNA expression was  
202 noted) (Fig. 3). Intense ACE2 expression was noted in the glandular cells as well as in the  
203 enterocytes in the lining epithelium of the lower GIT (Fig. 2e-h). The cellular expression of  
204 ACE2 was visible in the enterocyte cytoplasm and in the apical brush border (Fig. 2e-h,  
205 marked with arrow heads). The digestive system specific functional enrichment map for  
206 ACE2 gene were related to digestive functions like enzyme activity, amino acids transport,  
207 and peptide metabolism at the brush border membrane of enterocytes in the intestinal  
208 epithelium (Fig. S1, Table S1). TMPRSS2 was found enhanced in GIT and exocrine glands  
209 of pancreas (Fig. S2, Table S2) and found co-localized with ACE2 in enterocytes (Fig. S3).

### 210 **Discussion**

211 We found enriched transcriptomic and proteomic expression of SARS-CoV-2 binding  
212 receptor ACE2 in lower GIT (small intestine, colon, and rectum) and GB (Fig. 1-3, Table 1).  
213 The digestive system specific functional enrichment map of the ACE2 gene suggests its role  
214 in regulating secretory/absorptive functions at the brush border membrane of the enterocytes  
215 in the intestinal lining epithelium (Fig.S1, Table S1). The co-localized expression of SARS-  
216 CoV-2 cell entry associated protease TMPRSS2 in the enterocytes make these cells potential  
217 sites for viral infection (Fig. S2-3, Table S2).

218 ACE2 is a homologue of angiotensin-I converting enzyme (ACE), the key enzyme of the  
219 renin-angiotensin system (RAS). It is an integral membrane protein and localizes  
220 predominantly at the apical surface of polarized epithelial cells where it is proteolytically  
221 cleaved within its ectodomain to release a soluble form (21,22). Currently, SARS-CoV-2  
222 mediated binding of ACE2 and the following downstream events leading to tissue damage  
223 are little known. Presumptive understanding of SARS-CoV-2 driven pathology is being  
224 borrowed from SARS-CoV-1 which was the etiological basis of SARS pandemic in 2003.  
225 Uniquely, it acted on the same receptor as SARS-CoV-2 and led to many clinical  
226 manifestations similar to COVID-19 (23). Studies utilizing cell lines to decipher SARS  
227 pathology in lung tissue showed that the spike protein of SARS-CoV-1 (SARS-S) induced  
228 TNF $\alpha$  production which facilitated virus entry (24). TNF $\alpha$  also led to inflammation of the cell  
229 membrane and consequently tissue damage (22-24). SARS-CoV-1 was also showed to cause  
230 downregulation of ACE2 expression at the cell membrane level (22,25). Existing literature  
231 regarding expression of ACE2 in human tissues are rare. Hamming et al, studied ACE2

232 protein expression in human tissues in reference to SARS-CoV-1 (26). Our findings for  
233 ACE2 protein expression in digestive system components are in line with the findings of their  
234 study (26). Recently, enriched expressions of ACE2 (and TMPRSS2) in enterocytes and  
235 mucus producing cells were shown using single cell m-RNA expression studies (27,28).  
236 Enriched expression of SARS-CoV-2 binding receptor ACE2 in the mucosal glands and  
237 enterocytes (including brush border cells) in the lining epithelium (Fig. 2e-h, Table 1) of the  
238 lower GIT indicates that GI cells are potential sites for virus replication. Evidence of the viral  
239 shedding in the feces shown in some studies indicates possible replication of the virus inside  
240 the GI cells which, in turn may explain GI manifestations of COVID-19 in addition to disease  
241 recurrence (29,30). Recent *in situ* studies using recombinant strain of SARS-CoV-2 showed  
242 that the virus can potentially infect and replicate in human intestinal tissue (31,32). Further,  
243 GIT to pulmonary spread of SARS-CoV-2 infection has been indicated by a study by Sun *et*  
244 *al* who showed in a transgenic mouse expressing human ACE2 that a direct intragastric  
245 inoculation of SARS-CoV-2 can cause productive infection and lead to pulmonary  
246 pathological changes (33).

247 How the virus reaches the GI is arguable? Some authors speculated a fecal-oral route of entry  
248 (8). Shedding of infectious SARS-CoV-2 in feces was also detected in occasional COVID-19  
249 patients (12,13). We examined possibility of this route of entry based on the expression  
250 pattern of ACE2 along the length of the GIT (Fig. 1, 2, Table 1). Negligible or very low  
251 mRNA expression and undetectable proteomic expression of ACE2 in the mouth cavity  
252 (including tongue, oral mucosa, and salivary glands), esophagus, and stomach (Fig. 1, 2a-d,  
253 Table 1) indicate these parts of GIT can be resistant for the virus entry. But this observation  
254 does not negate a possible site of virus entry through the ACE2 receptors present in the lower  
255 GIT in case of fecal-oral transmission. It is then intriguing that how SARS-CoV-2 survives  
256 extremes of pH within the digestive system milieu (gastric-1.5 to 3.5, pancreatic-7.5, bile  
257 acid-7-8) while passing along the length of GIT. Recently, Chin *et al.*, 2020 showed *in vitro*  
258 that SARS-CoV-2 can survive at wide range of pH values at room temperature (pH3-10)  
259 (34). This can be further explained by an earlier study by Hirose *et al.*, who, in an  
260 experimental, model demonstrated that RNA viruses like influenza A and B (when  
261 swallowed) can survive extremes of pH and maintain infectivity with help of the mucus cover  
262 lining GIT allowing their safe passage and even excretion in feces (35). Mucus cells are  
263 abundant all along the length of the GIT which can contribute to the carriage and survival of  
264 SARS-CoV-2 thereby contributing to the so hypothesized fecal-oral transmission. This also  
265 hints that shedding of the virus in feces always may not be indicative of its replication in GI  
266 cells; all those patients who shed virus in stools don't necessarily present with digestive  
267 symptoms (29).

268 Healthy intestinal mucosa may not be well conducive for the entry of the virus due to the  
269 presence of unique multi-layer barrier system, though a prior inflammatory condition which  
270 disrupts mucosal barrier may render the lower GI entry of the SARS-CoV-2 using ACE2  
271 receptor and its replication inside tissue plausible (36). Inflammatory conditions in GIT  
272 enhance the expression of ACE2 in the luminal epithelium which can provide additional  
273 support for the entry of the virus (37). Once inside the GI cells, the virus can replicate there  
274 and may orchestrate viral toxin mediated cell injury ensuing further inflammation, thereby,  
275 giving rise to gastroenteritis like symptoms (diarrhea, nausea, and vomiting, abdominal pain)  
276 (22,24,38). Other than the fecal-oral route, an alternative route of viral entry to the GI cells  
277 may be through the tissue microvasculature. Though this may not be highly probable but this  
278 premise does warrant consideration. In that case, fecal viral shedding can happen after  
279 sloughing of the inflamed/necrosed intestinal mucosa. Currently, data is limited which



280 support presence of SARS-CoV-2 in the blood, however such evidence is available for other  
281 coronaviruses infections like SARS and MERS (29,39-41).

282 ACE2 is known to regulate sodium-dependent amino acid and glucose transporters in the  
283 enterocytes brush border which physiologically engage in the absorption of nutrients from the  
284 digested food, and maintain osmotic and electrolyte balance across the GI lining epithelium  
285 (11,14). In a recent study Yan et al., 2020 showed that SARS-CoV-2 can bind to the complex  
286 of ACE2 with BOAT1(Slc6a19)—a major sodium dependent neutral amino acid transporter  
287 present in the epithelial lining of human intestine (and also in kidneys) (1,42). The  
288 dysregulation of the intestinal ion transporters has been implicated in the pathophysiology of  
289 infectious diarrhea and malabsorption disorders (15,16). Literature also suggests that a  
290 dysregulation of these transporters can ensue interleukin/cytokine mediated intestinal  
291 inflammation and can give rise to digestive symptoms (14). An enhanced GI expression of  
292 ACE2 is known in inflammatory bowel diseases (IBDs) which present with similar symptoms  
293 as in COVID-19 patients (14,43).

294 Based on the findings of this study and supportive evidence from the literature, we propose  
295 that a virus binding-ACE2 mediated dysregulation of the sodium dependent nutrient  
296 transporters may be a plausible basis for the digestive symptoms in COVID-19. Prior  
297 intestinal inflammatory conditions like IBD may raise the susceptibility of SARS-CoV-2  
298 infection through fecal-oral transmission. ACE2 mediated dysregulation of SGLT1 and/or  
299 SLC5A1 at intestinal epithelium also links it to the pathogenesis of diabetes mellitus (18,19).  
300 The SGLT1 transporters are physiologically involved in active absorption of glucose across  
301 the intestinal epithelium and its virus binding receptor ACE2 mediated dysregulation may  
302 exacerbate the existing impaired glycemic control in COVID-19 patients with diabetes  
303 mellitus (19). (Sufficient data on glycemic control in COVID-19 patients is lacking for now,  
304 impaired glycemic control was stated as an independent risk factor predicting morbidity and  
305 mortality in SARS patients with diabetes mellitus (44).) ACE2 mediated downregulation of  
306 SGLT1 in intestinal epithelium prevents hyperglycemia in rat models of the diabetes mellitus  
307 (45,46). Though direct evidence is lacking in terms of the effect of SARS-CoV-2 binding on  
308 ACE2 on its signaling cascades, however, substantiation from SARS-CoV-1 studies (for  
309 SARS) suggests that it can downregulate ACE2 expression (25). Such an eventuality can lead  
310 to upregulation of SGLT1 thereby precipitating hyperglycemia (45,46). (SGLT1 inhibitors  
311 are being used in treatment of diabetes mellitus, their use in COVID-19 patients may need a  
312 rethinking for the dose adjustments (47).)

313 Our data showed undetectable expression of ACE2 and TMPRSS2 proteins in insulin  
314 producing Islets of Langerhans of the pancreas raising an insulin independent possibility of  
315 dysregulated intestinal SGLT1 transporters. This bolsters the rationale behind diabetes related  
316 increased morbidity/mortality in COVID-19 patients. Apart from intestine SGLT1 is known  
317 to be widely expressed in other human tissues like proximal tubule of kidney, heart, and liver  
318 ([proteintlas.org/ENSG00000100170-SLC5A1/tissue](http://proteintlas.org/ENSG00000100170-SLC5A1/tissue)) where it regulates the glucose  
319 absorption. An ACE2-mediated dysregulation of SGLT1 in COVID-19 patients warrants  
320 further investigation.

