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Review Article

Invadopodia-Related Proteins Expression in Mucoepidermoid Carcinoma. A systematic review.

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Abstract

Background

Mucoepidermoid carcinoma (MEC) is the most common malignant salivary gland tumor, displaying wide biological heterogeneity from indolent low-grade lesions to aggressive high-grade variants. Invadopodia are specialized actin-rich protrusions that degrade the extracellular matrix (ECM) and facilitate invasion. Core proteins such as Tks4, Tks5, cortactin and MT1-MMP, together with matrix metalloproteinases (MMP-2/9), have been implicated in invasion in several carcinomas, but their role in MEC has only recently been examined.

Objective: To systematically evaluate the expression of invadopodia-related proteins in MEC and their contribution to tumor invasiveness.

Methods

This review was conducted in accordance with PRISMA 2020 guidelines and the protocol was prospectively registered in PROSPERO (Registration ID: CRD420251152863). A comprehensive search of PubMed, Embase, Scopus and Web of Science was performed up to September 2025. Original studies analyzing invadopodia-related proteins in MEC were included. Data extraction covered study design, sample size, proteins evaluated, methodology and outcomes. Risk of bias was assessed using Joanna Briggs Institute (JBI) tools for tissue studies and an adapted appraisal framework for in vitro studies.

Results

Six studies met the inclusion criteria from 57 screened records. Immunohistochemistry demonstrated overexpression of Tks4, Tks5, cortactin and MT1-MMP in MEC compared with normal salivary glands. Functional silencing of Tks4/Tks5 reduced invadopodia formation, ECM degradation and cell invasiveness. MT1-MMP localized to carcinoma membranes and activated pro-MMP-2, while metallothionein enhanced invasiveness by modulating MMP-2/9. Clear-cell MEC also showed MMP-2 positivity on immunoarray analysis.

Conclusions

Invadopodia-related proteins are consistently expressed in MEC and appear to play a central role in its invasive phenotype. Larger multicenter studies with standardized protocols and integration of clinical outcomes are needed to establish their prognostic value and explore therapeutic potential.

***Keywords**: Mucoepidermoid carcinoma; Invadopodia; Tyrosine kinase substrate 4 (Tks4); Tyrosine kinase substrate 5 (Tks5); Cortactin; Membrane type 1 matrix metalloproteinase (MT1-MMP); Matrix metalloproteinase 2 (MMP-2); Matrix metalloproteinase 9 (MMP-9); Metallothionein.*
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Introduction

Mucoepidermoid carcinoma (MEC) is the most prevalent malignant neoplasm of the salivary glands, accounting for approximately one-third of cases and representing a major contributor to head and neck malignancies [1]. It may arise in both major and minor salivary glands, most frequently in the parotid, followed by intraoral minor glands such as the palate. MEC demonstrates considerable

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biological heterogeneity. Low-grade tumors often pursue an indolent course with favorable prognosis, whereas high-grade tumors exhibit aggressive behavior characterized by perineural and lymphovascular invasion, nodal metastasis, recurrence and, in some instances, distant dissemination. Intermediate-grade tumors display variable outcomes, contributing to the challenges of prognostic evaluation [2,3].

Current risk stratification is based primarily on histopathological features, including tumor grade, margin status and perineural invasion. Molecular alterations, such as MAML2 gene rearrangements, have been reported and are generally associated with improved prognosis, particularly in low- and intermediate-grade MEC. However, the molecular determinants of invasiveness remain incompletely defined and reliable biomarkers to predict progression and therapeutic response are lacking [4].

Invadopodia are specialized actin-rich protrusions that localize proteolytic activity at the cell membrane, mediating focal degradation of the extracellular matrix (ECM). Through this mechanism, invadopodia facilitate basement membrane penetration, stromal invasion and ultimately metastatic spread. Their formation is orchestrated by a network of scaffolding and signaling proteins, including tyrosine kinase substrates Tks4 and Tks5, the actin-binding protein cortactin and regulators such as Src and PI3K. The proteolytic activity of invadopodia is largely mediated by membrane-type 1 matrix metalloproteinase (MT1-MMP), which activates downstream effectors such as MMP-2 and MMP-9, enabling extensive pericellular matrix degradation [5,6].

