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Dual Roles of the Melanoma CAM (MelCAM/METCAM) in Malignant Progression of Melanoma

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1. Introduction

1.1 General properties and functions of METCAM/MUC18

Human METCAM (huMETCAM), a CAM in the immunoglobulin-like gene superfamily, is an integral membrane glycoprotein. Alternative names for METCAM are MUC18 [1], CD146 [2], MCAM [3], MelCAM [4], A32 [5], and S-endo 1 [6]. To avoid confusion with mucins and to reflect its biological functions, we have renamed MUC18 as METCAM (metastasis CAM), which means an immunoglobulin-like CAM that affects or regulates metastasis [7]. The huMETCAM has 646 amino acids that include a N-terminal extra-cellular domain of 558 amino acids, which has 28 amino acids characteristic of a signal peptide sequence at its N-terminus, a transmembrane domain of 24 amino acids (amino acid #559-583), and a cytoplasmic domain of 64 amino acids at the C-terminus. HuMETCAM has eight putative N-glycosylation sites (Asn-X-Ser/Thr), of which six are conserved, and are heavily glycosylated and sialylated resulting in an apparent molecular weight of 113,000-150,000. The extra-cellular domain of the protein comprises five immunoglobulin-like domains (V-V-C2-C2-C2) [1, 7] and an X domain [7]. The cytoplasmic tail contains peptide sequences that will potentially be phosphorylated by protein kinase A (PKA), protein kinase C (PKC), and casein kinase 2 (CK2) [1, 7-8]. My lab has also cloned and sequenced the mouse METCAM (moMETCAM) cDNA, which contains 648 amino acids with a 76.2% identity with huMETCAM, suggesting that moMETCAM is likely to have biochemical properties and biological functions similar to the human counterpart [9]. The structure of the huMETCAM protein is depicted in Fig. 1, suggesting that METCAM, similar to most CAMs, plays an active role in mediating cell-cell and cell-extracellular interactions, crosstalk with many intracellular signaling pathways, and modulating the social behaviors of cells [7]. It is now well documented that although tissue specific signatures exist in different cancer types, cancers from different tissues also express some common genes [10-12]. One group of them is cell adhesion molecules (CAMs). CAMs do not merely act as a molecular glue to hold together homotypic cells in a specific tissue or to facilitate interactions of heterotypic cells; CAMs also actively govern the social behaviors of cells by affecting the adhesion status of cells and modulating cell signaling [13]. They control cell motility and invasiveness by
mediating the remodeling of cytoskeleton [13]. They also actively mediate the cell-to-cell and cell-to-extracellular matrix interactions to allow cells to constantly respond to physiological fluctuations and to alter/remodel the surrounding microenvironment for survival [14]. They do so by crosstalk with cellular surface growth factor receptors, which interact with growth factors that may be secreted from stromal cells or released from circulation and embedded in the extracellular matrix [13-14]. Thus an altered expression of CAMs affects the motility and invasiveness of many tumor cells in vitro and metastasis in vivo [13-14]. CAMs also play an important role in the favorable soil that provides a proper microenvironment at a suitable period to awaken the dormant metastatic tumor cells to enter into an aggressive growth phase. Actually, the metastatic potential of a tumor cell, as documented in many carcinomas, is the consequence of a complex participation of many over- and under-expressed CAMs [13-14]. Based on the above information, aberrant expression of huMETCAM may also affect the motility and invasiveness of many tumor cells in vitro and metastasis in vivo. It is logical to hypothesize that HuMETCAM should play an important role in regulating the malignant progression of many cancer types [7, 13]. Nevertheless, in this chapter we will only review its positive or negative roles in the tumorigenesis and metastasis of human and mouse melanoma cells.