321 High expression of ACE2 in glandular cells of the GB indicates that this also can be a  
322 potential site for the virus replication. (Contrastingly, we found low m-RNA and undetectable  
323 proteomic expression of TMPRSS2 in glandular cells of GB, however, robust expression of  
324 another serine protease CTSL is noted in these cells in the records of Human Protein Atlas  
325 (48), which may be able to substitute for TMPRSS2 (1)) GB has a luminal connection to the  
326 duodenum through cystic and common bile duct (CBD). Though this connection is guarded

327 by a sphincter (of Oddi) present in duodenal mucosa, it doesn't create an anatomical barrier  
328 and, therefore, a viral invasion along the mucosal epithelium remains a possibility.

329 GB is the physiological storage site for the bile secreted from the hepatocytes, and pathology  
330 of this organ can also contribute to the digestive symptoms present in COVID-19 patients.  
331 GB has been a known reservoir for *Salmonella typhi*, a bacterium causing enteric fever, and  
332 one of the cited reasons for disease recurrence (49). The thick mucin secreted from its  
333 glandular cells can provide a protective environment for survival of SARS-CoV-2 (as we  
334 discussed above for GI lining epithelium) (35). Hence, GB homing may act as a mechanism  
335 for the replication of the virus even without ensuing a local tissue injury.

336 Continued replication of the SARS-CoV-2 in the intestinal tissue, and possibly in GB, may be  
337 a potential reason for the recurrence of SARS-CoV-2 in the light of the diagnostic tests as has  
338 been noted in some COVID-19 patients after being discharged from the hospital (40,50). A  
339 post-mortem study of these organs in COVID-19 patients may provide some confirmation in  
340 this regard.

341 Based on the observed pattern of tissue specific expression of ACE2 (which binds to SARS-  
342 CoV-2) in the components of the digestive system in normal individuals, we propose that an  
343 ACE2 based mechanism may be involved in the pathogenesis of digestive symptoms,  
344 increased diabetes-associated mortality risk, and disease recurrence in COVID-19.

345

#### 346 **Limitations**

347 All the aspects of the plausible SARS-CoV-2 binding receptor ACE2 mediated pathology in  
348 the digestive system which we have discussed above are based on the distribution of the virus  
349 cell entry related factors in the normal tissue. Hence, this study presents indirect evidence  
350 which needs to be validated in actual patients before reaching any conclusion.

351

#### 352 **Future directions**

353 Further studies are advisable to understand the molecular mechanisms involved in the SARS-  
354 CoV-2 binding receptor ACE2 mediated dysregulation of the intestinal nutrient transporters  
355 and finding out COVID-19 specific drug targets. Inter-individual variations in frequency of  
356 the digestive symptoms, diabetes associated mortality, and recurrences may depend upon the  
357 genotype specific variations in ACE2 expression and other patient specific characteristics  
358 (like age, sex, and comorbidity). A study of these variables in the disease pathogenesis may  
359 help in deciding personalized therapeutic management for the COVID-19 cases.

#### 360 **Conflict of Interest**

361 All the authors declare "No Conflict of Interest".

#### 362 **Author Contributions**

363 AK conceived the idea. AK wrote the first draft. MAF, VP, KR, MK, CK, KK, PK, PP, HN,  
364 RKN, SNP, RQ, and SK revised the draft. RKN, KR, PP, PK, and VP contributed to data  
365 analysis, and prepared tables and figures.

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## 368 **Data Availability**

369 Data used for this study can be accessed at the following link:  
370 <https://www.proteinatlas.org/about/download>

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373 availability of data in the public domain. This manuscript has been released as a pre-print at  
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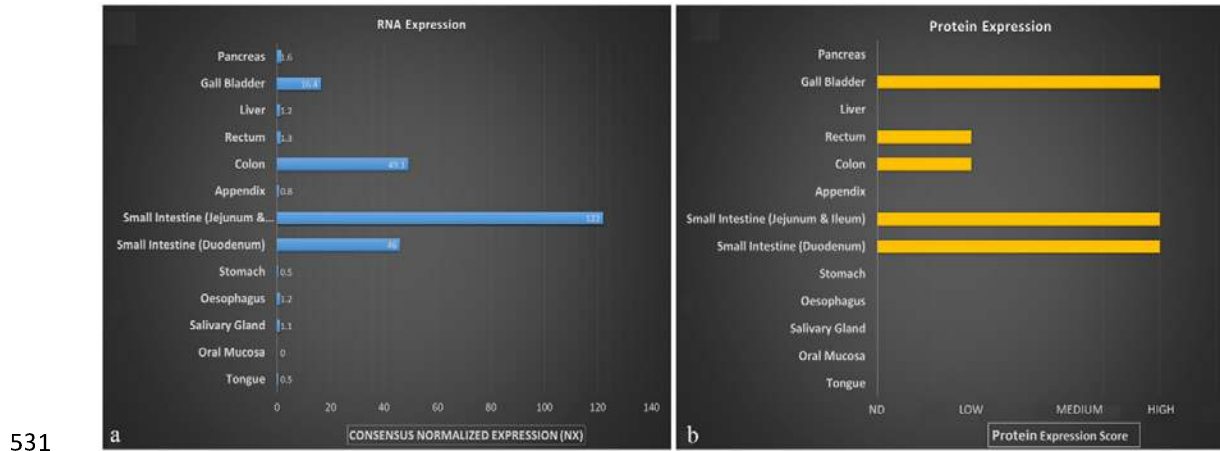
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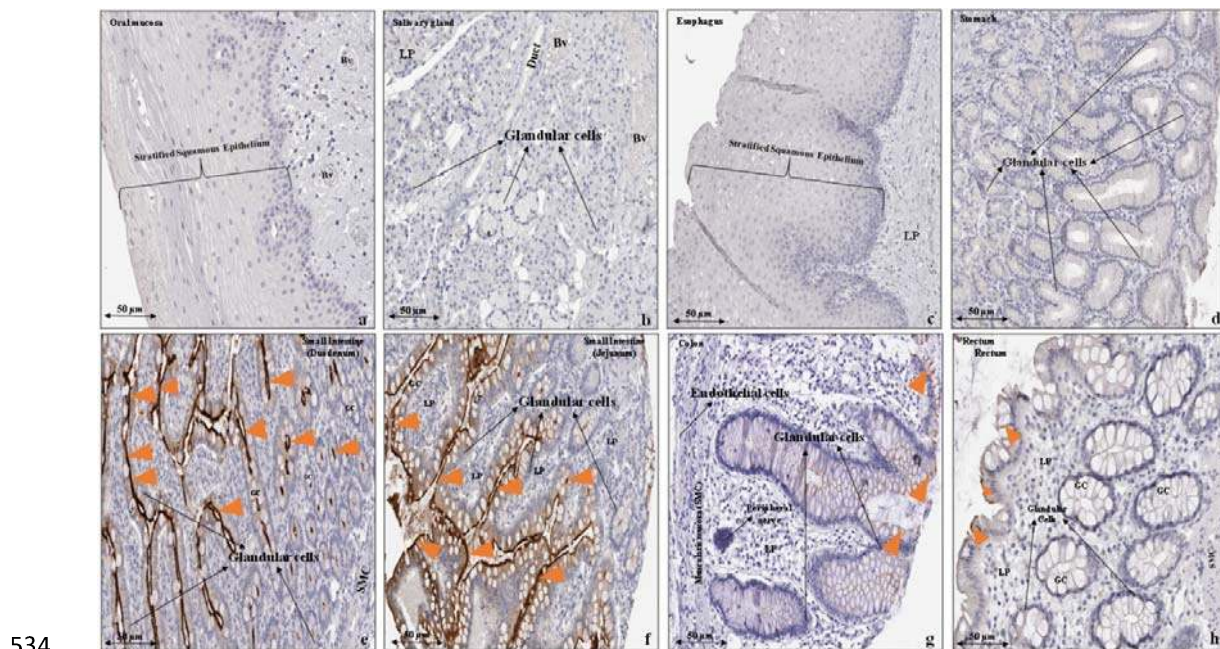
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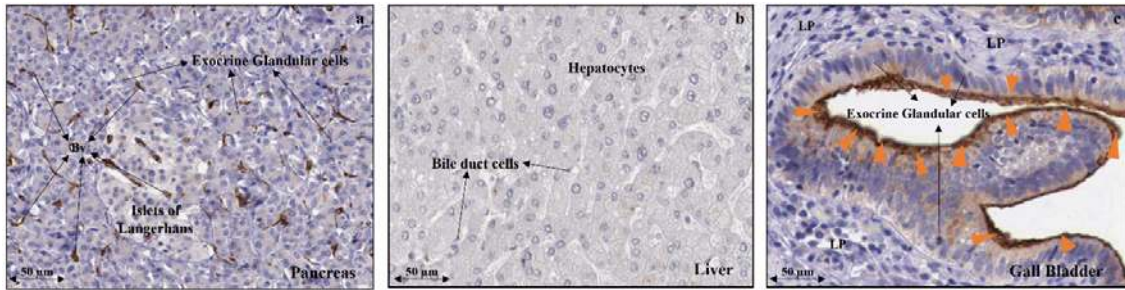
530 **Figures and Tables**



532 **Figure 1 Physiological expression of SARS-CoV-2 binding receptor ACE2 in human digestive**  
 533 **system a. mRNA b. Protein.** Data Source: The Human Protein Atlas.







