Minireview

DMBT1, a regulator of mucosal homeostasis through the linking of mucosal defense and regeneration?

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Abstract DMBT1 (deleted in malignant brain tumor 1), which encodes a large scavenger receptor cysteine rich (SRCR) B protein, has been proposed to be a tumor suppressor gene, due to the high frequency of its homozygous deletion and the lack of expression in a variety of cancers. However, studies on its physiological functions and its relationship with tumorigenesis are still at an initial stage. Two mucosal defense-related molecules, gp-340 and salivary agglutinin, have been identified to be alternatively spliced products of DMBT1, which suggests that DMBT1 is a pattern recognition receptor in innate immunity. Meanwhile, results from immunohistochemical staining and studies at the cellular level, began to associate DMBT1 with a proliferation to differentiation switching process in gastrointestinal epithelial cells. Together with its up-regulation in inflammation, these findings suggest that DMBT1 might be a local regulator of homeostasis, possibly through linking mucosal inflammation to the modulation of epithelial regeneration, and whose abnormality is a frequent cause of malignancy.

Key words: Deleted in malignant brain tumor 1; Mucosal defense; Epithelial differentiation; Tumorigenesis; Salivary agglutinin

1. Introduction

Human DMBT1 (deleted in malignant brain tumor 1) was cloned 5 years ago, from a homozygous deletion found in a medulloblastoma cell line at 10q25.3-q26.1 [1], a chromosomal region that frequently shows losses of heterozygosity (LOHs) in a variety of tumors [2–4]. The prototype protein deducted from the genomic sequence is composed of 13 highly homologous (87–100% identical) scavenger receptor cysteine rich (SRCR) domains separated by SIDs (SRCR-interspersed domains), which are followed by two CUB (C1r/C1s Uegf Bmp1) domains flanking the 14th SRCR and then a ZP (zona pellucida) domain toward the C-terminus [5]. A putative exon 55 that encodes 19 hydrophobic amino acids compatible with a transmembrane domain (TMD) has been identified at the genomic level. Unlike DMBT1 homologs in mouse [6] and rat [7], the TMD was not found at the cDNA level in human [5]. In addition to the 14 putative sites for N-linked glycosylation found in this deduced amino acid sequence [8], a high density of potential O-glycosylation sites was proposed within the SIDs [9]. SRCR, CUB and ZP domains have all been implicated in mediating protein–protein interactions [10–13]. The SRCR/CID boundaries generate multiple spliced form of this molecule [5,14]. Two human proteins, gp-340 and salivary agglutinin, both containing 14 SRCR domains, have been shown to be encoded by the DMBT1 gene [8,15,16]. The same gene is also believed to produce transcripts of different sizes in rabbit, mouse and rat, namely, hensin, CRP-ductin, and Ebnerine, respectively [17–19] (see their structure comparisons in these references and ref. [8]). Immunohistochemical staining and reverse transcriptase-polymerase chain reaction (RT-PCR) studies demonstrated a wide range of body locations for DMBT1, mostly of epithelial origin, with high levels found in the respiratory system (i.e. trachea and lung) and the alimentary system (particularly small intestine, also salivary gland and stomach) [1,8,18], and moderate levels in brain [18] and the reproductive system (i.e. testis and mammary gland) [8]. The currently available data suggests two functions for DMBT1, in mucosal defence and in epithelial differentiation [18]. We have reviewed the participation of DMBT1 in these two areas. By reviewing recent data on the better-studied gastric mucosa, we will illustrate how DMBT1 may carry out its dual functions within the same tissue.

2. DMBT1 and tumorigenesis

Initial demonstration of a frequent loss or reduction of the expression, and the deletion of the DMBT1 gene, possibly due to its increasing susceptibility to genomic instability, led to the assumption that it is a putative tumor suppressor for brain [1,20], gastrointestinal [21] and lung [22] cancers. However, recent work revealed further complexity between the abnormalities of DMBT1 and various cancers. Only infrequent and small mutations of the gene were found in gliomas [23], suggesting that DMBT1 polymorphisms are not likely primary targets of 10q loss in gliomagenesis [24]. Analysis of LOHs also showed DMBT1 unlikely to be a major inactivation tar-

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Abbreviations: SRCR, scavenger receptor cysteine rich; DMBT1, deleted in malignant brain tumor 1; LOHs, losses of heterozygosity; SID, SRCR-interspersed domain; CUB, C1r/C1s Uegf Bmp1; ZP, zona pellucida; RT-PCR, reverse transcriptase-polymerase chain reaction; sIgA, soluble immunoglobulin A; SP-D, surfactant protein D; SP-A, surfactant protein A

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get in the development of melanomas [25]. A mixed picture was presented for lung tumors, where both down-regulation [22,26] and insignificant reduction [27] of the DMBT1 level were reported. More intriguingly, up-regulation of DMBT1 has been detected in certain glioblastoma multiforme (GBM) [18], gastric adenocarcinoma (W. Kang et al., unpublished observation) and tumor-flanking tissues in lung [28]. These variations and inductions of the DMBT1 expression occur with high frequency, which strongly suggests an association between this molecule and tumorigenesis at different body locations. Clarification, of such a complicated issue, relies on conducting the functional studies both in vitro and in vivo, to elucidate the exact physiological roles of DMBT1. Several lines of evidences have been accumulated, which indicate a direct involvement of DMBT1 in epithelial differentiation, whose abnormality is a frequent cause of cancer.

