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TMEM Proteins in Cancer: A Review

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A transmembrane protein (TMEM) is a type of protein that spans biological membranes. Many of them extend through the lipid bilayer of the plasma membrane but others are located to the membrane of organelles. The TMEM family gathers proteins of mostly unknown functions. Many studies showed that TMEM expression can be down- or up-regulated in tumor tissues compared to adjacent healthy tissues. Indeed, some TMEMs such as TMEM48 or TMEM97 are defined as potential prognostic biomarkers for lung cancer. Furthermore, experimental evidence suggests that TMEM proteins can be described as tumor suppressors or oncogenes. TMEMs, such as TMEM45A and TMEM205, have also been implicated in tumor progression and invasion but also in chemoresistance. Thus, a better characterization of these proteins could help to better understand their implication in cancer and to allow the development of improved therapy strategies in the future. This review gives an overview of the implication of TMEM proteins in cancer.

Keywords: cancer, TMEM proteins, biomarkers, tumor suppressors, oncogenes, chemoresistance

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INTRODUCTION

A TMEM is a type of protein that spans the entire width of the lipid bilayer and to which it is permanently anchored. Many TMEMs function as channels to permit the transport of specific substances across the biological membranes. But the biological functions of many of them remain unknown mainly due to difficulties in the extraction and purification of these proteins. There are two ways to classify the TMEMs. The first one is according to their structure. Indeed there are two basic types of TMEMs, alpha-helical proteins and the beta-barrel proteins (Vinothkumar and Henderson, 2010). The second classification is according to their topology, this classification refers to the position of the N- and C-terminal domains (von Heijne, 2006).

Among TMEMs is the TMEM family. The proteins of this family are predicted to be components of various cell membranes, such as mitochondrial, endoplasmic reticulum, lysosome, and Golgi membranes. TMEMs are present in many cell types and fulfill important physiological functions such as epidermal keratinization (TMEM45A) (Hayez et al., 2014), autophagy, smooth muscle contraction (TMEM16) (Thomas-Gatewood et al., 2011), protein glycosylation (TMEM165) (Foulquier et al., 2012) and development and differentiation of the liver (TMEM97) (Malhotra et al., 1999). Among them, some members play a primordial

Abbreviations: BRCA1, breast cancer 1; CDK, cyclin-dependent kinase; DVL1, disheveled 1; EMT, epithelial-mesenchymal transition; ERK, extracellular signal-regulated kinase; GSK β , glycogen synthase kinase 3 β ; HDAC, histone deacetylase; HNSCC, head and neck squamous cell carcinoma; HPDE, normal pancreatic ductal epithelium; ICAM, intercellular adhesion molecule 1; IFN, interferon; IL, interleukin; MAC30, meningioma-associated protein; MEK, mitogen-activated protein kinase kinase; MMP, matrix metalloproteinase; mRNA, messenger ribonucleic acid; NDC1, transmembrane Nucleoporin; NSCLC, non-small cell lung cancer; PCNA, proliferating cell nuclear antigen; RAB8, Ras-related protein; SQCLC, squamous cell lung carcinoma; STXR6, syntaxin 6; TLR, toll-like receptor; TGF- β , transforming growth factor- β ; TNF, tumor necrosis factor; TMEM, transmembrane protein; UTR, untranslated region; VCAM, vascular cell adhesion molecule 1; ZO-1, zona occludens 1.

115 role in immune response (TMEM9B) (Dodeller et al., 2008).
116 Indeed, TMEM9B is a key component of inflammatory signaling
117 pathways through the enhancement of the production of pro-
118 inflammatory cytokines induced by TNF, IL1 β , and TLR ligands.

119 In many cancers, differential regulation of the expression of
120 TMEMs has been observed, such as in lymphomas (TMEM176)
121 (Cuajungco et al., 2012), colorectal cancer (TMEM25) (Hrasovec
122 et al., 2013), hepatic cancer (TMEM7) (Zhou et al., 2007),
123 and lung cancer (TMEM48) (Qiao et al., 2016). Some of
124 them are used as prognostic biomarkers. For example, in renal
125 cancers, many TMEMs with predicted ER localization have been
126 shown to be potential classifiers of cancer grade (TMEM45A,
127 TMEM116, TMEM207, TMEM213. . .) (Wrzesinski et al., 2015).
128 A large number of TMEMs have also been implicated in cancer
129 development and in drug resistance, suggesting that the TMEM
130 family is a prominent group for cancer research. Furthermore,
131 some of these proteins act as tumor suppressors (TMEM25,
132 TMEM7) (Zhou et al., 2007; Doolan et al., 2009) while others
133 act as pro-oncogenes (TMEM158, TMEM14A. . .) (Cheng et al.,
134 2015; Zhang et al., 2016). This review aims to describe the
135 implication of the TMEM proteins in cancer.

137 PART 1: TMEMs AS TUMOR 138 SUPPRESSORS 139

140
141 Some TMEMs have been described in the literature to act as
142 tumor suppressors. A downregulation of their expression is
143 generally observed in tumor tissue compared to adjacent healthy
144 tissue. It is for example the case for TMEM25. This protein is
145 a member of the immunoglobulin super-family and is involved
146 in immune response, growth factor signaling and cell adhesion.
147 TMEM25, which is expressed at low level in brain, has been
148 also detected in neuroblastoma, brain tumor, and gastric cancer
149 (Kato and Kato, 2004). The expression of this protein has
150 been studied in fresh tumor samples collected during surgical
151 colectomy from patients who had been diagnosed with primary
152 colorectal adenocarcinoma. TMEM25 mRNA expression was
153 significantly decreased in 68% of tumor tissues in comparison
154 to corresponding normal tissues. This downregulation has been
155 correlated with the hypermethylation of a specific CpG site in
156 the 5' UTR region of TMEM25 gene in a high proportion of
157 tumor samples (Hrasovec et al., 2013). Another study revealed
158 that TMEM25 expression in the tumor tissues was lower than
159 the one in normal healthy tissues in 50% of tumor samples
160 in human breast tumor biopsies. The expression of TMEM25
161 was correlated with a better overall survival and associated
162 with a longer survival time for patients who received adjuvant
163 chemotherapy. Furthermore, in triple-negative breast tumors,
164 TMEM25 was generally not expressed (Doolan et al., 2009). All
165 together these findings suggest that TMEM25 may be used as a
166 tumor biomarker of favorable prognosis.