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541 **Figure 3 Immunohistochemical expression of ACE2 protein in Human tissue a. Pancreas b.**

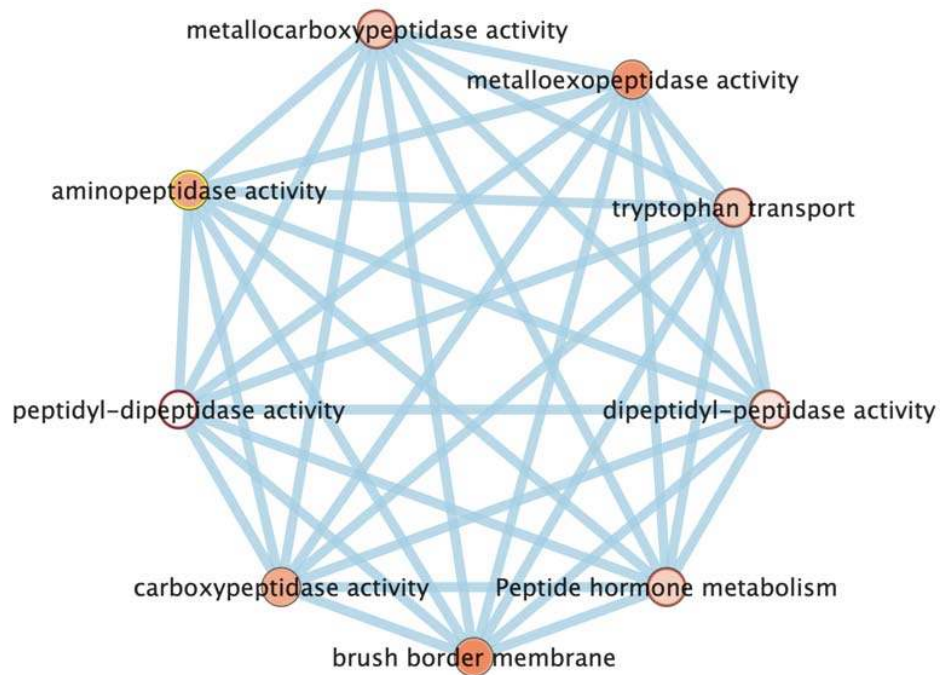
542 **Liver c. Gall bladder.** Orange arrow heads show antibody stained cells. (In pancreatic tissue blood

543 vessels (Bv) but not in the exocrine or endocrine glandular cells can be seen expressing ACE2.) Data

544 Source: The Human Protein Atlas. **Abbreviations:** Bv - Blood vessels, LP - Lamina propria, SMC -

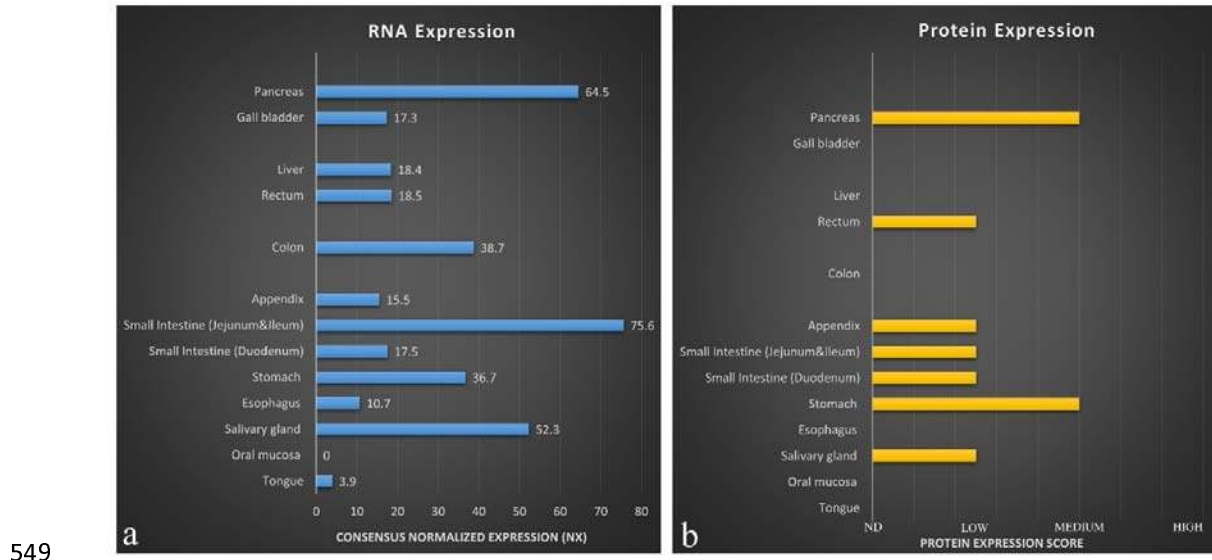
545 Smooth muscle cells.

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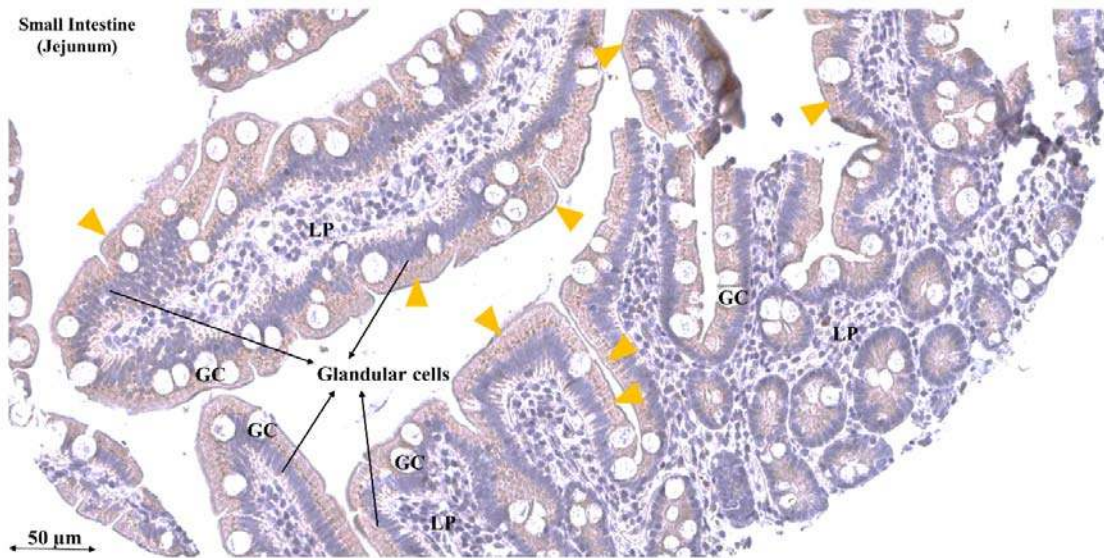


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548 **Figure S1 ACE2 gene enrichment map for Digestive system functions.**



**Figure S2 Physiological expression of SARS-CoV-2 cell entry associated protease TMPRSS2 in human digestive system a. mRNA b. Protein.** Data Source: The Human Protein Atlas.



**Figure S3 Immunohistochemical expression of TMPRSS2 protein in Small Intestine of human gastrointestinal tract Orange arrow heads show antibody stained cells.** Data Source: The Human Protein Atlas. **Abbreviations:** GC- goblet cells, LP - Lamina propria.

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559 Table 1 Physiological expression (mRNA and protein) of SARS-CoV-2 binding receptor  
560 ACE2 in human digestive system.

<b>Tissue</b>	<b>Cellular components</b>	<b>RNA Expression (NX)</b>	<b>Protein Expression</b>
Tongue	Squamous epithelial cells	0.5	Not detected
Oral mucosa	Squamous epithelial cells	0	Not detected
Salivary gland	Glandular cells	1.1	Not detected
Esophagus	Squamous epithelial cells	1.2	Not detected
Stomach	Glandular cells	0.5	Not detected
Small Intestine (Duodenum)	Glandular cells	46.0	High
Small Intestine (Jejunum&Ileum)	Glandular cells	122.0	High
Appendix	Glandular cells	0.8	Not detected
	Lymphoid tissue		Not detected
Colon	Endothelial cells	49.1	Not detected
	Glandular cells		Low
	Peripheral nerve/ganglion		Not detected
Rectum	Glandular cells	1.3	Low
Liver	Bile duct cells	1.2	Not detected
	Hepatocytes		Not detected
Gall bladder	Glandular cells	16.4	High
Pancreas	Exocrine glandular cells	1.6	Not detected
	Islets of Langerhans		Not detected

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566 **Table S1 ACE2 gene enrichment for Digestive system functions.**

<b>GO. ID</b>	<b>Description</b>	<b>P Value</b>	<b>FDR</b>	<b>Phenotype</b>	<b>Gene</b>
GO:0008241	Peptidyl-dipeptidase activity	0.00397219	0.00397219	1	ACE2
GO:0008239	Dipeptidyl-peptidase activity	0.01853691	0.01853691	1	ACE2
GO:0004181	Metallocarboxypeptidase activity	0.03707382	0.03707382	1	ACE2
GO:0004180	Carboxypeptidase activity	0.06090698	0.06090698	1	ACE2
GO:0004177	Aminopeptidase activity	0.06487918	0.06487918	1	ACE2
GO:0008235	Metalloexopeptidase activity	0.07944389	0.07944389	1	ACE2
GO:0140272	Exogenous protein binding	0.10062893	0.10062893	1	ACE2
GO:0008238	Exopeptidase activity	0.1509434	0.1509434	1	ACE2
GO:0008237	Metallopeptidase activity	0.23965574	0.23965574	1	ACE2
GO:0004175	Endopeptidase activity	0.58126448	0.58126448	1	ACE2
GO:0070011	Peptidase activity, acting on L-amino acid peptides	0.8142999	0.8142999	1	ACE2
GO:0008233	Peptidase activity	0.84872559	0.84872559	1	ACE2
GO:0005515	Protein binding	1	1	1	ACE2
GO:0140096	Catalytic activity, acting on a protein	1	1	1	ACE2
GO:0015827	Tryptophan transport	0.03708254	0.03708254	1	ACE2
GO:0051957	Positive regulation of amino acid transport	0.17614208	0.17614208	1	ACE2
GO:0032800	Receptor biosynthetic process	0.24103652	0.24103652	1	ACE2
GO:0003081	Regulation of systemic arterial blood pressure by renin-angiotensin	0.2595778	0.2595778	1	ACE2
GO:0051955	Regulation of amino acid transport	0.30593097	0.30593097	1	ACE2
GO:0016486	Peptide hormone processing	0.32447224	0.32447224	1	ACE2
GO:1901890	Positive regulation of cell junction assembly	0.33374288	0.33374288	1	ACE2
GO:0032892	Positive regulation of organic acid transport	0.33374288	0.33374288	1	ACE2

GO:0051954	Positive regulation of amine transport	0.34301352	0.34301352	1	ACE2
GO:1903793	Positive regulation of anion transport	0.49134368	0.49134368	1	ACE2
GO:0051952	Regulation of amine transport	0.87143974	0.87143974	1	ACE2
GO:0044070	Regulation of anion transport	0.91779292	0.91779292	1	ACE2
GO:0019538	Protein metabolic process	1	1	1	ACE2
GO:0019222	Regulation of metabolic process	1	1	1	ACE2
GO:0015849	Organic acid transport	1	1	1	ACE2
GO:0015711	Organic anion transport	1	1	1	ACE2
GO:0010817	Regulation of hormone levels	1	1	1	ACE2
GO:0009893	Positive regulation of metabolic process	1	1	1	ACE2
GO:0016485	Protein processing	1	1	1	ACE2
GO:0032879	Regulation of localization	1	1	1	ACE2
GO:0046942	Carboxylic acid transport	1	1	1	ACE2
GO:0043270	Positive regulation of ion transport	1	1	1	ACE2
GO:0043269	Regulation of ion transport	1	1	1	ACE2
GO:0043170	Macromolecule metabolic process	1	1	1	ACE2
GO:0043112	Receptor metabolic process	1	1	1	ACE2
GO:0042445	Hormone metabolic process	1	1	1	ACE2
GO:0008152	Metabolic process	1	1	1	ACE2
GO:0001816	Cytokine production	1	1	1	ACE2
GO:0001817	Regulation of cytokine production	1	1	1	ACE2
GO:0006820	Anion transport	1	1	1	ACE2
GO:0006812	Cation transport	1	1	1	ACE2
GO:0006811	Ion transport	1	1	1	ACE2
GO:0006807	Nitrogen compound metabolic process	1	1	1	ACE2
GO:0006518	Peptide metabolic process	1	1	1	ACE2