3. DMBT1 and epithelial development

DMBT1 was first related to epithelial differentiation through the functional studies of its orthologs, rabbit hensin and mouse CRP-ductin. Hensin was found to be responsible for the switch of the polarity and the induction of terminal differentiation, of intercalated epithelial cells in kidney [29,30], possibly as an inside-out signaling molecule. By means of its polymerization and deposition into the extracellular matrix [31]. The three molecules share strong staining in the crypt cells of the small intestine [6,18,32]. DMBT1 was also located primarily along the neck region of normal human gastric mucosa [33]. Both the crypt and isthmus regions are composed predominantly of stem/progenitor cells, which actively proliferate and differentiate along the axis of epithelial migration. Therefore such a characteristic localization of DMBT1 across species, implicates its role in the physiological renewing process of gastrointestinal epithelia. Immunohistochemical staining further revealed much stronger signals for DMBT1 in fetus than in adult, as well as a distinct spatial distribution, in gastrointestinal epithelium and epidermal cells [18], which suggests a role DMBT1 might also play in the developmental process at certain body locations. Tremendous progress has been made in the investigation of DMBT1 at genomic and transcript levels, which suggests a correlation between the abnormalities of the gene and/or the expression of DMBT1, and carcinogenesis in a variety of epithelia-related tumors. Both the lack/reduction of transcripts and up-regulation of the molecule have been detected for DMBT1 in lung and gastrointestinal cancers [21,26,28]. These findings apparently link the molecule to the process of epithelial development, because neoplasia results directly from the disorders in the growth of these cells. However, further investigation is required to clarify whether altered expressions of DMBT1 are among the causes or the consequences of tumorigenesis. In a recently conducted in vitro study, we demonstrated down-regulation/attenuation of DMBT1 in PMA induced differentiation of the gastric adenocarcinoma cell line AGS [33]. Further analysis using this model system, led to the identification of two intracellular signal molecules, protein kinase C and extracellular signal-regulated kinase (ERK) MAPK, to be involved in mediating both PMA regulation of the DMBT1 production and its induction of AGS differentiation. In a step-wise proliferation to differentiation switch constructed in AGS cells by promoting or inhibiting the activation of ERK, the corresponding changes of the expression of DMBT1 pinpoint its synthesis to be turned on in differentiation-committed cells arrested in G1 phase, before the induction of terminal differentiation-related phenotypes; and to be turned off after these phenotypes were steadily expressed (manuscript submitted). This particular stage of expression is supported by the tightly controlled spatial distribution of DMBT1 in gastrointestinal stem/progenitor cells [18,33]. These results also fit well into a recent report, which showed highly inducible expression of a rat DMBT1 in transit-amplifying ductular (oval) cells (possibly originating from endogenous stem cells) in regenerating rat liver [19]. Both lines of evidence collected from different assay systems indicate an important role for DMBT1 in cell fate decision (i.e. as a critical determinant of differentiation paths leading to certain cell lineages [19]) at an early stage of epithelial differentiation.