HuMETCAM is expressed in a limited number of normal tissues, such as hair follicular cells, smooth muscle cells, endothelial cells, cerebellum, normal mammary epithelial cells, basal cells of the lung, activated T cells, intermediate trophoblast, [15] and normal nasopharyngeal epithelial cells [16]. The protein is not expressed in melanocyte, but it is overly expressed in most (67%) malignant melanoma cells [1]. Thus it was postulated to play a role in the progression of human melanoma. Likewise, the expression of mouse METCAM (moMETCAM) was positively correlated with the metastatic ability of several mouse melanoma cell lines [9]. Since then, it has been proven that METCAM is not just correlative with the progression of melanoma, but also is capable of inducing non-metastatic human cutaneous melanoma cell lines to metastasize in various mouse models. First, it was shown that the stable ectopic expression of the huMETCAM cDNA gene in three non-metastatic human cutaneous melanoma cell lines increases the metastatic abilities of these cell lines in immune-deficient xenograft mouse models [3,17]. Second, it was shown that the stable ectopic expression of moMETCAM cDNA in two low-tumorigenic and low-metastatic mouse melanoma cell lines, K10 (tumor+/metlow) and K3 (tumor+/metlow), increases their metastatic abilities in immune-competent syngeneic C3H brown mice [18].
However, METCAM enables both human and mouse melanoma cells to metastasize only under an experimental metastasis assay (tail vein injection), not under a spontaneous metastasis assay (subcutaneous injection). In addition, the ectopic expression of METCAM in METCAM-minus melanoma cell lines has no effect or a slight suppressive effect on the tumorigenesis. Taken together, this suggests that METCAM promotes the metastasis of melanoma cells only at later stages of progression (it has been found that fibroblast growth factor-2 initiates the metastatic process) [19].

Recently, we further investigated the effect of moMETCAM expression on tumorigenesis and metastasis of a different mouse melanoma subline #9 of K1735 (K1735-9 or K9), which is also METCAM-minus and lowly metastatic, but has a highly tumorigenic phenotype (tumor+/metlow), in the syngeneic C3H mouse model. We tested the effect of ectopic expression of moMETCAM on in vitro growth rate, motility, and invasiveness and in vivo subcutaneous tumor growth and pulmonary metastasis. Similar to the two isogenic K10 and K3 sublines, ectopic expression of METCAM did not significantly affect in vitro growth rate, but greatly increased in vitro motility and invasiveness. Surprisingly, unlike K10 and K3 sublines, ectopic expression of METCAM in K9 cells decreased tumorigenicity and suppressed their ability to establish pulmonary nodules. The suppressive effect of METCAM is not limited to the K9 mouse melanoma cell line, but is also observed in two human ovarian cancer cell lines (our unpublished results).

We suggest that METCAM-mediated tumorigenesis and metastasis of melanoma cells and other cancer cells is dependent on intrinsic co-factors of different K1735 sublines and cancer types. The establishment of an immune-competent syngeneic mouse model for the METCAM-mediated progression is physiologically more relevant to and should provide knowledge more applicable to clinical melanoma than immune-deficient xenograft mouse models. The putative mechanisms of METCAM-mediated promotion/suppression of melanoma progression will also be discussed.

![Tumor Weight of Melanomas](image)

Fig. 2. Effect of over-expression of huMETCAM on tumor formation of two human melanoma cell lines, SK and XP-44 [17]. SK-METCAM and XP44-METCAM were two clones of human melanoma cell lines, SK and XP44, respectively, which were transfected with huMETCAM and expressed a high level of huMETCAM. Statistical analysis was not possible because detailed data was not provided.

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2. Metcam and melanoma tumorigenesis

Over-expression of *METCAM* had a slight tumor suppression effect on tumorigenesis of human melanoma cells in xenograft mice [17], as shown in Fig. 2, but it had no effect on tumorigenesis of two sublines, #3 (K3) and #10 (K10), of the mouse melanoma cell line K1735 in syngeneic mice [18]. Fig. 3 only shows the effect of *moMETCAM* on the tumorigenesis of K3.