167 Another example is TMEM7. This protein of 232 amino
168 acids has a single transmembrane domain and is expressed
169 in the liver. The gene coding for TMEM7 is localized in the
170 short arm of chromosome 3, which is commonly deleted in
171 cancer cells (Huebner, 2001). Chromosomal regions that are

172 deleted in cancer are generally the loci of tumor suppressor
173 genes, suggesting that TMEM7 is a candidate suppressor gene.
174 This protein has been studied in 18 hepatocellular carcinoma
175 cell lines but also in primary tumors obtained from surgical
176 resection of hepatocellular carcinoma from 17 patients. Each
177 tumor sample was matched with its corresponding healthy liver
178 tissue. In the absence of homozygous deletion, TMEM7 is down
179 regulated in 33% of the cell lines and 85% of the tumor samples
180 compared to healthy tissue. Tumor suppressor genes located at
181 chromosomal regions deleted in some cancer cells are found to be
182 silenced by promoter methylation in other cell lines. In two lines
183 of the latter that displayed TMEM7 downregulation, 5-aza-2'-
184 deoxycytidine, a DNA methylation inhibitor and trichostatin A,
185 a HDAC inhibitor, increased TMEM7 expression suggesting that
186 aberrant methylation and histone deacetylation are responsible
187 for the transcriptional silencing of this gene. The study of
188 this protein also showed that INF- α induced TMEM7 mRNA
189 expression and the restoration of its expression by overexpression
190 or by induction with IFN- α decreased the proliferation and the
191 invasion of hepatocellular carcinoma cell lines (SNU398 and
192 PLC/PRF/5 or HLF and MHCC97 respectively). These data have
193 also been validated *in vivo*. Indeed, ectopic expression of TMEM7
194 in two TMEM7 deficient hepatocarcinoma cell lines decreased
195 tumor growth in nude mice (Zhou et al., 2007). All these data
196 highlight the tumor suppressor role of TMEM7 in hepatocellular
197 carcinoma.

198 Two recent studies also showed that TMEM176A could
199 act as tumor suppressor. The first one was performed in
200 esophageal squamous cell carcinoma. Wang et al. analyzed
201 the methylation profile of TMEM176A promoter in 13 cell
202 lines (BIC1, TE1, TE3, TE13, KYSE140, KYSE180, KYSE410,
203 KYSE450, KYSE520, Segl, KYSE150, YES2, and COLO680N) and
204 267 primary esophageal squamous cell carcinoma. The results
205 showed the loss of TMEM176 expression in 12 cell lines (TE1,
206 TE3, TE13, KYSE140, KYSE180, KYSE410, KYSE450, KYSE520,
207 Segl, KYSE150, YES2, and COLO680N) in association with a
208 complete methylation of its promoter. It also revealed that 66%
209 of primary tumors presented TMEM176A promoter methylation.
210 This methylation and TMEM176A decreased expression were
211 correlated with poor overall survival. The restoration in two
212 cell lines, KYSE410 and KYSE150, of TMEM176A expression
213 with 5'-aza-2'-deoxycytidine treatment and the downregulation
214 of TMEM176A in BIC1 cells showed that TMEM176A inhibited
215 cell invasion and migration and induced apoptosis. Furthermore,
216 TMEM176A inhibited cell growth both *in vitro* and *in vivo*
217 with a decrease in tumor volume when TMEM176A was re-
218 expressed (Wang et al., 2017). A very similar study has been
219 performed in colorectal cancer. It revealed that 50% of the
220 primary tumors presented methylation of TMEM176 promoter.
221 The results also showed a normal expression of TMEM176A
222 in LS180 and SW620 cell lines, a decreased expression in
223 HT29 and SW480 cell lines and a total loss of expression
224 in LOVO, HCT116, RKO, and DLD1 cell lines respectively
225 associated with no methylation, partial methylation and total
226 methylation of TMEM176A promoter. In colorectal cancer as
227 well as in esophageal squamous cell carcinoma, TMEM176A
228 overexpression inhibited cell migration and invasion, induced

apoptosis and inhibited cell growth both *in vitro* and *in vivo* (Gao et al., 2017). These two studies together presented TMEM176A as tumor suppressor of esophageal squamous cell carcinoma and colorectal cancer.

The last protein described in this part is TMEM97. This protein, also named MAC30, is a member of the insulin-like growth factor binding proteins (Murphy et al., 1993). TMEM97 mRNA is expressed in the fetal liver but not in adult liver suggesting a role in development and differentiation of the liver (Malhotra et al., 1999). In 2001 and 2002, two studies showed that the expression of TMEM97 can be induced by other genes like BRCA1 but also be downregulated by others like p53 suggesting that the expression of this gene can be deregulated in cancers (Kannan et al., 2001; Atalay et al., 2002). Indeed, the expression of TMEM97 is increased in several types of cancer as described later in this review, except in pancreatic and renal cancers that both display a low expression level of TMEM97 protein and mRNA. In 2004, 30 pancreatic cancer tissues obtained from patients after tumor resection and 19 non-cancerous pancreatic tissues obtained through an organ donor program have been used to analyze the expression level of TMEM97 in pancreatic cancer both at the mRNA level by RT-qPCR and at the protein level by histochemistry. 50% of pancreatic cancer biopsies displayed a lower, TMEM97 expression compared to normal pancreatic tissue, 20% displayed no change and 30% presented higher TMEM97 levels. These results highlighted a high variability regarding TMEM97 expression levels in pancreatic cancer. Similar observations have been made in pancreatic cancer cell lines (Aspc-1, BxPc-3, Capan-1, Colo-357, T3M4, Mia-PaCa-2, and Panc-1 cells). The protein expression and localization of TMEM97 were also analyzed and TMEM97 was observed in islets and acinar cells of normal pancreatic cells, markedly in tubular complexes but at low levels in pancreatic cancer cells. Knowing that tubular complexes are considered as potential pre-neoplastic lesions, the observed reduction of TMEM97 expression in pancreatic cancer suggests that this gene might act as a tumor suppressor in this disease (Kayed et al., 2004). This hypothesis may also be true for prostate cancer since miR-152-3p downregulation and promoter methylation were found to be prevalent in primary prostate cancers. TMEM97, which is overexpressed in this type of cancer, is a target of miR-152-3p (Ramalho-Carvalho et al., 2018).

PART 2: TMEMs AS ONCOGENES

Many TMEMs are up regulated in cancer. Some of them are implicated in tumor progression, invasion and in the formation of metastasis while others are associated with poor prognosis and can be used as prognostic biomarker. The studies behind these conclusions are summarized here under.

TMEMs as Prognostic Biomarkers

TMEM48, also named NDC1 is localized to the nuclear pore complexes. This nucleoporin has six membrane-spanning segments and is crucial for nuclear pore complexes and nuclear envelope assembly (Stavru et al., 2006). The integrity of the

nuclear envelope and a correct nucleocytoplasmic transport are important for many cellular processes such as genome stability, DNA replication, or DNA repair (D'Angelo and Hetzer, 2008). Nucleoporin deregulation has been implicated in several malignancies such as breast cancers (Agudo et al., 2004; Kau et al., 2004) in multiple tumors including melanoma, pancreatic, breast, colon, gastric, prostate, esophageal, lung cancer, and lymphomas (Mahipal and Malafa, 2016). A study based on 60 patients with NSCLC showed that TMEM48 expression was significantly higher in cancer tissues compared to healthy tissues. This overexpression was associated with poor prognosis, lymph node metastasis, increased tumor size and short survival (Qiao et al., 2016). All together these results suggest that, since TMEM48 mRNA expression is increased in non-small lung carcinoma in association with advanced tumor stage, TMEM48 may be a potential prognostic factor for NSCLC.