4. DMBT1 and innate immunity

On the other hand, increasing data point the involvement of DMBT1in the body's first line defense. After the two innate immune molecules in human, salivary agglutinin and gp-340, were identified to be alternatively spliced forms of DMBT1 [8,15,16], a further study strikingly revealed that a synthetic 16-mer peptide from the SRCR domains of salivary agglutinin bound a wide range of bacteria, including *Streptococcus mutans*, *Escherichia coli*, *Lactobacillus casei*, *Helicobacter pylori* and *Prevotella intermedia*, and mediated the agglutination of *S. mutans* [9]. This is the first evidence showing that SRCR B domains are responsible for the broad pathogenic recognition of certain host molecules, and the potential protective effect it could mediate. In addition, salivary agglutinin forms heterotypic complexes with soluble immunoglobulin A (sIgA) in a calcium dependent manner [34,35], which was suggested to be essential for the interaction between agglutinin and a surface protein antigen of *S. mutans* [35]. Gp-340 binds to collectins surfactant protein (SP)-D and SP-A, two active components in innate pulmonary defense [36]. RT-PCR and immunohistochemical staining revealed an epithelia-associated distribution shared by SP-D and DMBT1 along the body mucosa or ducts of glands [8,37,38], which allows them frequent contact with pathogens that invade the inner surface of the body. Epithelial cells have been regarded as first line defense components to protect mucosal surface, by actively secreting several pro-inflammatory cytokines [33–35] and becoming antigen-presenting cells [36,37] upon microbial challenges. Up-regulation of DMBT1 was detected in the pulmonary cell line A549 coinciding with the induction of cytokine IL-8 and IL-6 upon the inflammatory challenge [33], as well as in the epithelia of inflammatory pulmonary tissues [28], which suggests the increase of DMBT1 to be part of the epithelial responses to local inflammation. Moreover, DMBT1 and its ligand SP-D are both synthesized by type II cells in lung, indicating their possible collaboration in the mucosal immune processes [33]. Gp-340 was also shown to stimulate random migration (chemokinesis) of alveolar macrophages, suggesting its direct regulation of tissue macrophages [39]. Taken together, DBMT1 is acting as a typical pattern recognition receptor in the body's innate anti-microbial process, through interactions with both invading pathogens and many other local defense components. Using RT-PCR, transcripts of DMBT1 were detected throughout the immune system: in spleen and

thymus, alveolar macrophages, T cell line Jurkat and B cell line Raji [8,18]. Although the expression level might be very low, and the epithelium cannot be ruled out as being to be the major source of DMBT1 expression in lymphoid-organs, these data may still suggest additional functions for DMBT1 in the regulation of acquired immunity, as having been reported for other proteins in SRCR B family [10,40].

5. DMBT1, a linkage between mucosal defense and epithelial regeneration?

Based primarily on genomic mutation, expression and localization studies, Mollenhauer and co-workers first proposed dual functions for DMBT1 in mucosal defense and epithelial differentiation [18]. They drew a parallel between DMBT1 and its homolog bovine gallbladder mucin (BGM) [41], as well as another collectin-binding mucin Mac-2 [18,42], to explain the multifunctioning potential of DMBT1. However, the primarily known function of BGM is in the formation of crystal through its binding to lipid components and calcium-binding protein in bile [43,44]. Since particular attention in illustrating the dual function of DMBT1 has been drawn in the lung and gastrointestinal mucosa where the highest level of its expression was found in adults [1,8], two epithelial cell lines derived from the lung and gastric mucosa were compared for their responses to PMA treatment. This in vitro study allowed the demonstration of inflammation-related up-regulation of DMBT1 in pulmonary epithelia, and differentiation-related down-regulation of this molecule in gastric epithelia [33]. Both findings are in line with the immunohistochemical analysis, which showed an increasing level of DMBT1 in inflammatory lung tissues [28], and predominant distribution of DMBT1 in stem/progenitor cells rather than in terminally differentiated cells in gastrointestinal epithelia [6,18,33]. Therefore it appears that the two distinct functions of DMBT1 might be body location-related, and epithelial differentiation stage specific [33]. In the gastrointestinal tract, DMBT1 was found to be secreted from the apical membrane of epithelia onto the mucosal surface, where binding of invading pathogens such as *S. mutans* and *H. pylori* [15], and host defense components such as SP-D [45] and sIgA [35], could take place. All these ligands are involved in local inflammation in gastric mucosa [46]. DMBT1 homologs have also been identified as putative receptor for trefoil factors, the peptides known to play a major role in the acute phase protection of mucosa surface upon tissue injury [47]. Thus the protective function of DMBT1 should be considered to cover a wider area, rather than only monolayers of epithelia, as has been proposed by Mollenhauer J et al. [41]. It seems likely that the interactions of DMBT1 with many of these proteins, may be mediated by one, or more, of the SRCR domains present in DMBT1. Meanwhile, the CUB and ZP domains on its C-terminus may interact with growth factors [48] or cell surface molecules [13]. Thus, the local environmental signals could apparently be integrated by DMBT1, and be transmitted to the stem/progenitor cells through certain interactions it may have with the surface of these cells. This might be one efficient means, by which the speed of epithelial regeneration could be better modulated according to the specific physiological and pathological needs, through triggering immediate differentiation of the progenitor cells, and perhaps also stimulating their proliferation (Fig. 1). The promotion of the regeneration machinery would be particularly important following mucosal damage, such as in times of a severe local inflammation in spite of origins, or in the development of an ulcer. Rapid regeneration of mucosal epithelia should be regarded as an active part of the local defense mechanism, which would effectively limit the spread of an infection, and the tissue damage resulting from exceeding inflammatory reactions [47]. The size of DMBT1 and the many protein–protein interaction interphases it has, make this molecule one of the ideal linkages between the mucosal defense and the regulation of epithelial development. It might act in synergy, or in complement, with other immune cytokines and growth factors, to maintain the