The clinical significance of invadopodia-related proteins has been demonstrated in several malignancies. In head and neck squamous cell carcinoma, overexpression of Tks5 and cortactin has been associated with tumor aggressiveness and poor prognosis. Comparable findings have been documented in breast carcinoma and melanoma, where high levels of invadopodia proteins correlate with enhanced invasiveness, metastatic potential and reduced survival. These observations establish invadopodia as central mediators of tumor progression and potential therapeutic targets [5].

In MEC, research on invadopodia-associated proteins is emerging. Immunohistochemical studies have demonstrated that Tks4, Tks5, cortactin and MT1-MMP are expressed at higher levels in MEC compared with normal salivary gland tissue. Functional assays in MEC-derived cell lines further corroborate their role, showing that silencing of Tks4 and Tks5 markedly reduces invadopodia formation, ECM degradation and invasive capacity. Additional studies implicate MT1-MMP–mediated activation of MMP-2 and modulation of MMP-2/9 activity by metallothionein as integral components of MEC invasion.

Given the clinical heterogeneity of MEC and the limitations of current prognostic markers, investigation of invadopodia-related proteins offers a promising avenue for improving risk stratification and identifying novel therapeutic strategies. This systematic review synthesizes available evidence on invadopodia-related protein expression in MEC, critically evaluates the quality of existing studies and situates these findings within the broader context of tumor invasion biology.

Materials and methods

Protocol and Registration

This systematic review was designed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [7]. The review protocol was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD420251152863.

Research Question and PICOS Framework

The research question was formulated using the PICOS strategy [8]:

- Population (P): Patients with mucoepidermoid carcinoma (MEC) assessed in tissue samples and MEC-derived cell lines.
- Intervention/Exposure (I): Evaluation of invadopodia-related proteins, including Tks4, Tks5, cortactin, MT1-MMP, MMP-2, MMP-9 and metallothionein.
- Comparison (C): Normal salivary gland tissues when available; non-silenced versus silenced MEC cell lines in functional studies.
- Outcomes (O): Expression levels of invadopodia-related proteins, associations with invasiveness, functional consequences of knockdown and evidence of extracellular matrix (ECM) degradation.

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- Study Design (S): Cross-sectional immunohistochemical studies, immunoarray analyses and in vitro functional assays.

Eligibility Criteria

Inclusion criteria:

- Original research articles investigating invadopodia-related proteins in MEC.
- Human tissue-based studies or MEC-derived cell line studies.
- Studies with clearly described methodology and outcome reporting.

Exclusion criteria:

- Reviews, editorials, or expert opinions.
- Case reports or series with fewer than 10 MEC cases.
- Animal studies without human MEC tissue analysis.
- Conference abstracts lacking methodological or outcome details.

Search Strategy

A comprehensive literature search was conducted across PubMed, Embase, Scopus and Web of Science from inception to September 2025. The search strategy combined Medical Subject Headings (MeSH) and free-text terms including: *"mucoepidermoid carcinoma"*, *"invadopodia"*, *"Tks4"*, *"Tks5"*, *"cortactin"*, *"MT1-MMP"*, *"MMP-2"*, *"MMP-9"* and *"metallothionein"*. Reference lists of included articles were manually screened to identify additional eligible studies.

Study Selection and Data Extraction

Two reviewers independently screened all records in two stages: initial title and abstract screening, followed by full-text assessment. Disagreements were resolved through discussion or adjudication by a third reviewer. A standardized data extraction sheet was used to capture study design, sample characteristics, proteins investigated, methodological details, expression patterns and main findings.

Study Risk of Bias Assessment

Risk of bias was assessed independently by two reviewers, with disagreements resolved by consensus or a third reviewer. For tissue-based immunohistochemical studies, the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Analytical Cross-Sectional Studies was used. For in vitro functional studies, an adapted appraisal framework was applied, evaluating: clarity of objectives, cell line authentication, appropriate controls, blinding of outcome assessment, completeness of data reporting and consideration of confounding variables. No automation tools were used in the bias assessment process.

Effect Measures

For each outcome, the effect measures were: (1) for expression differences between MEC and normal tissue: standardized mean difference or qualitative comparison (higher/lower expression) as reported by original studies; (2) for functional knockdown studies: percentage reduction in invadopodia formation, ECM degradation, or invasion relative to control; (3) for correlational analyses: correlation coefficients (e.g., Spearman's rho) when available.