TMEM45A is a TMEM of 275 amino acids, predicted to have 5 or 7 transmembrane domains and localized in the trans Golgi apparatus. Very little is known about this protein except that TMEM45A is highly expressed in the skin and is associated with epiderm keratinization (Hayez et al., 2014). This protein is overexpressed in many cancers: breast cancer, liver cancer, renal cancer, glioma, head and neck cancer, ductal cancer, and ovarian (Flamant et al., 2012; Lee et al., 2012; Guo et al., 2015; Sun et al., 2015; Wrzesinski et al., 2015; Manawapat-Klopfer et al., 2016). In the cases of breast cancer and cervical lesions, a higher expression level of TMEM45A has been correlated with a lower patient overall survival suggesting that TMEM45A is a potential biomarker for aggressiveness of breast cancer and cervical lesions (Flamant et al., 2012; Manawapat-Klopfer et al., 2016).

Despite the putative tumor suppressor role of TMEM97 in pancreatic and prostate cancers, this protein is overexpressed in different types of cancer and associated with tumor progression, recurrence and poor survival. It is the case in breast, gastric, colon, epithelial ovarian, oral squamous, and NSCLC. Indeed, the expression of TMEM97 has been analyzed in 20 cases of NSCLC compared to adjacent healthy tissue: 65% of patients showed a higher expression level of TMEM97 in tumor tissue compared to healthy tissue. Furthermore, the expression of this protein has been correlated with poor tumor differentiation and a shorter patient survival (Han et al., 2013). A similar study performed in human SQCLC showed TMEM97 overexpression in 26 of the 32 tumor samples in comparison to corresponding non-tumor tissues. TMEM97 overexpression was associated with poor tumor differentiation and shorter overall patient survival (Ding et al., 2016). Another study in breast cancer revealed that 59.7% of tumor samples displayed a higher expression level of TMEM97 compared to healthy tissue and that this overexpression correlated with larger tumor size and tumor recurrences. One study on ovarian cancer showed that high expression of TMEM97 was correlated with high histological grade and tumor recurrence (Xiao et al., 2013; Yang et al., 2013). All these studies demonstrated that TMEM97 expression could affect the prognosis of NSCLC, SQCLC, ovarian and breast cancer patients.

Another important TMEM protein is TMEM16A. TMEM16A, also known as anoctamin-1, is expressed in

343 cerebral artery smooth muscle cells and is predicted to have eight
344 transmembrane domains. This protein is a TMEM that functions
345 as a calcium-activated Cl⁻ channel (Thomas-Gatewood et al.,
346 2011). TMEM16A has recently been shown to be upregulated
347 in several cancers including HNSCC, esophageal, breast and
348 gastric cancers. In HNSCC, the expression of TMEM16A
349 has been studied by fluorescence *in situ* hybridization and
350 immunohistochemistry on several primary tumors. The results
351 demonstrated that TMEM16A was highly expressed in 4–19%
352 of the samples and that higher TMEM16A expression strongly
353 correlated with poor prognosis of HNSCC patients (Ruiz et al.,
354 2012). In another study in HNSCC, TMEM16A has been
355 shown to be overexpressed in 84% of tumor samples (Carles
356 et al., 2006). In the context of gastric cancer, the expression of
357 TMEM16A has been evidenced to be higher in tumor tissue than
358 in adjacent non-tumor tissue. Furthermore, the expression of this
359 protein has been correlated with the tumor stage and negatively
360 correlated with patient survival in this cancer type (Liu et al.,
361 2015). TMEM16A is thus proposed to be a negative prognostic
362 factor.

363 Two other TMEMs have been described as prognosis
364 biomarker. In glioma, TMEM140 expression has been analyzed
365 in 47 of the 70 glioma samples by immunohistochemistry. The
366 results showed a higher expression in tumor tissue than in the
367 control brain tissue and a correlation with poor prognosis in this
368 cancer (Li et al., 2015a,b). In lung cancer, TMEM45B expression
369 has been analyzed in 110 tumor tissue samples and 35 non-tumor
370 tissue samples. TMEM45B was shown to be upregulated in lung
371 cancer and its expression was negatively correlated with overall
372 survival (Hu et al., 2016).

373 TMEMs Involved in Tumor Growth

374 Besides the evidence for a correlation between TMEM expression
375 and patient survival, some of these proteins have been shown
376 to be directly involved in tumor growth but the mechanisms by
377 which they act are not always known.

378 With an Identified Pathway

379 The first protein described in this part is TMEM158. The
380 gene coding for this protein is known to be upregulated
381 during Ras-induced senescence in human diploid fibroblasts
382 infected with rasV12-containing retrovirus (Barradas et al.,
383 2002). TMEM158 is overexpressed in Wilms tumors (also
384 known as nephroblastoma) with somatic mutations in catenin
385 beta-1 gene suggesting a relationship between the Ras and
386 Wnt signaling pathways (Zirn et al., 2006). TMEM158 is also
387 overexpressed in ovarian cancer in 84% of the 25 tumor
388 samples which were analyzed. The involvement of TMEM158
389 in tumor growth has been studied in two ovarian cancer cell
390 lines, HO-8910 and A2780. This protein was evidenced to
391 regulate cell proliferation, adhesion, and invasion. Furthermore,
392 TMEM158 knockdown inhibited tumor growth of HO-8910
393 cell line in nude mice highlighting the role of this protein in
394 tumorigenicity. TMEM158 silencing led to the deregulation of
395 the expression of different genes, including a downregulation
396 of ICAM1 and VCAM1 expression. These two proteins are
397 involved in cell adhesion. TMEM158 silencing also impaired the

400 TGF- β signaling pathway (Cheng et al., 2015). All these results
401 showed that TMEM158 may work as an oncogene in ovarian
402 cancer.

403 The implication of TMEM48 in NSCLC progression has been
404 studied in two cell lines that overexpressed this protein, A549
405 and H1299. The results suggested a role of TMEM48 in cell
406 proliferation, migration and invasion. Indeed, the silencing of
407 this gene impaired cell proliferation, induced cell cycle arrest
408 and decreased the migration and invasive ability of NSCLC cells.
409 The downregulation of TMEM48 also induced cell apoptosis
410 in association with a decrease or an increase in anti- or pro-
411 apoptotic gene expression respectively. One of these two cell
412 lines (A549) was also used to study the involvement of TMEM48
413 in tumorigenicity *in vivo* and the data revealed that TMEM48
414 is involved in tumor formation from A549 cells in nude mice.
415 A marked decrease in tumor weight (50%) was evidenced when
416 TMEM48 was silenced. All these evidences showed a role of
417 TMEM48 in lung cancer progression (Qiao et al., 2016). A recent
418 study demonstrated that TMEM48 suppression by miR-421
419 increased the expression of the apoptotic and tumor suppressor
420 proteins caspase 3, PTEN and p53 in A549 cells (Akkafa
421 et al., 2018). These results suggest that TMEM48 modulates the
422 apoptotic pathway.