GO:0006508	Proteolysis	1	1	1	ACE2
GO:0071705	Nitrogen compound transport	1	1	1	ACE2
GO:0071704	Organic substance metabolic process	1	1	1	ACE2
GO:0071702	Organic substance transport	1	1	1	ACE2
GO:0051604	Protein maturation	1	1	1	ACE2
GO:0051050	Positive regulation of transport	1	1	1	ACE2
GO:0051049	Regulation of transport	1	1	1	ACE2
GO:0031526	Brush border membrane	0.08612643	0.08612643	1	ACE2
GO:0005903	Brush border	0.16610098	0.16610098	1	ACE2
REAC:R-HSA-2980736	Peptide hormone metabolism	0.03360393	0.03360393	1	ACE2
REAC:R-HSA-392499	Metabolism of proteins	0.760808	0.760808	1	ACE2

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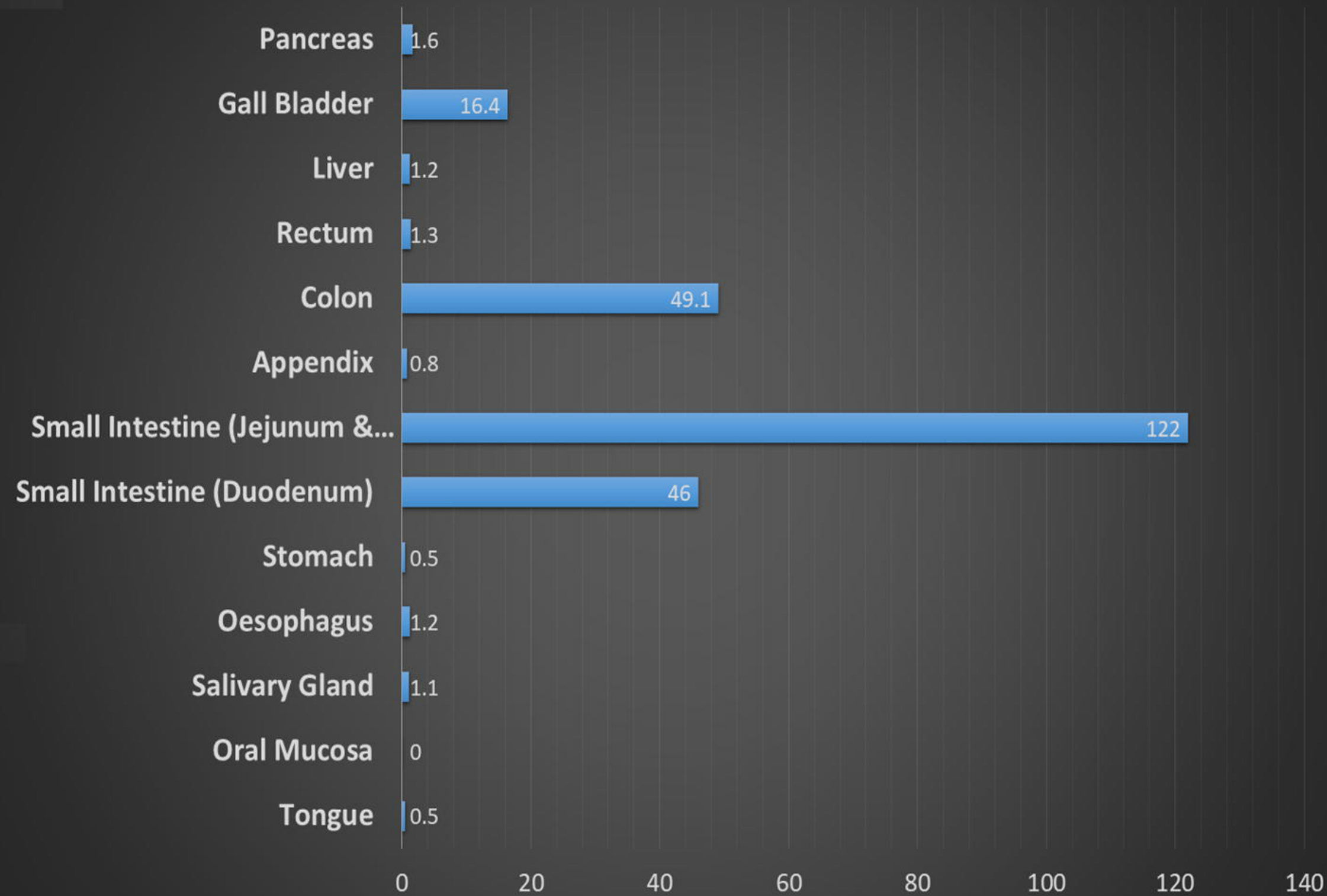
584 **Table S2 Physiological expression (mRNA and protein) of SARS-CoV-2 cell entry**  
 585 **associated protease TMPRSS2 in human digestive system.**

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<b>Tissue</b>	<b>Cellular components</b>	<b>RNA Expression (NX)</b>	<b>Protein Expression</b>
Tongue	Squamous epithelial cells	3.9	Not detected
Oral mucosa	Squamous epithelial cells	0	Not detected
Salivary gland	Glandular cells	52.3	Low
Esophagus	Squamous epithelial cells	10.7	Not detected
Stomach	Glandular cells	36.7	Medium
Small Intestine (Duodenum)	Glandular cells	17.5	Low
Small Intestine (Jejunum & Ileum)	Glandular cells	75.6	Low
Appendix	Glandular cells	15.5	Low
	Lymphoid Tissue		Not detected
Colon	Endothelia cells	38.7	Not detected
	Glandular cells		Not detected
Rectum	Glandular cells	18.5	Low
Liver	Bile duct cells	18.4	Not detected
	Hepatocytes		Not detected
Gall bladder	Glandular cells	17.3	Not detected
Pancreas	Exocrine glandular cells	64.5	Medium
	Islets of Langerhans		Not detected

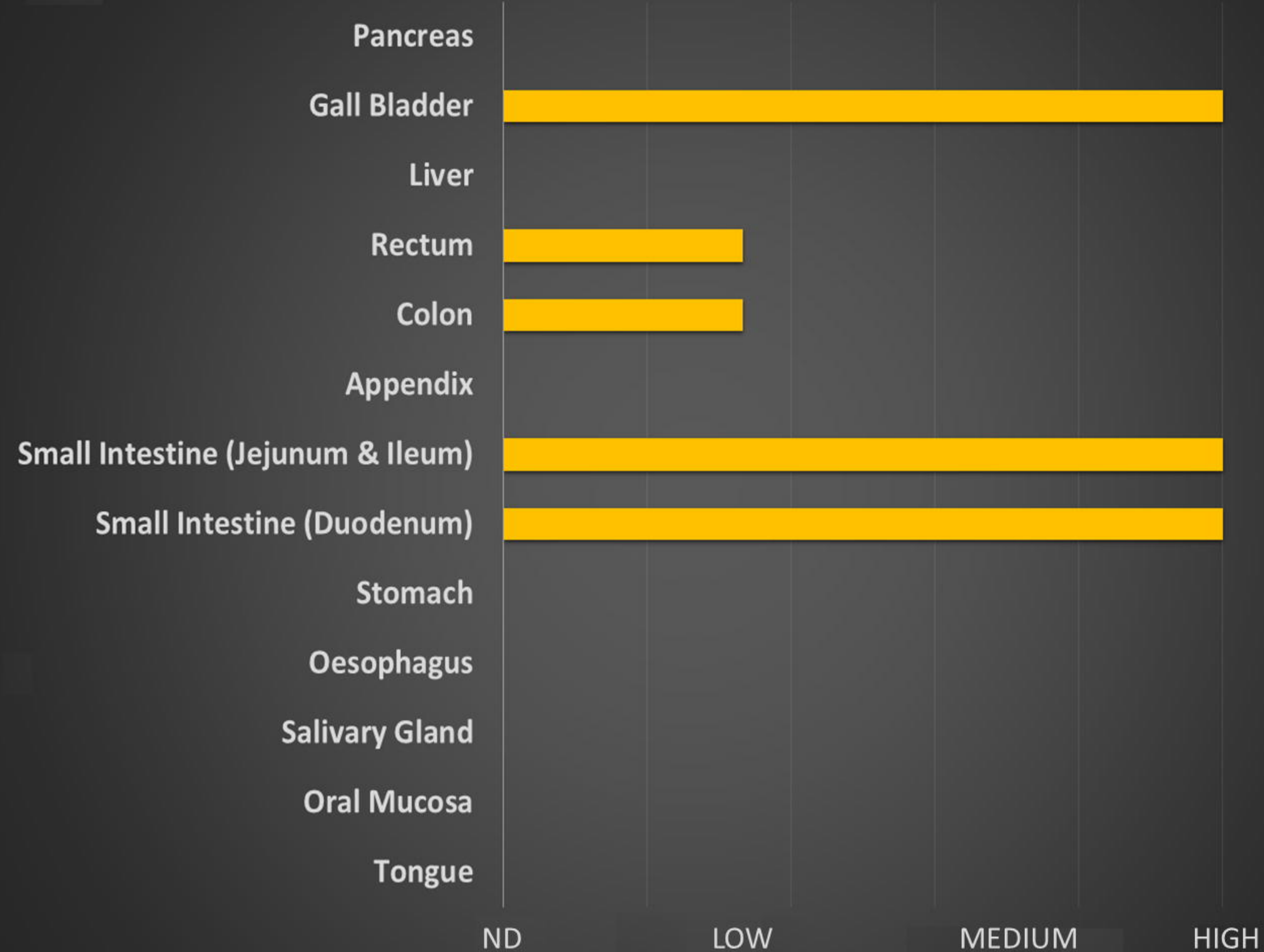
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### RNA Expression



CONSENSUS NORMALIZED EXPRESSION (NX)