![Fig. 3. Effect of over-expression of *moMETCAM* on tumor formation of a mouse melanoma cell line K1735 subline #3 (K3) [18]. K3-METCAM (High) and K3-METCAM (Low) were two K3 clones transfected with *moMETCAM* cDNA that expressed a high and a low level of *moMETCAM*, respectively. K3-Vector, as a negative control, was one clone transfected with an empty vector and did not express any *moMETCAM*. Asterisks show the results of the clone used as the references for the P-value calculation. The P-values should be compared with the reference (asterisk) on the same row.](image)

Fig. 4. Effect of over-expression of *huMETCAM* on tumor formation of a human melanoma cell line SB-2 [3]. SB-2 is a human melanoma cell line, which did not express any *huMETCAM*. SB-2-neo is the SB-2 cells transfected with the empty vector, as a negative control. SB-2-METCAM is a clone of the SB-2 cells which were transfected with *huMETCAM* cDNA and expressed a high level of *huMETCAM*. Since tumor formation was only shown in one nude mouse for each clone, statistical analysis was not possible.
Only one group showed that over-expression of \textit{METCAM} increased tumorigenesis of a human melanoma cell line in xenograft mice \cite{3}; however the results were questionable because only the tumorigenicity of one mouse injected with \textit{METCAM}-expressing clone and one mouse with control cells was shown and thus no standard deviations were indicated and no statistical analysis done, as shown in Fig. 4.

The most convincing evidence for its tumor suppressor effect is in the subline #9 of the mouse melanoma cell line \textit{K1735} (K1735-9 or K9) in syngeneic C3H mice. Over-expression of \textit{moMETCAM} in the K9 cells significantly decreased subcutaneous tumorigenesis in immunocompetent syngeneic C3H mice \cite{20-21}, as shown in Fig. 5.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig5.png}
\caption{Effect of over-expression of \textit{moMETCAM} on tumor formation of a mouse melanoma K1735 subline #9 (K1735-9 or K9) in immune competent syngeneic C3H mice \cite{20-21}. K9-METCAM (High) and K9-METCAM (Low) were two transfected clones, which expressed a high and a low level of \textit{moMETCAM}, respectively. K9-Vector was one clone transfected with the empty vector, as a negative control. K9 was the K1735 subline #9 cells, also as a negative control. Both K9-Vector and K9 did not express any \textit{moMETCAM}.}
\end{figure}

3. Metcam and melanoma metastasis

\textit{HuMETCAM/MUC18} was originally found to be abundantly expressed on the cellular surface of most malignant human melanomas; since then, it has been postulated to play a role in the progression of human melanoma \cite{1}. This notion is also supported by the positive correlation of \textit{moMETCAM} expression with the metastatic ability of several mouse melanoma cell lines \cite{9}. Definitive proof comes from the results that the stable, ectopic expression of \textit{HuMETCAM} cDNA gene in three non-metastatic human cutaneous melanoma cell lines increases the metastatic abilities of these cell lines in immune-deficient mouse models \cite{3, 17}. Furthermore, the stable, ectopic expression of \textit{moMETCAM} cDNA in two low-metastatic mouse melanoma cell lines increases the metastatic abilities of these cell lines in immune-competent syngeneic mice \cite{18}, as shown in Figs. 6 & 7.

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Fig. 6. Enforced expression of moMETCAM increased lung nodule formation of mouse melanoma K1735-3 (K3) cells in syngeneic C3H mice. K4, the highly tumorigenic and metastatic subline #4 of K1735 (Tumor\textsuperscript{+++}/Met\textsuperscript{high}), was used as a positive control. K3-METCAM clone expressed a high level of moMETCAM. K3, K3-Vector, and K3-METCAM (Rev), in which the moMETCAM cDNA was inserted into the expression vector in anti-sense orientation, were the control clones that did not express any moMETCAM.

Fig. 7. Enforced expression of moMETCAM increased lung nodule formation of mouse melanoma K1735-10 (K10) cells in syngeneic C3H mice. The K10-METCAM clone expressed a high level of moMETCAM. K10, K10-Vector, and K10-METCAM (Rev), in which the moMETCAM cDNA was inserted into the expression vector in anti-sense orientation, were the control clones that did not express any moMETCAM.

However, METCAM enables melanoma cells to establish pulmonary metastasis only when the cells are injected into the tail vein (experimental metastasis assay) [3, 17-18], thus bypassing the initial stages of metastasis. No metastasis was found when METCAM-expressing melanoma cells were injected subcutaneously (spontaneous metastasis assay) either in immune-deficient mouse models [3, 17] or in immune-competent syngeneic mouse

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models [18]. Taken together, METCAM promotes the metastasis of melanoma cells, but at later stages [7]; thus over-expression of METCAM did not initiate the metastasis of melanoma cells. This result is consistent with the recent observation that fibroblast growth factor 2, but not huMETCAM, nor integrin, actually initiates the malignant progression of subcutaneous melanocyte into melanoma [19].