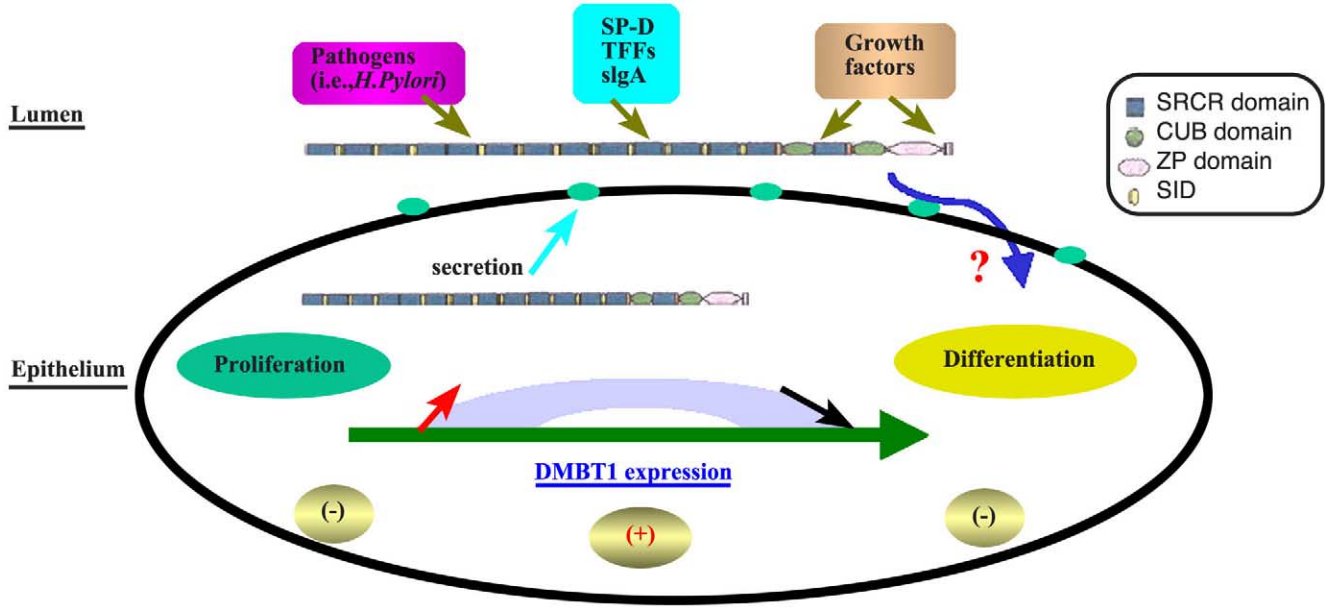

Fig. 1. Schematic representation of the epithelial differentiation associated regulation of the expression of DMBT1 in gastrointestinal tract, and of its potential roles in linking the mucosal inflammation to the modulation of epithelia differentiation, through its multiple bindings of pathogens and/or host defense components, growth factors and cell surface receptor(s).

integrity and the functions of the body mucosa. It is therefore not surprising that the abnormalities of DMBT1, a molecule that is closely related to epithelial protection/regeneration, can be found with high frequency in epithelial malignancy [1,21,26].

6. Conclusion

Present research work on DMBT1 is focused primarily on mutation, expression and localization analysis, which sometimes yield contradictory results, regarding the significance of mutation/deletion and expression level of the DMBT1 gene in carcinogenesis. These types of studies have laid the foundations of the possible roles DMBT1 might play. However the complexity in the functions of this molecule and its relationship with different tumors, as well as its tremendous potential in mediating protein–protein, protein–cell and cell–extracellular matrix interactions, require more direct functional studies to be carried out in vitro and in vivo, which will shed light on the exact roles of DMBT1 and the underlying molecular mechanisms, and how these functions might change at distinct body locations, and according to the combinations of environmental signals under a whole variety of physiological and pathological conditions. It is crucial to generate the knock out model in mice, to which appropriate challenges could be applied to facilitate the in vivo comparison of the specific roles of DMBT1 in epithelial regeneration and local inflammatory reaction. Biochemical analysis is also needed, in identifying and characterizing the potential carbohydrate and lipid, along side protein ligands, for DMBT1. In combination with approaches at genomic, animal and tissue levels, cellular work has proved to be a powerful tool, which should be further explored to help reveal the molecular mechanisms. These include the regulation of the gene expression, identification of possible cell surface receptors and intracellular signal pathways, by which DMBT1 influences particular cellular events. Our understanding of this multifunctional molecule and future perspective of treating certain types of cancer/infection would be greatly enhanced through these efforts.

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