Synthesis Methods

Studies were grouped for synthesis based on the invadopodia-related protein investigated (scaffolding proteins: Tks4/Tks5/cortactin; proteolytic enzymes: MT1-MMP/MMP-2/MMP-9; modulators: metallothionein). Eligibility for each synthesis was determined by tabulating study characteristics (sample size, protein assessed, methodology) and comparing against planned outcome groups. Data were prepared for synthesis by converting reported statistics where possible; missing summary statistics (e.g., standard deviations not reported) were noted as such and not imputed. Results were tabulated and visually displayed using summary tables. No sensitivity analyses or quantitative meta-analyses were conducted due to heterogeneity in methodologies and outcome reporting across the six included studies.

Reporting Bias Assessment

Risk of bias due to missing results (reporting biases) was assessed by comparing outcomes reported in each study

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Review Article

against methods sections and expected outcomes based on the study aims. No evidence of selective outcome reporting was identified; however, the possibility of publication bias cannot be excluded given the small number of studies.

Certainty Assessment

Certainty in the body of evidence for each outcome was assessed using an adapted GRADE approach for non-interventional systematic reviews, considering: study limitations (risk of bias), inconsistency (variability in results across studies), indirectness (relevance to clinical MEC populations), imprecision (small sample sizes, wide confidence intervals) and publication bias. Certainty was rated as high, moderate, low, or very low.

Results

Study Selection

A total of 57 records were identified across the databases. After removal of duplicates and title/abstract screening, 12 full-text articles were assessed for eligibility. Six studies fulfilled the inclusion criteria and were included in the final review.

Study Characteristics

The included studies comprised four tissue-based investigations and two in vitro functional studies (Table 1). Sample sizes for tissue-based studies ranged from 19 to 27 MEC cases, with normal salivary gland tissue used as controls in two reports. The studies spanned from 2004 to 2025 and were conducted in Brazil, Japan and South Korea. Proteins assessed included Tks4, Tks5, cortactin, MT1-MMP, MMP-2, MMP-9 and metallothionein.

Table 1: Characteristics of Included Studies

Author (Year)	Study title	Study type	Sample (MEC cases)	Control group	Proteins assessed	Methods	Key Findings
Loureiro et al. (2025) [9]	Invadopodia Related-Proteins Expression in Mucoepidermoid Carcinoma	Cross-sectional IHC + functional assays	27 MEC	10 normal salivary glands	Tks4, Tks5, cortactin, MT1-MMP	IHC, IF, siRNA knockdown	Overexpression in MEC vs controls; knockdown of Tks4/Tks5 reduced invadopodia activity and gelatin degradation
De Oliveira et al. (2022) [10]	Cross-talk of proteins related to invadopodia and the invasion process in salivary gland mucoepidermoid carcinoma	Cross-sectional IHC	19 MEC	10 normal salivary glands	Tks4, Tks5, cortactin, MT1-MMP	IHC	Coordinated expression of invadopodia proteins; correlation between Tks4 and Tks5
Loureiro et al. (2022) [11]	Tyrosine kinase proteins tks4 and tks5 participate in the invasiveness of salivary gland mucoepidermoid carcinoma	In vitro functional study	MEC cell lines	None	Tks4, Tks5	siRNA knockdown, invasion assays	Silencing Tks4/Tks5 reduced invasion, ECM degradation and invadopodia activity
Aquime et al. (2020) [12]	Metallothionein Expression and its Influence on the In Vitro Biological Behavior of Mucoepidermoid Carcinoma	In vitro functional study	MEC cell line	None	Metallothionein, MMP-2, MMP-9	RT-PCR, Western blot, invasion assays	Metallothionein expression increased invasiveness through modulation of MMP-2/9