### Protein Expression

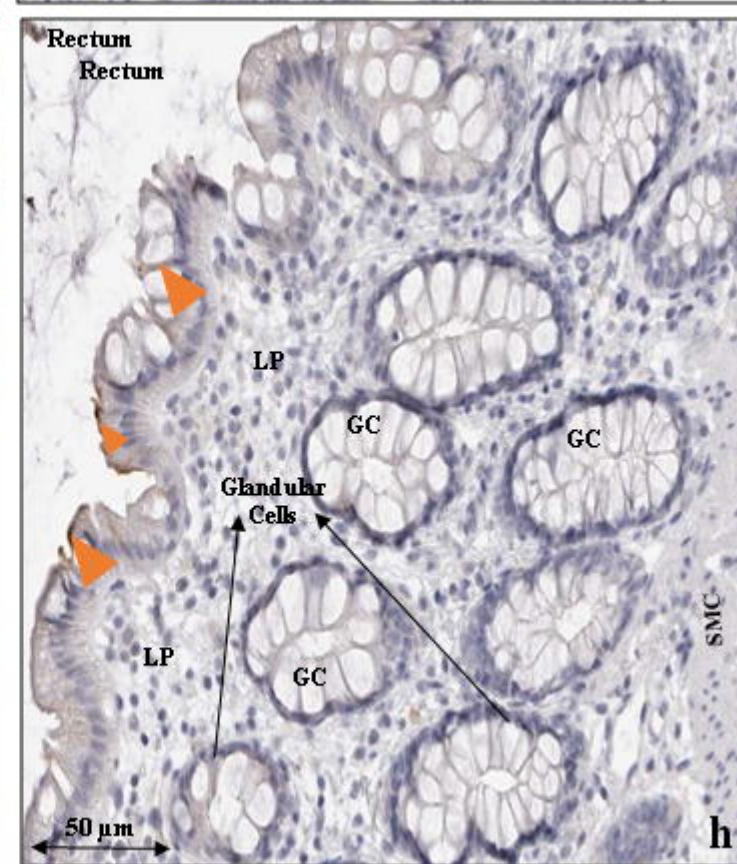
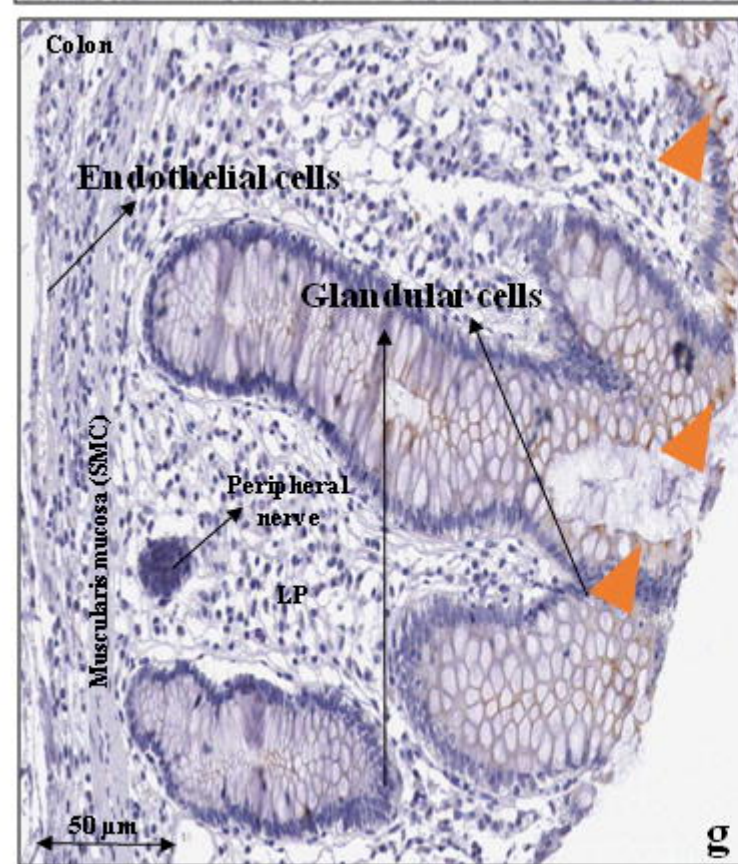
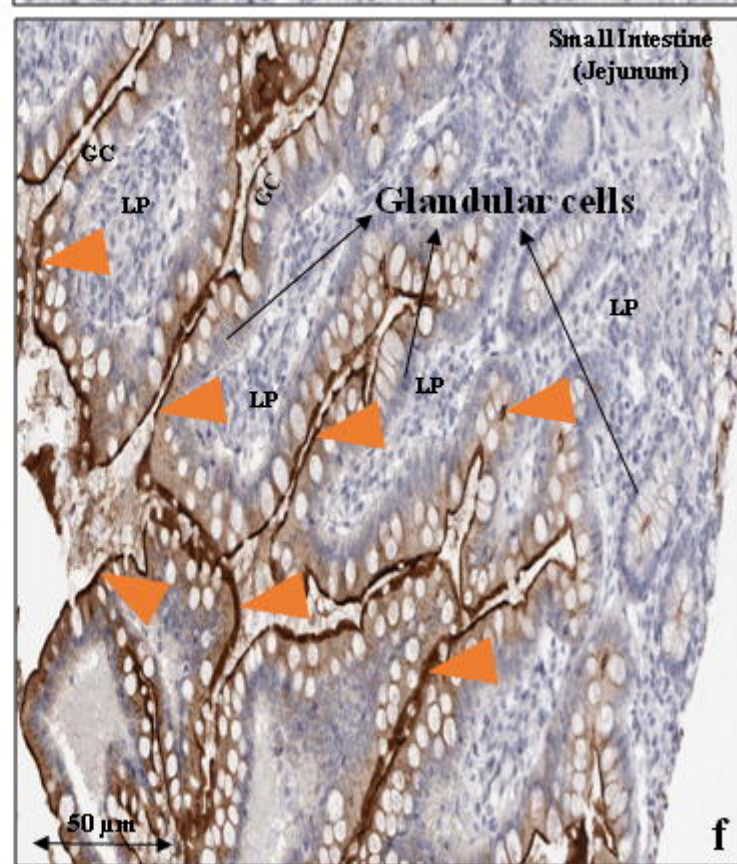
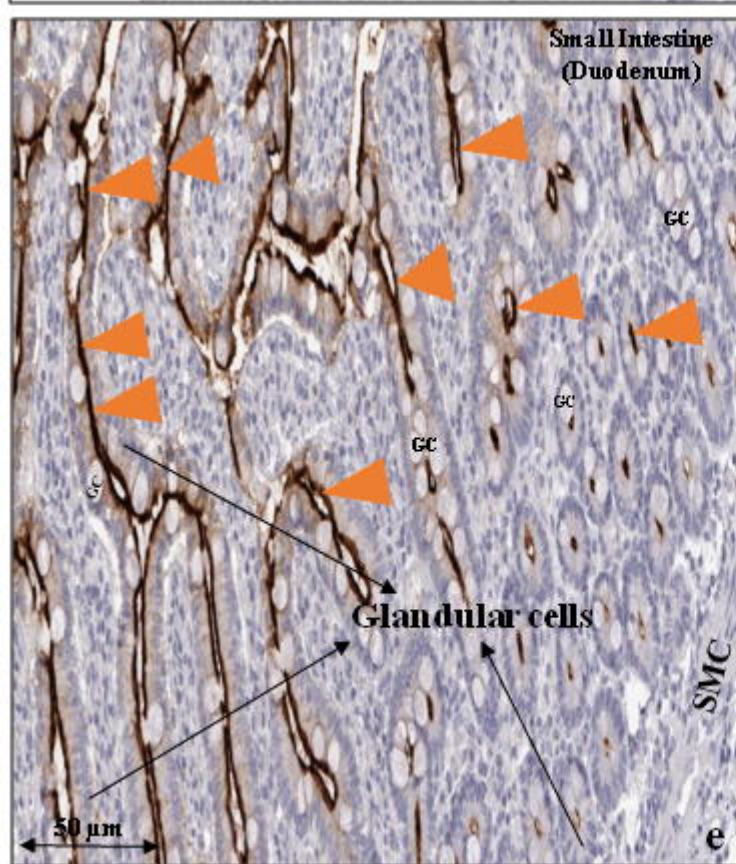
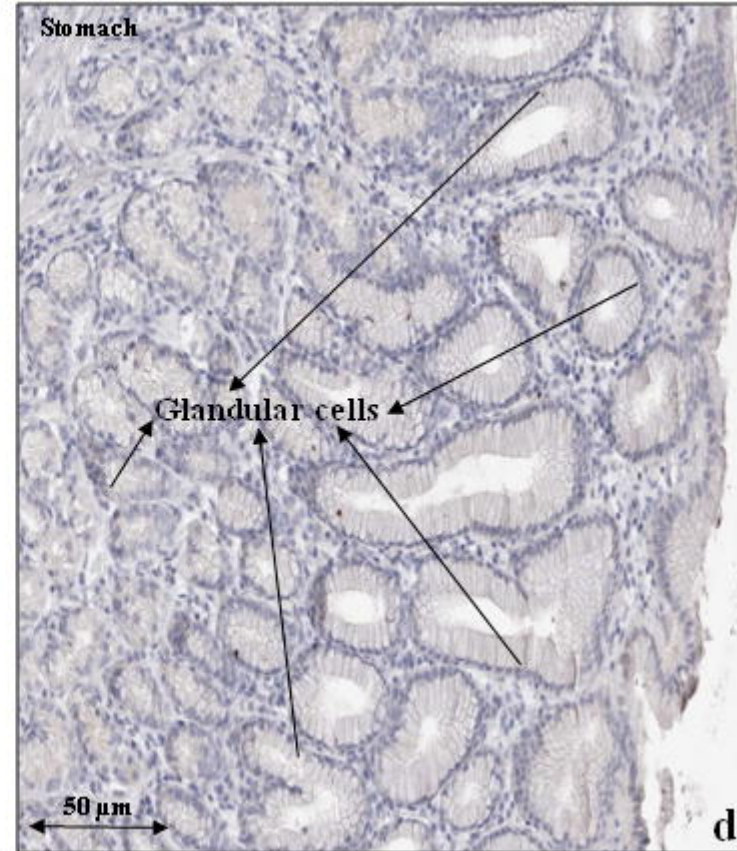
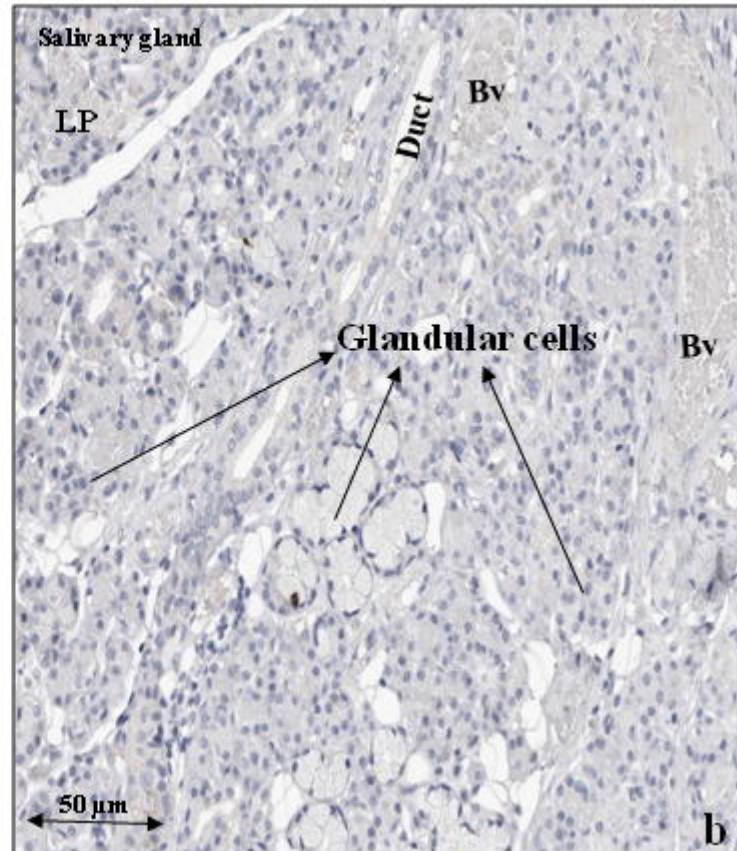
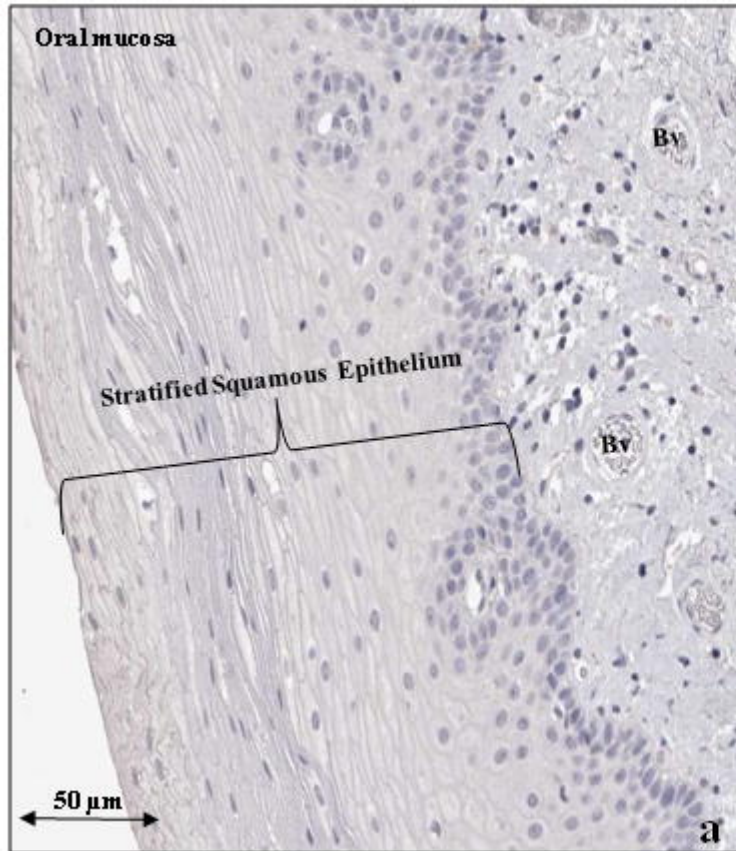