423 TMEM14A is a TMEM with three transmembrane domains,
424 localized in mitochondria. This protein is deregulated in different
425 types of cancer such as ovarian cancer, colon cancer and
426 hepatocellular carcinoma (Hodo et al., 2010; Smith et al., 2010;
427 Zhang et al., 2016). In the context of ovarian cancer, TMEM14A
428 is involved in cell proliferation as shown by a cell cycle arrest
429 when TMEM14A was invalidated in two ovarian cancer cell lines,
430 A2780 and HO-8910. TMEM14A up regulation also increased
431 the cell invasive ability of ovarian cancer cells highlighting a
432 potential role of this protein to promote metastasis. Further
433 investigations showed that TMEM14A knockdown may down-
434 regulate the protein expression of PCNA, cyclins and MMPs.
435 It may also downregulate TGF- β signaling (Zhang et al., 2016).
436 These results could explain the decrease in cell proliferation and
437 invasiveness in ovarian cancer cell lines when TMEM14A was
438 invalidated.

439 TMEM97 is found deregulated in several types of cancer
440 but this protein has been particularly involved in the tumor
441 growth of two cancers: glioma and gastric cancer. Indeed, the
442 silencing of TMEM97 expression in glioma U373 and U87 cells
443 inhibited cell proliferation and cell cycle progression associated
444 with a decrease in cyclin B1, E, CDK2 and CDK4 expression,
445 but also in cell invasiveness. TMEM97 silencing also induced the
446 deregulation of the expression of EMT markers like β -catenin,
447 Twist and E-cadherin (Qiu et al., 2015). The downregulation
448 of TMEM97 in gastric cancer BGC-823 and AGS cell lines
449 inhibited the cell proliferation and mobility with a decrease in
450 Akt phosphorylation, hence suggesting that Akt may mediate the
451 TMEM97-induced inhibition of proliferation (Xu et al., 2014).
452 The invalidation of TMEM97 also induced an inhibition of cell
453 migration and invasion by reducing the expression of cyclin
454 B1 and WAVE2. These data showed that TMEM97 plays an
455 important role in tumor growth and aggressiveness in glioma and
456 gastric cancer.

457 Another TMEM protein involved in tumor growth is
458 TMEM16A. In human colorectal cancer cells, the mRNA and
459 protein expression of TMEM16A has been reported in several
460 cell lines like SW620, HCT116 and LS174T but not in HCT8
461 and SW480. TMEM16A knockdown in SW620 cell line inhibited
462 cell proliferation, migration and invasion. These effects were
463 mediated through a decrease in the expression of cyclin D1
464 and in the phosphorylation of MEK and ERK1/2. Furthermore,
465 invalidation of TMEM16A expression led to a delay in cell cycle
466 progression (Sui et al., 2014). TMEM16A expression is also
467 regulated epigenetically. Indeed, inhibition of HDAC class I and
468 II by siRNA or pharmacological agents decreased the expression
469 of TMEM16A. HDAC3 seems to be the most important one
470 in this regard. Hence, the inhibition of HDAC3 may exert
471 suppressive effect on cancer cell viability via the downregulation
472 of TMEM16A in prostate or breast cancer (Matsuba et al.,
473 2014). TMEM16A has also been well-studied in gastric cancer.
474 Knockdown in AGS and BGC-823 gastric cancer cell lines
475 inhibited cell migration and invasion via a downregulation of
476 E-cadherin expression (EMT marker) probably via a decrease
477 in TGF- β secretion since the supplementation of exogenous
478 TGF- β restored E-cadherin expression and cell migration
479 and invasion (Liu et al., 2015). TMEM16A silencing was
480 also shown to induce apoptosis in human prostate cancer
481 PC3 cells by upregulating TGF- β signaling (Song et al.,
482 2018). In pancreatic ductal adenocarcinoma, TMEM16A is
483 overexpressed in several cancer cell lines (Mia PaCa-2, Panc-
484 1, BxPC-3, and AsPC-1) in comparison to HPDE-derived
485 cells. The invalidation of TMEM16A expression in these cell
486 lines using siRNA showed an implication of this protein in
487 cell migration but not in the proliferation illustrating that
488 TMEM16A modulates the metastatic potential of pancreatic
489 cancer cells. Contrary to colorectal cancer, the molecular
490 mechanism underlying this effect is still unknown (Sauter et al.,
491 2015).

492 The last TMEM described in this part is a very peculiar TMEM
493 protein, TMEM88. This protein is a potential 2-transmembrane
494 type protein that interacts with an important component of
495 Wnt signaling pathway: DVL1 (Lee et al., 2010). According
496 to the localization of its partner DVL1, TMEM88 may be
497 localized in the cytoplasm or to the plasma membrane. This
498 protein is overexpressed in cancer tissue compared to non-
499 cancerous tissue in different types of cancer such as in lung,
500 colon, gastric, breast cancer (Yu et al., 2015; Zhang et al., 2015)
501 and can be involved in the tumor initiation and progression
502 through Wnt signaling pathway (Ge et al., 2018). For the
503 majority of these cancer types, immunohistochemistry analysis
504 demonstrated a cytosolic localization. But in the context of
505 NSCLC, two different subcellular localizations for TMEM88 have
506 been reported, suggesting different roles in tumor development
507 depending on its localization. Indeed, an *in vitro* analysis
508 on nine lung cancer cell lines (A549, H1299, H460, H292,
509 SPC-A-1, LTEP-A-2, LK2, PG-BE1, and PG-LH7) showed that
510 the overexpression of membrane-associated TMEM88 led to
511 the inhibition of the canonical Wnt pathway through the
512 downregulation of the expression of effectors like cyclin D1,
513 MMP-7, and c-Myc. The increase in membrane-associated

TMEM88 expression also led to a decrease of proliferation, 514
colony formation, migration and invasion and to a decrease in 515
tumor growth *in vivo* highlighting the tumor suppressor role 516
of TMEM88 when it is localized to the membrane of the cell. 517
Furthermore, TMEM88 promoter methylation is associated with 518
unfavorable prognosis in NSCLC (Ma et al., 2017). On the 519
contrary, its cytosolic localization is correlated with a low level 520
of differentiation of the tumor and poor prognosis of patients 521
with NSCLC. Furthermore *in vitro* analysis demonstrated 522
that the overexpression or downregulation of this protein 523
respectively enhanced or suppressed NSCLC cell migration and 524
invasion through a deregulation of the EMT signaling pathway. 525
Indeed, the TMEM88-DVL complex increased p38 and GSK3 β 526
phosphorylation leading to a stabilization of the protein SNAIL 527
and hence to a decreased occludin and zonula occludens- 528
1 (ZO-1) expression. Moreover, *in vivo* analysis showed that 529
the number of lung metastatic nodules increased in the mice 530
transplanted with cell lines expressing cytosolic TMEM88 (Zhang 531
et al., 2015). Very similar results have also been observed 532
in triple-negative breast cancer (Yu et al., 2015). These data 533
confirmed that, in NSCLC and breast cancer, the cytosolic 534
localization of TMEM88 conferred an oncogenic role to the 535
protein. 536