METCAM increases the progression of most melanoma cell lines with the exception of one mouse melanoma subline, K1735-9. We found over-expression of moMETCAM in one mouse melanoma K1735 subline #9 (K1735-9 or K9) decreased pulmonary lung nodule formation when cells were injected into tail veins (experimental metastasis test) [20-21], as shown in Fig. 8.

![Lung Nodule formation of K1735-9](image)

Fig. 8. Enforced expression of moMETCAM suppressed lung nodule formation of mouse melanoma K1735-9 (K9) cells in syngeneic C3H mice. Clones K9-METCAM (High) and K9-METCAM (Low) clones expressed high and low levels of moMETCAM, respectively. K9-Vector, K9, and K9-METCAM (Rev), in which the moMETCAM cDNA was inserted into the expression vector in anti-sense orientation, were the control clones that did not express any moMETCAM.

Summary

Table 1 summarizes the possible role of METCAM in the tumorigenesis and metastasis of various melanoma cells.

| Melanoma cells                      | Tumorigenesis   | Metastasis                  | References |
|-------------------------------------|-----------------|-----------------------------|------------|
| Clinical melanoma and human melanoma cell lines | No effect       | Increasing (effect is in the late stages) | 3, 17      |
| Mouse melanoma K1735 sublines #3 and #10 | No effect or slight suppression | Increasing (effect is in the late stages) | 9, 18      |
| Mouse melanoma K1735 subline #9     | Suppression     | Suppression                 | 20, 21     |

Table 1. The role of METCAM in the tumorigenesis and metastasis of melanoma cells.
As shown in Table 1, *huMETCAM* does not affect the tumorigenesis of most melanoma cell lines, but it increases metastasis, thus is a metastatic gene, for most melanoma cell lines. However, in one case it acts as a tumor suppressor and a metastasis suppressor for a mouse melanoma subline.

### 4. Mechanisms of metcam-mediated melanoma progression

How does *METCAM* mediate or regulate tumorigenesis and metastasis of melanoma cells? We may be able to find some common clues to begin understanding its mechanisms by deducing knowledge learned from the tumorigenesis of other tumors [10-14, 22] and the *huMETCAM*-mediated progression of melanoma [23-25] and tumor angiogenesis [2, 26-29].

First, the transcriptional expression of *METCAM* gene may be regulated by PKA/CREB (cAMP-responsive element binding protein), AP-2α [24-25] and other transcription factors, such as SP-1, c-Myc, N-Oct2, Ets, CarG, Egr-1, and transcription factors binding to insulin response elements [7]. Among these potential regulators, it is well documented that the AP-2α transcription factor plays a crucial tumor suppressor role in the progression of melanoma [25]. However, the roles of other transcription regulators, tissue specific enhancers and repressors, epigenetic control, and control at the level of chromatin remodeling of the gene have still yet to be investigated [7].

Second, since the cytoplasmic tail of *METCAM* contains consensus sequences potentially to be phosphorylated by PKA, PKC, and CK2, it may manifest its functions by cross-talk with various signaling pathways mediated by these protein kinases [7]. For example, *METCAM* expression in melanoma cells is reciprocally regulated by AKT, in which AKT up-regulates the level *METCAM* and over-expression of *METCAM* activates endogenous AKT, which in turn inhibits apoptosis and increases survival ability [23]. However the detailed mechanism of how AKT up-regulates the expression of *METCAM* has not been worked out. PKA, PKC, and CK2 may phosphorylate the cytoplasmic tail of *METCAM*, which then facilitates its interaction with FAK, thus promoting cytoskeleton remodeling. Alternatively, after phosphorylation of its cytoplasmic tail by these protein kinases, *METCAM* may interact with the downstream effectors of Ras, activating ERK and JNK, which in turn may transcriptionally activate the expression of AKT or other genes that promote the proliferation and angiogenesis of tumor cells. Though *METCAM* has not been shown to be a substrate of CK2, which has been shown to phosphorylate other CAMs, such as CD44, E-cadherin, L1-CAM, and vitronectin, it is also likely that CK2 may be able to phosphorylate *METCAM* and link it to AKT and affect the proliferation, survival and other tumorigenesis-related functions of tumor cells [30].