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Review Article

Kim et al. (2010) [13]	Immunohistochemical Array for Clear Cell Type Mucoepidermoid Carcinoma	Cross-sectional immunoarray	Clear-cell MEC (n not specified)	Clear cell odontogenic carcinoma and normal gingiva	MMP-2	Tissue microarray, IHC	MMP-2 expressed in clear-cell MEC, suggesting ECM degradation involvement
Kayano et al. (2004) [14]	Activation of pro-MMP-2 mediated by MT1-MMP in human salivary gland carcinomas	Cross-sectional IHC + zymography	Salivary gland carcinomas including MEC (n not specified)	Adjacent tissue	MT1-MMP, MMP-2	IHC, gelatin zymography	MT1-MMP localized to carcinoma cell membranes; activation of pro-MMP-2

Risk of Bias in Studies

Risk of bias assessments for each included study are presented in Table 2. Overall, tissue-based studies demonstrated low to moderate risk of bias, with the main limitations being small sample sizes and lack of blinding in outcome assessment. In vitro studies showed moderate risk of bias due to limited reporting of cell line authentication and absence of blinding.

Table 2: Risk of Bias Assessment for Included Studies

Study	Domain assessed	Judgement	Supporting evidence
Loureiro et al. (2025)	Sample representativeness	Low	27 MEC cases, consecutive or representative
	Blinding of outcome assessment	Unclear	Not explicitly stated
	Adequate control group	Low	10 normal salivary glands
	Complete outcome data	Low	All cases reported
De Oliveira et al. (2022)	Sample representativeness	Moderate	19 MEC cases, single center
	Blinding of outcome assessment	Unclear	Not explicitly stated
	Adequate control group	Low	10 normal salivary glands
Loureiro et al. (2022)	Cell line authentication	Unclear	Not explicitly stated
	Appropriate controls	Low	Non-silenced controls used
	Blinding	High	No blinding described
Aquime et al. (2020)	Cell line authentication	Unclear	Not explicitly stated
	Appropriate controls	Low	Controls included
	Blinding	High	No blinding described
Kim et al. (2010)	Sample representativeness	High	Clear-cell MEC only, n not specified
	Blinding	Unclear	Not stated
Kayano et al. (2004)	Sample representativeness	Moderate	Multiple carcinoma types, MEC subset unclear
	Blinding	Unclear	Not stated

Results of Syntheses

Scaffolding proteins (Tks4, Tks5, cortactin): Across three studies (Loureiro 2025, De Oliveira 2022, Loureiro 2022), Tks4, Tks5 and cortactin were consistently overexpressed in MEC tissue compared with normal salivary glands. The correlation between Tks4 and Tks5 expression was strong (reported r values not specified but described as significant). Heterogeneity across studies was low with respect to direction of effect but moderate regarding magnitude due to different scoring systems.

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Review Article

Proteolytic proteins (MT1-MMP, MMP-2, MMP-9): MT1-MMP was overexpressed in MEC tissue (Loureiro 2025, Kayano 2004) and localized to carcinoma cell membranes. MMP-2 activation by MT1-MMP was demonstrated via gelatin zymography (Kayano 2004). MMP-2 expression in clear-cell MEC was confirmed (Kim 2010). No substantial heterogeneity was observed.

Modulators (Metallothionein): One in vitro study (Aquime 2020) demonstrated that metallothionein upregulation enhances MEC cell invasiveness via MMP-2/9 modulation. Heterogeneity could not be assessed due to a single study.

Sensitivity analyses: Not applicable, as no quantitative meta-analysis was performed.

Reporting Biases

Risk of bias due to missing results was assessed as low for all included studies, as outcomes reported in the results sections matched those specified in the methods. However, the small number of studies (n=6) raises the possibility of publication bias, as studies with negative or null findings may be less likely to be published.

Certainty of Evidence

For Tks4/Tks5/cortactin expression: Moderate certainty – consistent overexpression across multiple studies, but imprecision due to small sample sizes and lack of blinding.

For MT1-MMP/MMP-2 proteolytic function: Low certainty – limited by small number of studies and incomplete reporting of MEC-specific data in older studies.

For metallothionein role: Very low certainty – single in vitro study, no tissue validation.

Discussion

This systematic review synthesizes current evidence regarding the role of invadopodia-related proteins in mucoepidermoid carcinoma (MEC) and demonstrates their consistent overexpression and functional involvement in tumor invasiveness. Across six included studies, the evidence converges on a model in which invadopodia scaffolding proteins such as Tks4 and Tks5, actin regulators like cortactin and proteolytic enzymes including MT1-MMP and MMP-2/9, cooperate to drive extracellular matrix (ECM) degradation and facilitate invasion.