537 Depending of cancer stage, TGF- β signaling can have
538 different impact on tumor growth. Indeed, in early stage
539 TGF- β plays a tumor suppressor role whereas in advanced
540 stage, cancer cells benefit from TGF- β to initiate proliferation,
541 invasion, and metastasis dissemination. It seems that several
542 TMEM proteins are involved in tumor growth through
543 TGF- β pathway modulation in order to facilitate malignant
544 progression (Figure 1). Indeed, TMEM16A, TMEM158,
545 TMEM14A, TMEM97, TMEM88 and probably TMEM45A
546 interacts with several components of the TGF- β -induced signal
547 transduction. 548

549 Through an Unknown Pathway

550 Other TMEMs have also an impact on tumor growth but the
551 mechanisms by which they act are still unknown. Such an
552 example is TMEM140 that is up regulated in cancer tissue
553 compared to healthy tissue. TMEM140 has been involved in
554 the regulation of the growth of glioma *in vitro* and *in vivo*.
555 Indeed, when TMEM140 is silenced in two glioma cell lines
556 *in vitro*, U87 and U373, the proliferation decreased with a
557 higher proportion of cells in G1 phase and the cell viability
558 decreased due to the activation of the apoptotic pathway.
559 Furthermore, the knockdown of TMEM140 led to a decreased
560 cell adhesion, migration and invasion. It has also been shown
561 that the invalidation of this protein inhibited tumor growth
562 *in vivo* with a decrease in the size and the weight of tumors
563 in the invalidated group compared to the control group (Li
564 et al., 2015a,b). These findings demonstrate that TMEM140 can
565 be used as a prognosis biomarker but also as a therapeutic
566 target. 567

568 Two other TMEM proteins have been involved in tumor
569 progression, TMEM45A and TMEM45B, already described
570 above. TMEM45A is implicated in cell proliferation, migration,
571 and invasion of different cancers like glioma (U251 and U373

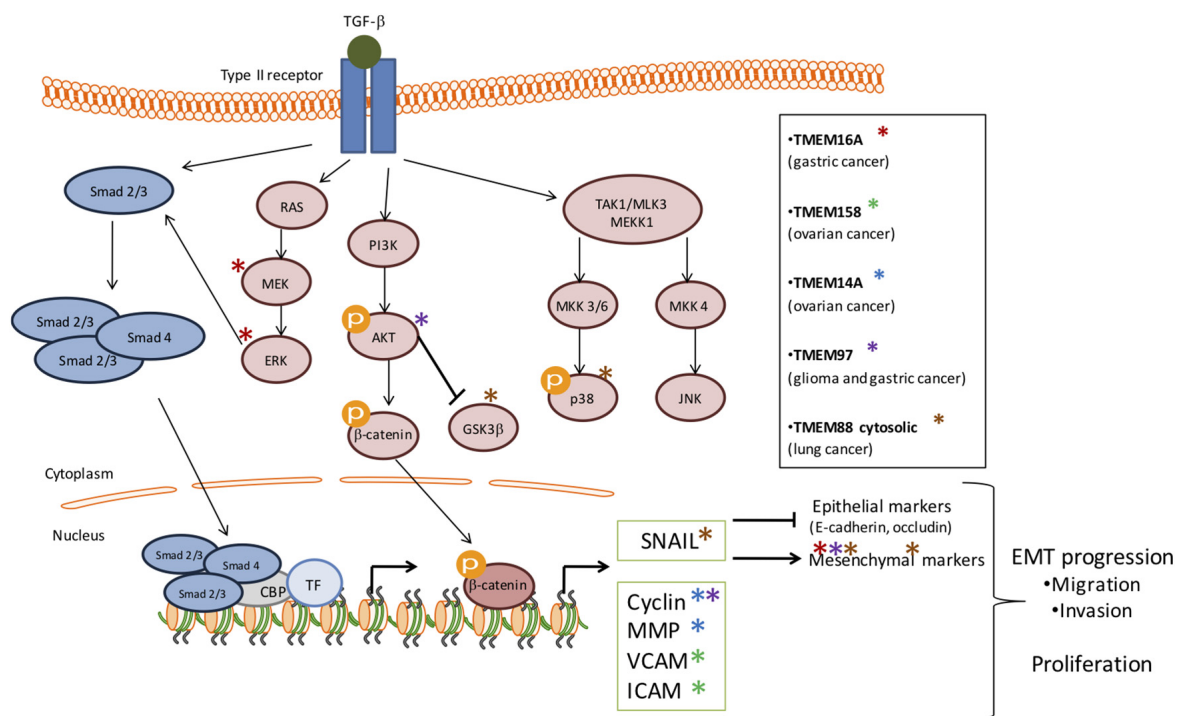


FIGURE 1 | Schematic representation of the involvement of several TMEMs in tumor growth through the TGF- β signaling pathway. The activation of TGF- β signaling pathway has been implicated in many cellular processes and in tumor growth. This activation is induced by its ligand which then activates the phosphorylation of serine/threonine residues and triggers phosphorylation of the intracellular effectors, SMADs (blue). TGF- β receptors can also activate Smad-independent pathways (pink). In early stage TGF- β plays a tumor suppressor role whereas, in advanced stage, cancer cells benefit from TGF- β to initiate proliferation, invasion and metastasis dissemination. It seems that several TMEM proteins are involved in tumor growth through TGF- β activation in order to facilitate malignant progression and EMT progression. The stars represent the effectors deregulated by TMEMs.

cells) and ovarian cancer (HO-8910 and A2780 cells) (Guo et al., 2015; Sun et al., 2015). In the context of ovarian cancer, TMEM45A protein expression had been positively correlated to TGF- β signaling pathway and this data could explain the impact of TMEM45A inactivation in this cancer (Guo et al., 2015). On the other hand, TMEM45B is up-regulated in human lung cancer and promotes tumorigenicity *in vivo*. Inactivation of TMEM45B in A549 and NCI-H1975 cells led to the inhibition of cell proliferation, migration, and invasion highlighting its role in tumor growth in lung cancer (Hu et al., 2016). In the case of pancreatic cancer, TMEM45B had also been involved in proliferation, invasion, and migration since its silencing in SW1990 and PANC-1 cell lines induced an inhibition of cell proliferation associated with cell cycle arrest. It also led to a decrease in cell mobility and invasiveness. Conversely, the overexpression of TMEM45B in CFPAC-1 cells promoted cell proliferation, invasion and migration (Zhao et al., 2016). TMEM45B is also upregulated in osteosarcoma cell lines. Its knockdown suppressed the proliferation, migration, and invasion of U2OS cells *in vitro* as well as tumor growth in nude mice. These effects were associated with a decrease in the expression of β -catenin, cyclin D1 and c-Myc (Li et al., 2017). Similar results were obtained in gastric cancer cells, in which TMEM45B silencing was associated with a decrease in the abundance of p-STAT3 and p-JAK2 (Shen et al., 2018). These two proteins can

be described as potential prognosis markers but also as regulators of tumor growth in several types of cancer.