Third, after the engagement of *METCAM* with the ligand(s) or extracellular matrix, it may transmit the outside-in signals into tumor cells by activating FAK and the downstream signaling components, promoting cytoskeleton remodeling and increasing tumor cell motility and invasiveness [2, 7].

Fourth, from what we know about the roles of other CAMs in the progression of other tumors [10-14, 22], it is logical to postulate that *METCAM* may affect cancer cell progression by cross-talk with signaling pathways that affect apoptosis, survival and proliferation and angiogenesis of tumor cells [7, 13, 22]. Thus *METCAM* may affect tumorigenesis and metastasis by altering the expression of various indexes in apoptosis, survival signaling, proliferation signaling, and angiogenesis. To support this notion, we have found that *METCAM* promotes the progression of prostate cancer cells by increasing proliferative
ability (with elevated levels of Ki67 and PCNA), by increasing survival ability (with an elevated level of phosphorylated AKT), and by increasing angiogenic ability (with elevated levels of VEGF, VEGFR2, and CD31) [31]; but it has no effect on the process of apoptosis. In fact, METCAM promotes the progression of melanoma cells differently by preventing the apoptosis of melanoma cells [32] and reciprocally affecting the expression of a survival index, phospho-AKT [23]. Further systematic studies by using specific RNAi’s to knockdown the downstream effectors one by one in METCAM-expressing clones may be necessary to further understand this aspect of the mechanism.

Fifth, METCAM may mediate the hematogenous spreading of melanoma cells, which had been implicated by its expression in endothelial cells, as well as in malignant melanoma cells [26]. Furthermore it has been shown to be present in the junctions of endothelial cells [27-28] and essential for tumor angiogenesis in at least three tumor cell lines [29] and human prostate cancer LNCaP cells [31, 33]. It is highly likely that METCAM expression may promote the hematogenous spreading of melanoma cells. However, it is not known if METCAM plays a role in the lymphatic spread of cancer cells. Recent results from one group showed that METCAM is one of the lymphatic metastasis-associated genes, which is up-regulated in malignant mouse hepatocarcinoma [34]; suggesting that METCAM may also play a role in promoting lymphatic metastasis of melanoma cells. But the details of how METCAM mediates hematogenous or lymphatic spreading of melanoma cells have still yet to be investigated. Labeling the cells with viable dyes and following the process in real time by using a non-intruding, but highly photo-penetrating imaging method of photoacoustic tomography (PAT) [35-36] may be useful for monitoring each step in the METCAM-mediated progression. For the METCAM-mediated dynamic spreading of melanoma cells in vivo, the PAT imaging method coupled with using hairless syngeneic mouse animal models [37] should reveal the process more clearly and in real time.

Sixth, METCAM has been shown to express in normal mesenchymal cells (smooth muscle, endothelium, and Schwann cells) in the tissue stroma and to be a marker for the mesenchymal stem cells [38]. METCAM may play an important role in regulating melanoma dormancy or awakening, driving or preventing melanoma cells to pre-metastatic niche, and formatting a microenvironment for favorable or unfavorable melanoma growth in secondary sites.

Seventh, METCAM may affect the progression of cancer cells by interactions with the host immune system, which, however, has been shown to have a paradoxical role in tumor progression [39]. Recently one group has shown that a subset of host B lymphocytes may control melanoma metastasis through METCAM-dependent interaction [40]. On the other hand, it is highly likely that the tumor suppression effect of METCAM expression in melanoma K1735-9 subline may be due to the interaction of METCAM-expressing cells with the host immune defense system in the immunocompetent syngeneic C3H brown mouse, since the intrinsic motility and invasiveness of mouse melanoma K1735-9 was increased by METCAM expression [20-21]. For example, the surface METCAM expressed in this particular melanoma cell line may have a homophilic interaction with the NK cells, which also express METCAM, and enhance the cytotoxic functions of NK cells [41]. This hypothesis should be testable by studying the METCAM-mediated progression of METCAM-expressing K1735-9 cells in mice treated with antibodies against CD4+T cells, CD8+T cells, or NK cells, or mice with a combined treatment with the antibodies to impair the functions of these immune cells.
Eighth, malignant progression of cancer cells has been shown to associate with abnormal glycosylation, resulting in expression of altered carbohydrate determinants [42]. Thus, the glycosylated status of METCAM in different cancer types may be different from normal cells, thus manifesting positive or negative effect on the progression of melanoma cells. This aspect of the METCAM-mediate cancer progression has not been well studied, but is especially intriguing since METCAM possesses six conserved N-glycosylation sites in the extracellular domain [7-9].