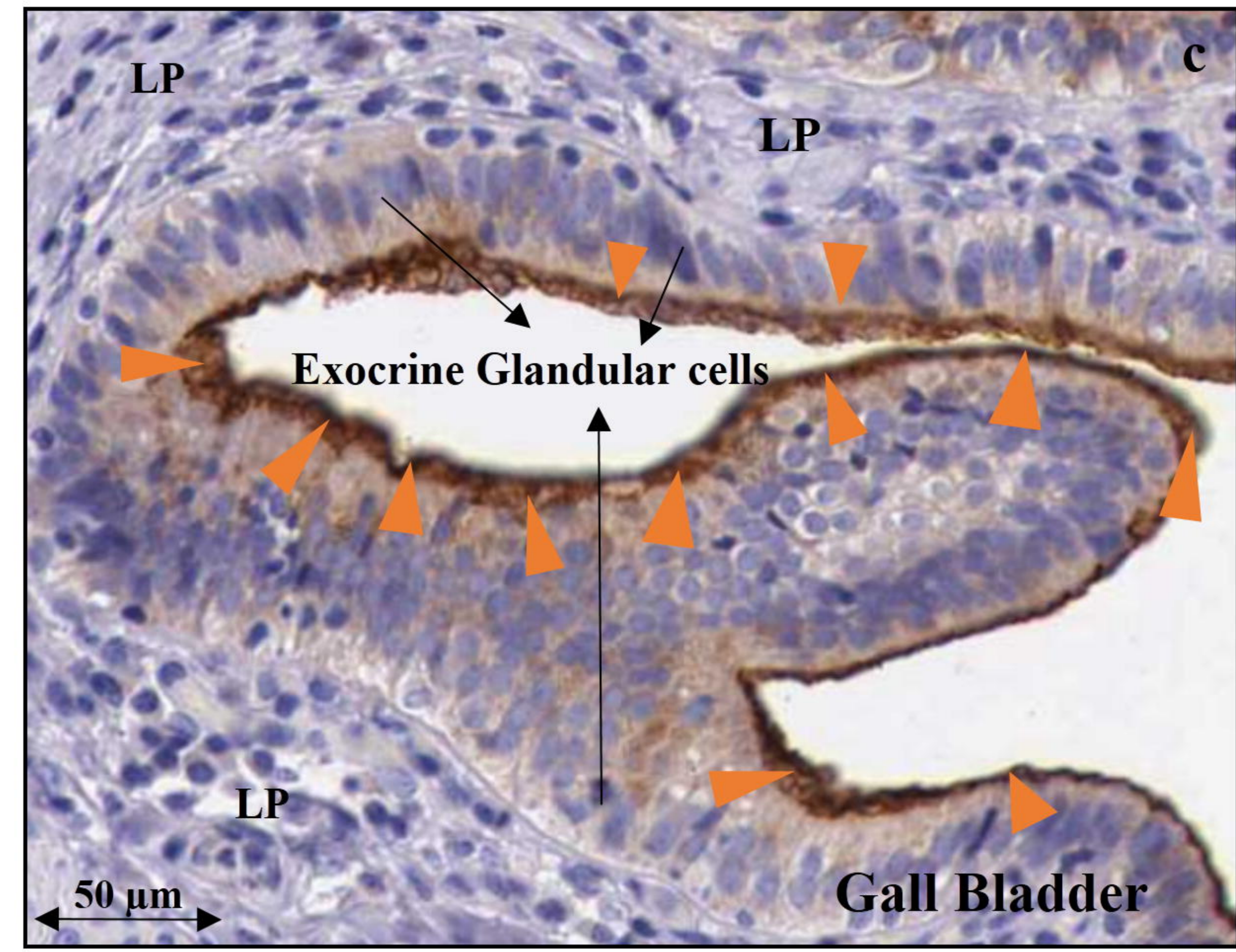
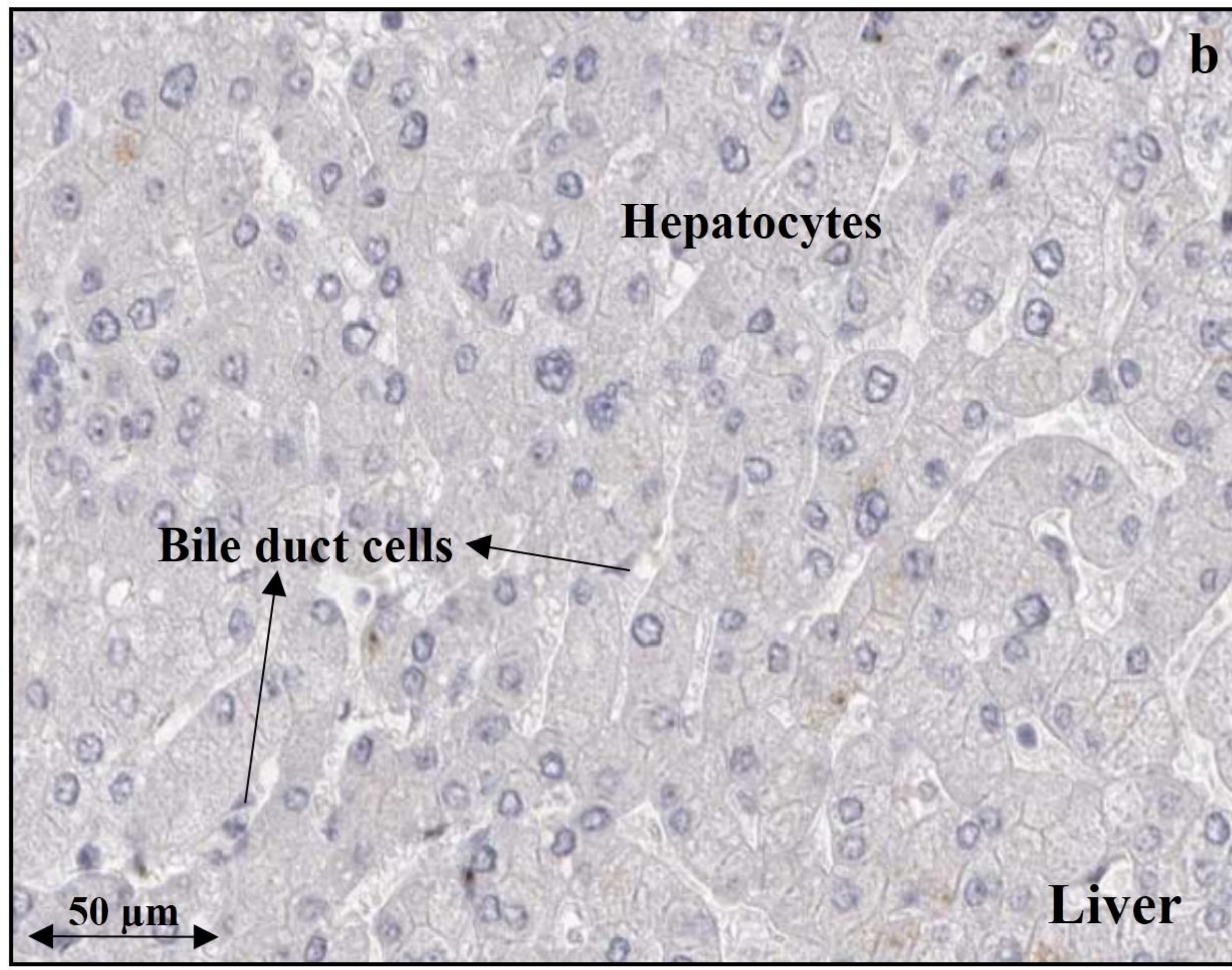
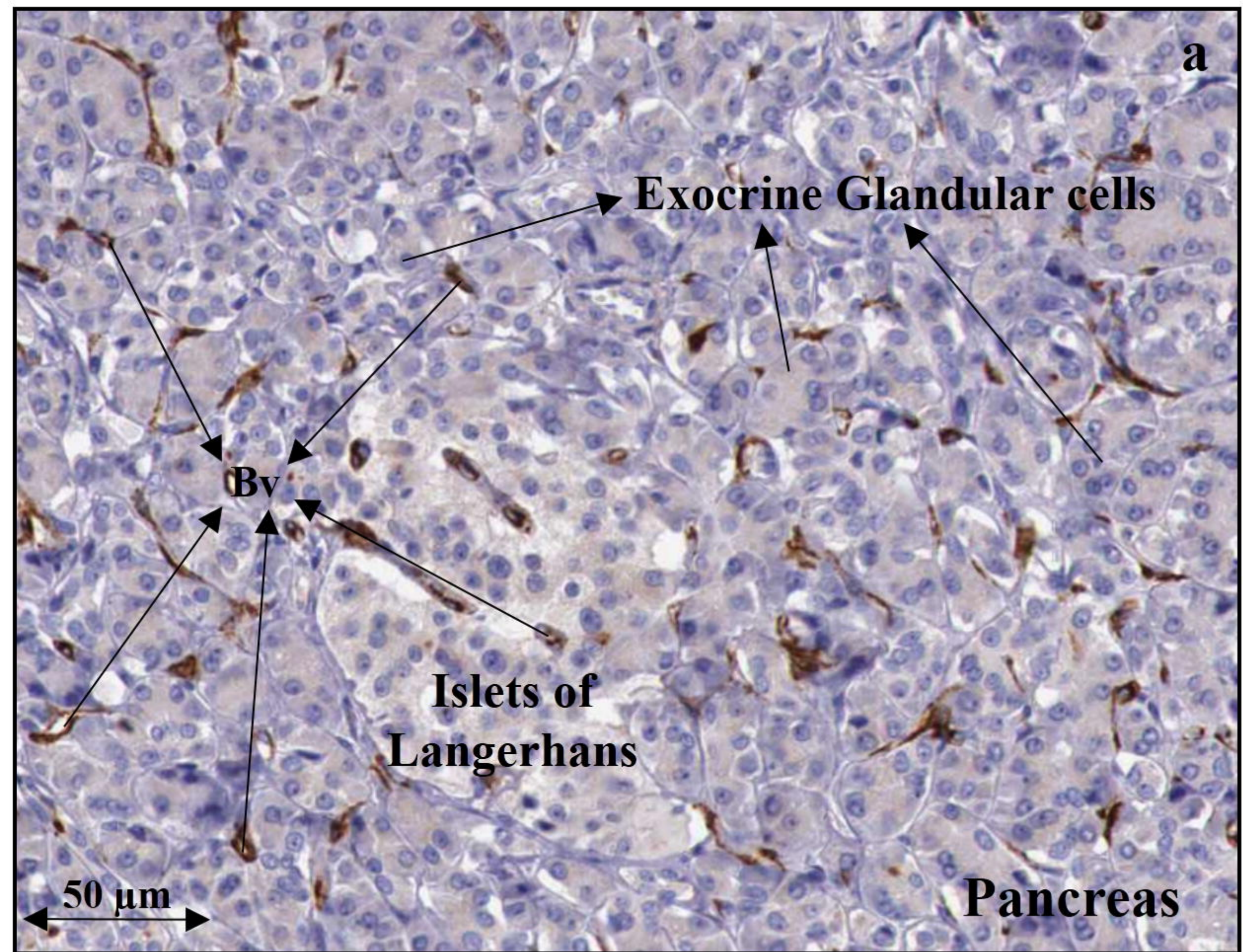
Protein Expression Score