PART 3: TMEMs INVOLVED IN CHEMORESISTANCE

Although mutagenic alterations have long been associated with cancer development or drug resistance, epigenetic modifications and tumor microenvironment have also been linked to chemoresistance. Both epigenetic modifications and the tumor microenvironment can impact the expression or the localization of several TMEMs leading to a deregulation of treatment responses. The first example is hypoxia, one component of the tumor microenvironment. Indeed, in hypoxic condition (<1% of O₂), hepatocellular carcinoma cells (HepG2) (Sermeus et al., 2008) and breast cancer cells (MDA-MB-231) (Flamant et al., 2010) were protected against cell death normally induced by chemotherapeutic drugs. In this condition, TMEM45A was shown to be upregulated and its silencing led to a decrease in this protective effect conferred by hypoxia against cell death induced by chemotherapeutic agents. These results suggest that, in hypoxic condition, TMEM45A is involved in the chemoresistance of breast and liver cancers. However, the mechanism underlying this protection is still unknown (Flamant et al., 2012).

685 The second example is related to epigenetic modifications,
 686 in particular DNA methylation. Indeed, in ovarian cancer, it
 687 has been shown *in vivo*, that the methylation profile of some
 688 promoters was different in xenografts resistant to cisplatin
 689 compared to control ones. This observation has been associated
 690 with a differential expression profile of the genes whose
 691 expression is regulated by these promoters. It is the case for
 692 TMEM88, which is a DNA methylation-regulated gene. The
 693 hypomethylation of TMEM88 promoter observed in ovarian
 694 cancer led to an increased expression of the protein and
 695 to platinum resistance. Indeed, knowing that TMEM88 was
 696 involved in Wnt signaling pathway, De Leon et al investigated
 697 the possible association of Wnt pathway and the observed
 698 phenotype. First of all, TMEM88 downregulation led to an
 699 increase in Wnt target gene expression such as β -catenin
 700 or Jun, validating the interaction between TMEM88 and
 701 Wnt pathway in ovarian cancer. Then, they studied the link
 702 between this interaction and the observed chemoresistance.
 703 TMEM88 overexpression in resistant cells inhibited the Wnt
 704 signaling pathway associated with a decrease in target gene
 705 expression while the activation of the Wnt pathway in resistant
 706 cells increased the chemosensitivity of the cells to cisplatin.
 707 Furthermore, the invalidation of TMEM88 in cisplatin resistant
 708 cells increased the sensitivity of the cells to the chemotherapeutic
 709 drug. This increase in chemosensitivity was associated to

a decrease in cell proliferation allowing the escape of the
 cells from the genotoxic effects of cisplatin (de Leon et al.,
 2016).

Another TMEM involved in chemoresistance is TMEM205,
 also known as MBC3205. This protein of 21 kDa has four
 transmembrane domains and belongs to the group of secreted
 proteins (Clark et al., 2003). In 2011, a study revealed that
 TMEM205 is highly expressed in the pancreas, adrenal gland,
 liver, mammary gland and kidney (Shen et al., 2010). This
 study also showed that, in epidermoid carcinoma, this protein
 had the particularity to translocate in the presence of
 cisplatin. Indeed, TMEM205 is located at the cell surface
 but in the presence of the chemotherapeutic drug, the
 protein is translocated in an intracellular compartment at
 the periphery of the nucleus. Furthermore, its expression is
 increased in a cell line resistant to cisplatin and
 TMEM205 overexpression conferred resistance to cisplatin
 (Shen et al., 2010). Another study demonstrated that
 TMEM205 colocalized with RAB8, a marker of recycling
 endosomes. Interestingly, TMEM205 also colocalized with
 syntaxin 6 (STXR6), a regulator of protein trafficking, which
 is translocated at the same subcellular localization that
 TMEM205 in the presence of cisplatin. Then, the
 translocation of TMEM205 may allow the exocytosis of
 platinum containing vesicles, which thus results in the
 accumulation of the drug outside the cell (Shen and
 Gottesman, 2012).