We should always keep in mind that the mechanisms of METCAM-mediated melanoma progression may be slightly different in different melanoma cell lines due to their different intrinsic properties, which provide different co-factors and/or different ligand(s) that either positively or negatively regulate the METCAM-mediated tumorigenesis and metastasis. To further understand the role of METCAM in these processes, it is essential to identify the co-factors and the METCAM-cognate heterophilic ligand(s), which modulate the biological functions of METCAM. The endeavor in this direction appears to be promising: from our preliminary attempts we may have successfully found a possible candidate of METCAM’s heterophilic ligand in METCAM-expressing human melanoma SK-Mel-28 cells [7].

Mechanisms of METCAM-mediated negative role in the progression of melanoma cells have not been studied at all. In some cancers does METCAM behave like E-cadherin, which always plays a negative role in the tumorigenesis and metastasis of melanoma as well as most epithelial cancer cells [13]. But even E-cadherin may function differently in different cancer cells. For example, its expression is temporally different and correlates with different stages during the progression of ovarian cancer [43]: E-cadherin is not expressed in the ovarian surface epithelial cells, but is expressed in premalignant lesions and in well-differentiated tumors, and finally is not expressed in late-stage invasive tumors [43]. Alternatively, METCAM may behave differently from E-cadherin by being modulated by different cofactors or ligands, which are expressed at different stages of the cancer. The tumor suppressor role of METCAM is not restricted to the mouse melanoma K9 subline and it was first suggested in breast cancer cells [44]; however, the tumor suppression of METCAM in breast cancer cell lines could not be reproduced [45]. Recently we also found the tumor suppressor role of METCAM in two human ovarian cancer cell lines [46]. The tumor suppressor role of METCAM in ovarian cancer cells is different from mouse melanoma subline K9 in that the METCAM expression suppressed the intrinsic motility and invasiveness of human ovarian cancer cells [46]. Our preliminary results appear to suggest an alternative mechanism that a soluble form of METCAM, which is produced by MMPs in the METCAM-expressing cells, may mediate the suppressive effect in ovarian cancer cells, similar to the production of a soluble form of P-cadherin by the induced MMPs in breast cancer cells, which then dictates, instead of suppresses, the aggressive behavior of the breast cancer cells [47].

5. Conclusion and clinical applications

METCAM may have a key positive function in the progression of most melanoma cell lines. On the other hand, it may also have a key function in suppressing the progression of a few melanoma cell lines. To further understand its mechanisms in these processes, it is crucial to define its functional domains, identify its cognate ligand(s) and cofactor regulators, and study its cross-talk with members of various signaling pathways [7]. These model systems may be useful for real time observation of the dynamic process of cancer progression by
using a non-intrusive and high photo-penetrating imaging system, such as the newly developed photoacoustic tomography (PAT), to further understanding the process in mouse models [35-36]. The knowledge gained would also be useful for designing effective means to decrease or even to block the metastatic potential of these cancers. Along these lines, preclinical trials using a fully humanized anti-METCAM antibody against melanoma growth and metastasis [48-49] and using a mouse anti-METCAM monoclonal antibody against angiogenesis and tumor growth of hepatocarcinoma, leiomyosarcoma, and pancreatic cancer [29] have been successfully demonstrated. Alternatively, small soluble peptides derived from METCAM may also be useful for blocking the tumor formation and tumor angiogenesis of melanoma cells [33, 50-51]. The attachment of these reagents to nanoparticles may be another alternative for therapeutic use [52].

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7. References

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