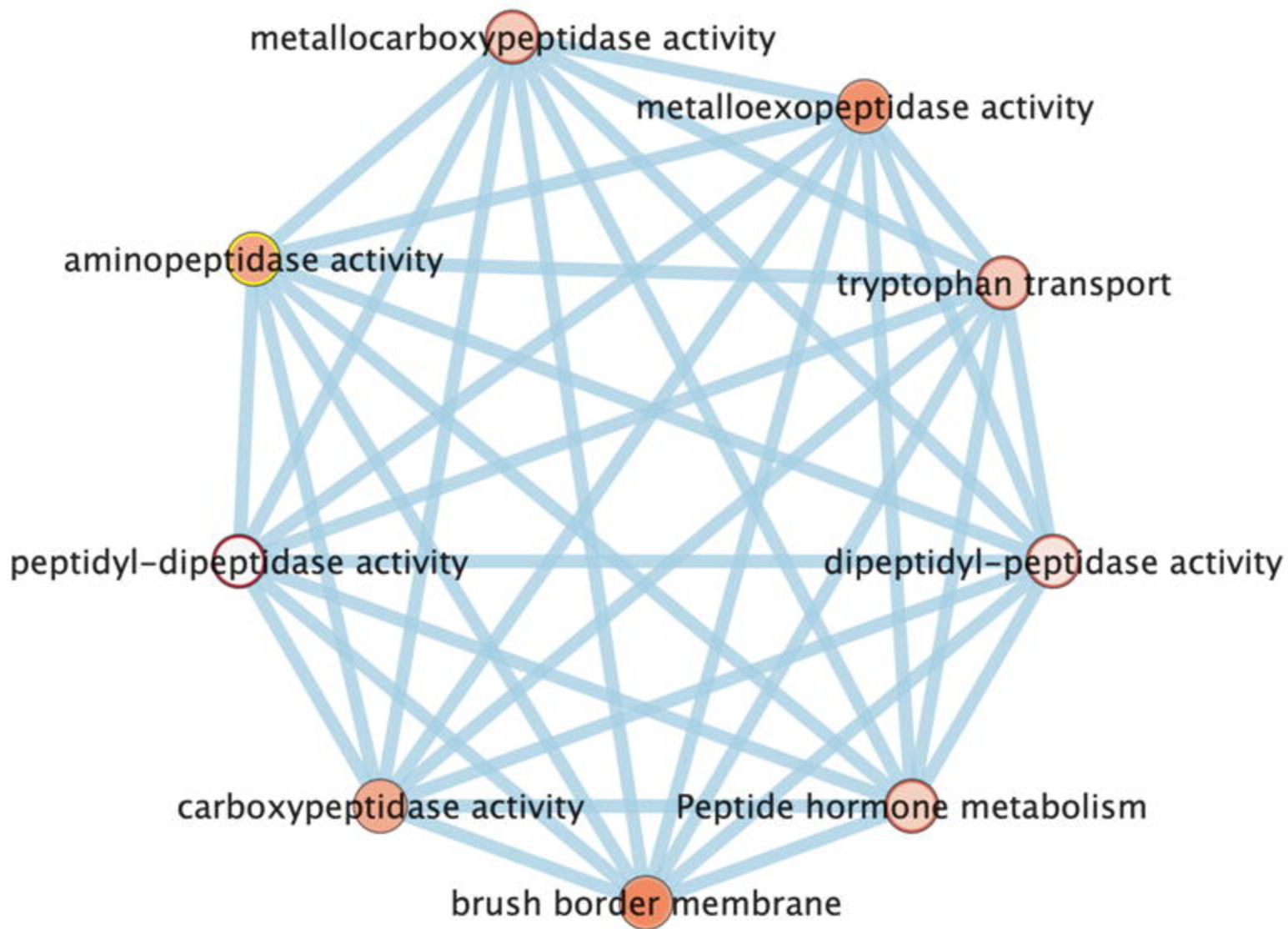
a

b

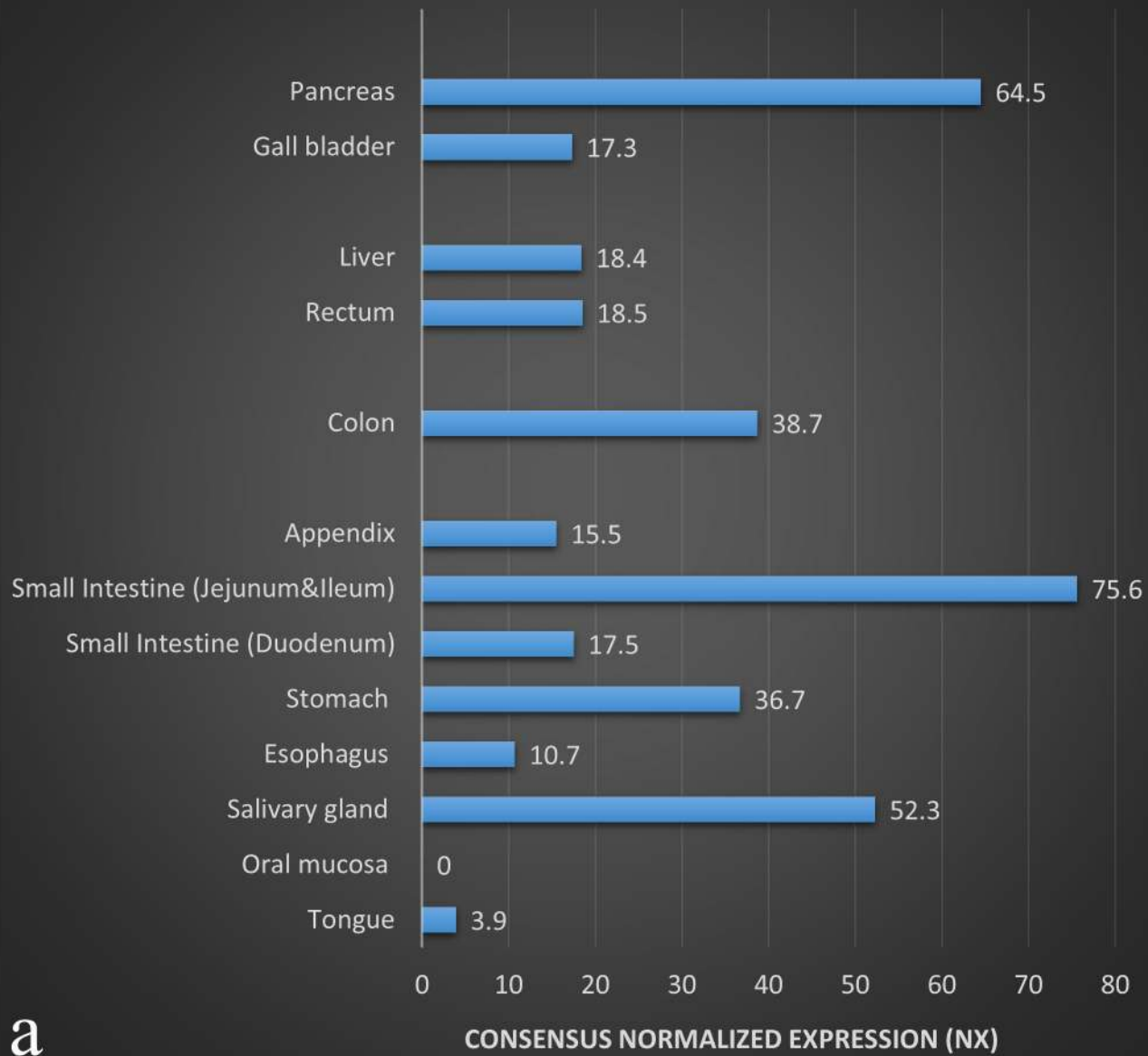






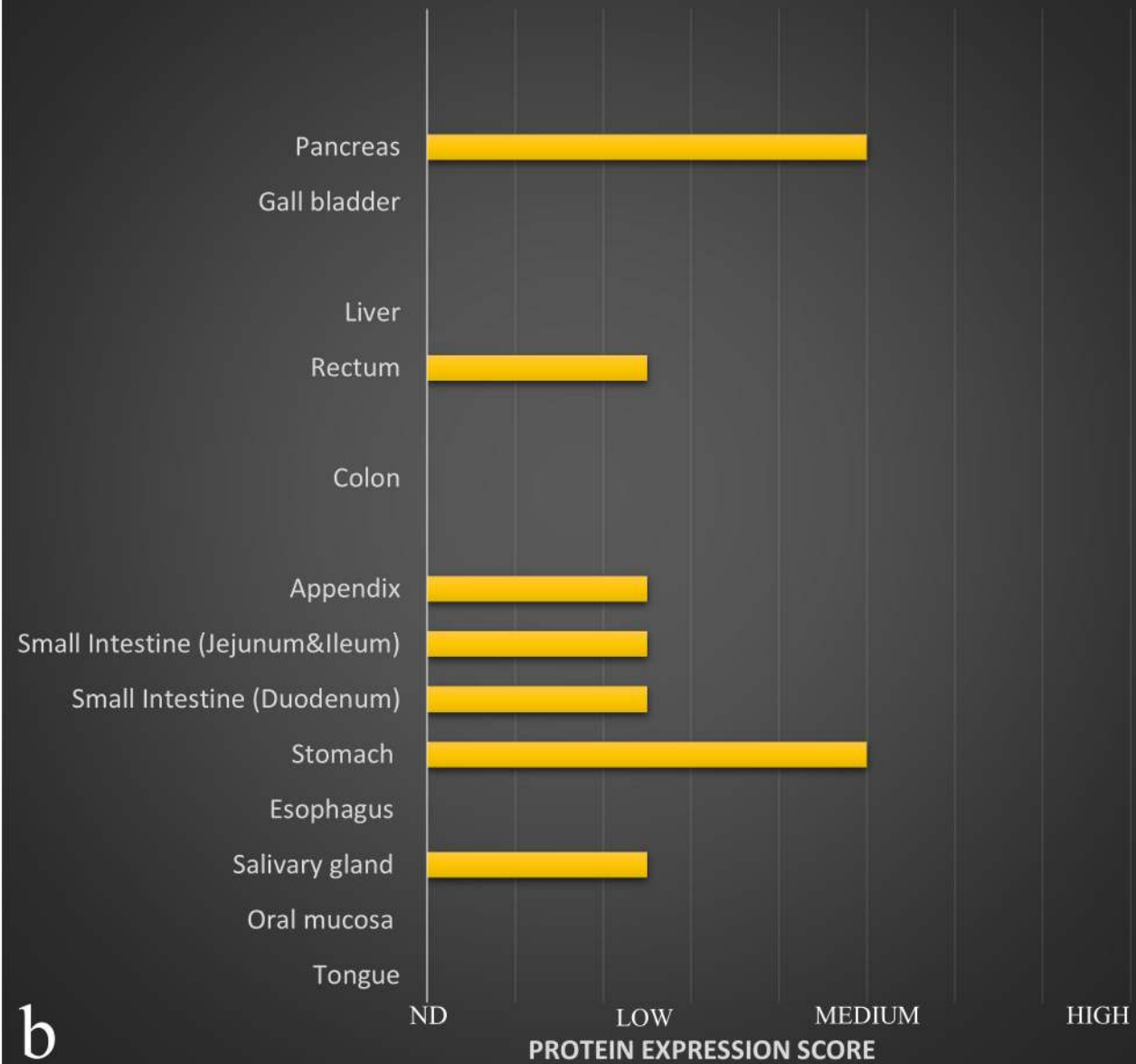


## RNA Expression



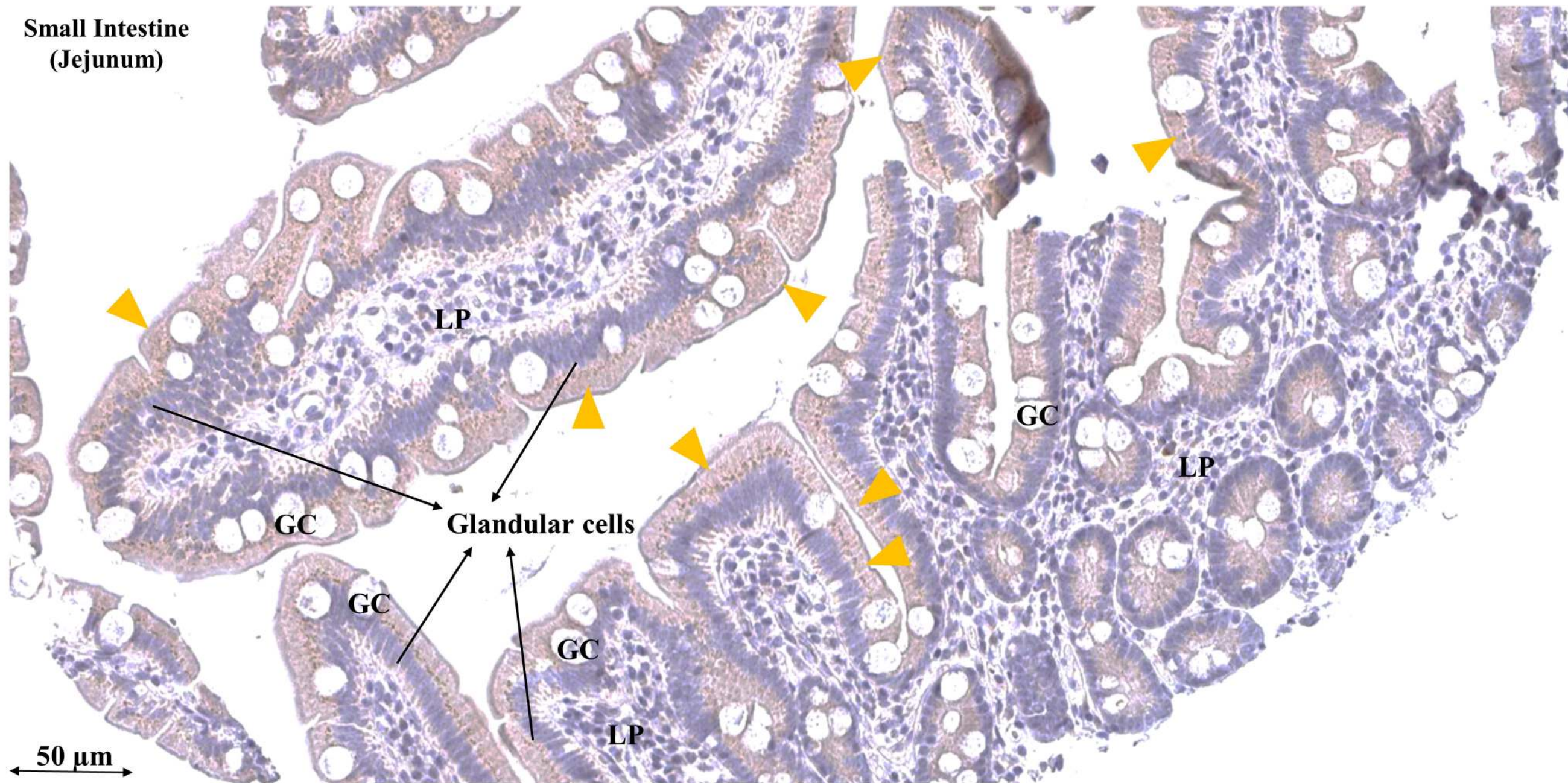
a

## Protein Expression

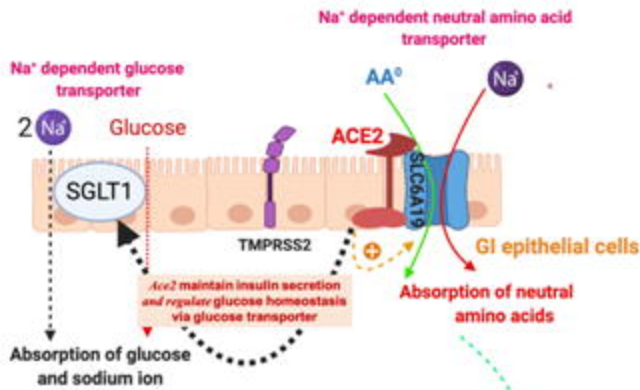


b

**Small Intestine  
(Jejunum)**



## Physiological Condition



Maintain the fluid and electrolyte homeostasis

## Pathological Condition (SARS-CoV-2 infection)