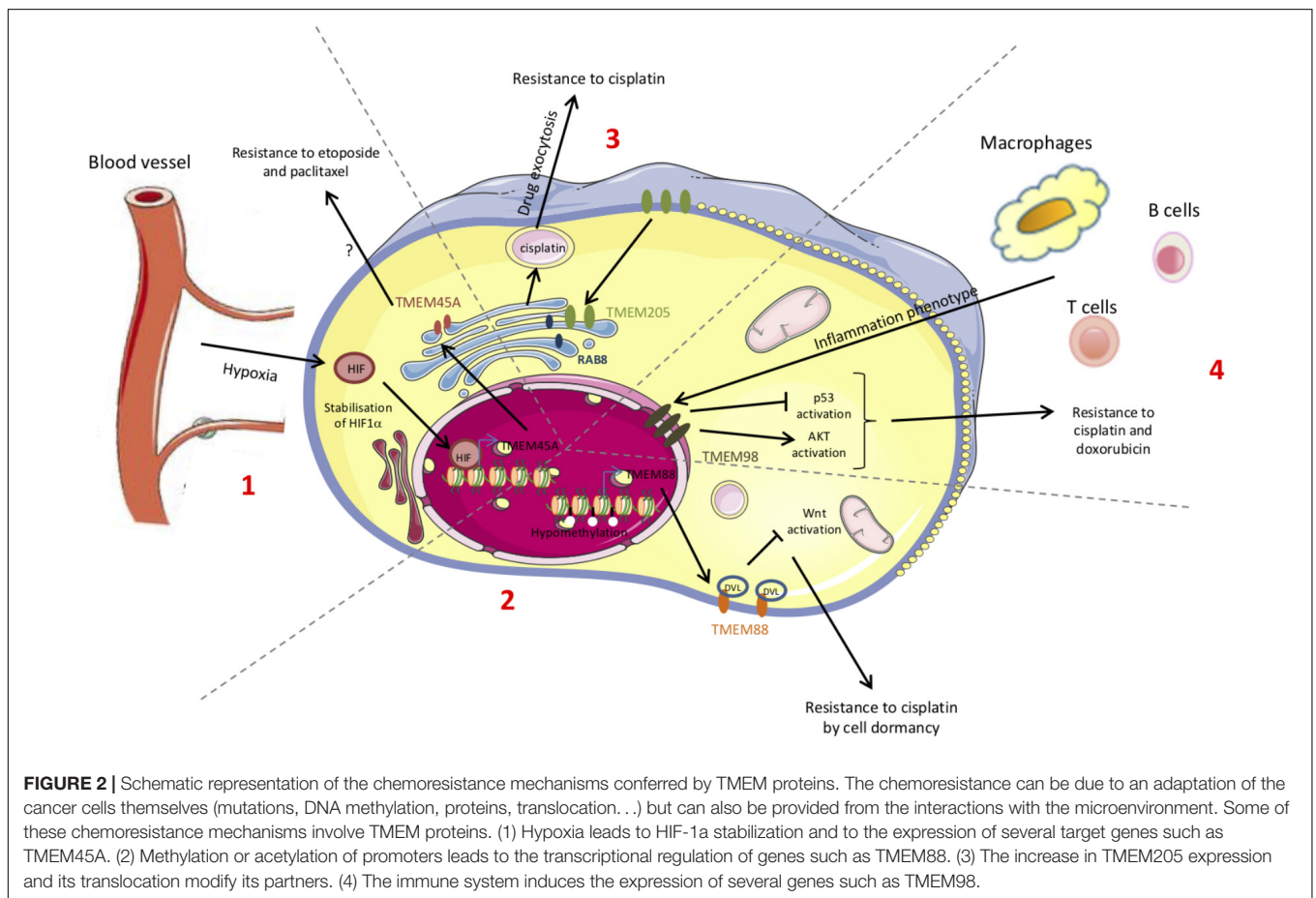


TABLE 1 |

TMEM	Localization	Function	Cancer		Models		Involvement in cancer	Reference
			Patient	In vitro	In vivo	In vitro		
TMEM25	Unknown	Immune response	Colorectal adenocarcinoma	/	/	/	Tumor suppressor	Katoh and Katoh, 2004; Doolan et al., 2009; Hrasovec et al., 2013
TMEM7	Unknown	Interaction with olfactory receptors	Primary hepatocarcinoma	Hepatocarcinoma	Hepatocarcinoma	SNU398, PLC/PRF/5, HLF, MHCC97	Tumor suppressor	Zhou et al., 2007
TMEM176A	Golgi apparatus (cis)	Unknown	Esophageal squamous cell carcinoma and colorectal cancer	Esophageal squamous cell carcinoma and colorectal cancer	Esophageal squamous cell carcinoma and colorectal cancer	BIC1, TE1, TE3, TE13, KYSE140, KYSE180, KYSE410, KYSE450, KYSE520, Segi, KYSE150, YES2, COLO680N and LS180, SW620, HT29, SW480, LOVO, HCT116, RKO and DLD1	Tumor suppressor	Gao et al., 2017; Wang et al., 2017
TMEM97	Unknown	Cholesterol level, growth and differentiation of the liver	Pancreatic cancer	Pancreatic cancer	Pancreatic cancer	Aspc-1, BxPc-3, Capan-1, Colo-357, T3M4, Mia-Paca-1, Panc-1	Tumor suppressor	Murphy et al., 1993; Malhotra et al., 1999; Kannan et al., 2001; Atalay et al., 2002; Kaye et al., 2004
TMEM48	Nuclear pore complexes	Assembly and insertion of nuclear pore complexes to the nuclear membrane	Ovarian, breast, lung cancer	Glioma and gastric cancer	Lung carcinoma	U373, U87 and BGC-823, AGS	Oncogene/chemoresistance	Chen et al., 2007; Han et al., 2013; Xiao et al., 2013; Yang et al., 2013; Xu et al., 2014; Qiu et al., 2015; Ding et al., 2016, 2017

(Continued)

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TABLE 1 | Continued

TMEM	Localization		Function	Cancer		Models		Involvement in cancer	Reference
	In vitro	In vivo		In vitro	In vivo	In vitro	In vivo		
TMEM45A	Golgi apparatus (trans)		Association with epidermal keratinization	Breast, liver, renal, head and neck, ductal, ovarian cancers and glioma	/	Glioma, hepatocellular carcinoma, ovarian, breast, cancers	U251, U373, HO-8910, A2780, HepG2, MDA-MB231	Oncogene/chemoresistance	Sermeus et al., 2008; Flamant et al., 2010, 2012; Lee et al., 2012; Hayez et al., 2014; Guo et al., 2015; Sun et al., 2015; Wrzesinski et al., 2015; Manawapat-Klopfer et al., 2016
TMEM16A	Plasma membrane		Calcium activated chloride channels	Head and neck, esophageal, breast, prostate, gastric, colorectal cancer	/	Head and neck, gastric, colorectal cancers	Cal-27, Cal-33, BHY, SW620, HCT116, LS174T, AGS, BGC-823	Oncogene	Carles et al., 2006; Thomas-Gatewood et al., 2011; Ruiz et al., 2012; Sui et al., 2014; Liu et al., 2015; Sauter et al., 2015
TMEM140	Unknown		Unknown	Glioma	/	Glioma	/	Oncogene	Liu et al., 2015; Li et al., 2015a
TMEM158	Unknown		Hypothetical function in a neuronal survival pathway	Ovarian cancer	Ovarian cancer	Ovarian cancer	HO-8910, A2780	Oncogene	Barradas et al., 2002; Zirn et al., 2006; Cheng et al., 2015
TMEM14A	Mitochondria		Inhibition of apoptosis	Hepatocellular carcinoma, ovarian and colon cancers	/	Ovarian cancer	A2780, HO-8910	Oncogene	Hodo et al., 2010; Smith et al., 2010; Zhang et al., 2016
TMEM88	Plasma membrane		Inhibition of Wnt/beta-catenin signaling pathway (membrane associated) and heart development	Lung, breast, colon cancers and hepatocellular, gastric carcinoma	Lung cancer	Lung cancer	A549, H1299, H460, H292, SPC-A-1, LTEP-A-2, LK2, PG-BE1 and PG-LH7	Tumor suppressor if membrane associated/chemoresistance	Lee et al., 2010; Yu et al., 2015; Zhang et al., 2015; de Leon et al., 2016; Ge et al., 2018
TMEM45B	Cytosolic		Unknown	Lung cancer	Lung cancer	Lung, pancreatic cancers	A549, H1299, A549, NCI-H1975, SW1990, PANC-1	Oncogene if cytosolic	Hu et al., 2016; Zhao et al., 2016
	Unknown		Unknown	Osteosarcoma	Osteosarcoma	Osteosarcoma	U2OS	Oncogene	Li et al., 2017
	Unknown		Unknown	Gastric cancer	/	Gastric cancer	BGC-823, MGC-803, SGC-7901, HGC-27	Oncogene	Shen et al., 2018
TMEM205	Plasma membrane or perinuclear		Hypothetical role in secretion or vesicular trafficking	/	/	Epidermoid carcinoma	KB-3-1, KB-CP3, KB-C.5, Balb/3T3	Oncogene/chemoresistance	Clark et al., 2003; Shen et al., 2010; Shen and Gottesman, 2012
TMEM88	Unknown		Unknown	Lung cancer and hepatocellular carcinoma	Hepatocellular carcinoma	Lung cancer and hepatocellular carcinoma	A549, H460, MHCC97L/CisR, MHCC97L/DoxR	Oncogene/chemoresistance	Ng et al., 2014; Fu et al., 2015; Mao et al., 2015

1027 In the tumor microenvironment, the immune system
 1028 plays a crucial role that modulates tumor growth.
 1029 Furthermore, cancer-associated inflammation also plays a
 1030 role in chemoresistance (Chen et al., 2007). In this context,
 1031 TMEM98, which has immune-related properties, mainly
 1032 regarding the differentiation of T helper (Th) 1 cells, may
 1033 be proposed as a novel chemoresistance-conferring gene (Fu
 1034 et al., 2015). There are two RNA splicing forms of TMEM98
 1035 reported in the NCBI database, TMEM98-v1 and TMEM98-
 1036 v2 respectively. Although there is a slight difference between
 1037 them in the 5' UTR sequence, their coding products are
 1038 almost the same, which consists of 226 amino acids and
 1039 a molecular weight of 24.6 kDa. In lung cancer, TMEM98
 1040 mRNA expression is higher in cancer tissues compared to
 1041 healthy tissues. Furthermore, in two lung cancer cell lines,
 1042 A549 and H460, the silencing of TMEM98 inhibited cell
 1043 proliferation and suppressed the invasion and the migration
 1044 of cancer cells meaning that this protein can have an impact
 1045 in tumor growth (Mao et al., 2015). Knowing that tumor
 1046 progression and chemoresistance can be accompanied with
 1047 inflammation injuries and the link between TMEM98 and
 1048 inflammation, this protein is a very interesting target for further
 1049 investigations on anti-cancer drug resistance. In the case of
 1050 hepatocellular carcinoma, TMEM98 has been identified as
 1051 a chemoresistance-associated gene. Indeed, its expression is
 1052 increased in two chemoresistant cell lines, MHCC97L/CisR
 1053 and MHCC97L/DoxR resistant to cisplatin and doxorubicin
 1054 respectively. Furthermore, the level of the upregulation increased
 1055 with the degree of chemoresistance. This study also showed
 1056 that TMEM98 mRNA expression was higher in tumor tissue
 1057 of patients who received a transarterial chemoembolization
 1058 treatment. Moreover, the patients who did not respond
 1059 well to the treatment had higher TMEM98 expression level.
 1060 These data demonstrated that this protein is involved in
 1061 chemoresistance of hepatocellular carcinoma. In order to
 1062 identify the mechanism of TMEM88 in chemoresistance,
 1063 further investigation had been performed. In the absence of
 1064 TMEM88 in resistant cell lines, a repression of activation
 1065 of AKT in association with a repression of its downstream
 1066 targets had been observed. Furthermore, the silencing of
 1067 TMEM88 restored p53 phosphorylation and activation under
 1068 cisplatin or doxorubicin treatment. These data showed that
 1069 the chemoresistance induced by TMEM88 is associated with
 1070 AKT activation and the repression of p53 activation (Ng et al.,
 1071 2014).

1072 The platinum-based chemotherapy is used for the treatment
 1073 of several cancers such as lung cancer. In this model,
 1074 the high expression level of TMEM97 has been correlated
 1075 with the resistance of cancer to platinum-based treatment
 1076 but also with poor patient survival (Chen et al., 2016;
 1077 Ding et al., 2017). Indeed, Chen et al. (2015), showed that
 1078 only 4% of patients with elevated expression of TMEM97
 1079 showed responses to therapy while 65% of patients with low
 1080 expression of TMEM97 responded to the treatment (Chen
 1081 et al., 2016). This study proposed TMEM97 as a biomarker
 1082 of prognosis but also of the responses of NSCLC patients to
 1083 chemotherapies.

1084 Two other TMEMs could have an impact in chemoresistance
 1085 via the immune system, TMEM176A and TMEM176B. These
 1086 two proteins can physically interact one with the other and are
 1087 both localized in the plasma membrane and vesicular intracellular
 1088 compartments (Cuajungco et al., 2012). The expression of these
 1089 two proteins is increased in lymphoma, which may allow
 1090 the cancer cells to evade the immune system or negatively
 1091 impact their detection by immune system (Cuajungco et al.,
 1092 2012).

1093 Knowing that many chemotherapeutic drugs induced
 1094 cancer cell death, several TMEMs could also have an impact
 1095 in chemoresistance by exerting an anti-apoptotic function.
 1096 TMEM48 is such an example for lung cancer (Qiao et al.,
 1097 2016), TMEM14A for ovarian cancer (Zhang et al., 2016) and
 1098 TMEM45B for lung and pancreatic cancers (Hu et al., 2016; Zhao
 1099 et al., 2016).

1100 The resistance to chemotherapy is not only due to the
 1101 adaptation of cancer cells themselves but can involve tumor
 1102 microenvironment. Furthermore, the mechanisms underlying
 1103 the resistance to treatment can differ according to the
 1104 cancer type and to the chemotherapeutic drug. The studies
 1105 reported in this review showed that some TMEM proteins
 1106 are involved in resistance to treatment and so can be used
 1107 as new therapeutic targets (Figure 2). Finally, since TGF-
 1108 β -induced quiescence renders cancer cells resistant to some
 1109 anticancer agents (Brown et al., 2017; Tamai et al., 2017)
 1110 and since many TMEM proteins interfere with TGF- β -induced
 1111 intracellular signaling, TGF- β pathway is probably one of the
 1112 key mechanisms through which TMEM proteins exert their
 1113 effects.

1114 CONCLUSION

1115 Despite the different role and localization of TMEM proteins,
 1116 many of them are implicated in cancer (Table 1). Some
 1117 of them can be correlated with stages and patient survival
 1118 and so be used as biomarkers and/or classifiers. Others have
 1119 a role in carcinogenesis and tumor progression, but for
 1120 most of them, the mechanism involved is still unknown.
 1121 A better characterization of these proteins could help to
 1122 better understand their implication in cancer. A few of
 1123 them are even involved in chemoresistance and could be
 1124 used as new therapeutic targets to enhance the efficiency of
 1125 chemotherapies.

1126 AUTHOR CONTRIBUTIONS

1127 KS wrote the review and designed the figures and the table. CM
 1128 supervised the whole work, contributed to writing, and critically
 1129 revised the paper. 1133 [Q11](#)
1134 [Q10](#)

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1140 [Q12](#)

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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