Loureiro et al. (2025) [9] and De Oliveira et al. (2022) [10] provided compelling immunohistochemical evidence of elevated expression of Tks4, Tks5, cortactin and MT1-MMP in MEC tissue compared with normal salivary glands. The observation by De Oliveira et al. (2022) [10] that Tks4 and Tks5 expression strongly correlate suggests synergistic roles in invadopodia assembly and stability, reinforcing their significance as core scaffolding proteins. These findings were mechanistically validated by Loureiro et al. (2022) [11], who demonstrated through siRNA-mediated silencing experiments that knockdown of Tks4 and Tks5 in MEC cell lines resulted in significant reductions in invadopodia formation, ECM degradation and invasion. This direct functional evidence bridges the gap between descriptive tissue-based findings and biological mechanism, establishing a causal relationship between invadopodia proteins and MEC invasiveness.

The proteolytic machinery underlying invadopodia activity was further elucidated by studies of MT1-MMP and matrix metalloproteinases. Loureiro et al. (2025) [9] confirmed MT1-MMP overexpression in MEC, while Kayano et al. (2004) [14] localized MT1-MMP to carcinoma cell membranes in salivary gland carcinomas, demonstrating its role in activating pro-MMP-2. This places MT1-MMP as a central effector linking invadopodia scaffolds to downstream proteolysis. Kim et al. (2010) [13] corroborated the protease pathway by identifying MMP-2 expression in clear-cell MEC, thereby supporting the importance of MMP activity across histological subtypes. Aquime et al. (2020) [12] expanded this proteolytic perspective by demonstrating that metallothionein upregulation in MEC cell lines enhances invasiveness through modulation of MMP-2 and MMP-9 activity. When considered together, these studies establish a coherent cascade in which invadopodia scaffolding proteins regulate cytoskeletal assembly, while MT1-MMP initiates a proteolytic axis involving MMP-2/9 that culminates in ECM degradation and invasion.

Strengths of the evidence include the consistency of findings across independent studies and methodologies. Tissue-based immunohistochemical studies confirmed differential protein expression compared with controls, while functional assays in MEC cell lines provided direct mechanistic validation. The integration of protease studies further reinforced the biological plausibility of the invadopodia machinery as a driver of MEC invasion. The use of normal salivary gland tissue as controls in some studies adds rigor by establishing baseline expression levels.

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Review Article

Limitations of the evidence include small sample sizes, as most studies analyzed fewer than 30 MEC cases, limiting statistical power and generalizability. The majority of studies were single-center and retrospective, increasing the risk of selection bias. Immunohistochemical scoring methods varied, with differences in antibody clones, staining thresholds and interpretation criteria, complicating cross-study comparison. Additionally, none of the studies integrated molecular expression findings with clinical outcomes such as recurrence, metastasis, or overall survival, leaving the prognostic significance of invadopodia proteins in MEC unresolved. Functional studies, while valuable, were limited to in vitro models and may not fully replicate the tumor microenvironment in vivo.

Future Research Directions

Future research should address the following priorities identified from the current evidence:

1. Multicenter cohort studies with larger sample sizes (≥100 MEC cases) to validate the prognostic value of invadopodia proteins across different MEC grades and subtypes.

2. Standardization of immunohistochemical protocols including antibody clones, scoring systems (e.g., H-score, automated digital pathology) and cut-off values to enable cross-study comparability and meta-analysis.

3. Integration with clinical outcomes such as disease-free survival, overall survival, recurrence rates and nodal metastasis to establish clinicopathological correlations.

4. Spatial proteomics and multiplex immunofluorescence to assess co-localization of invadopodia proteins (e.g., Tks4 with MT1-MMP) within the same tumor regions and their relationship to invasive fronts.

5. Preclinical in vivo studies using animal models (e.g., orthotopic xenografts) to investigate the role of invadopodia proteins in MEC progression and metastasis in a physiologically relevant microenvironment.

6. Therapeutic targeting studies evaluating small-molecule inhibitors of Tks4/Tks5 or MT1-MMP in MEC cell lines and animal models to explore translational potential.

7. Longitudinal studies examining whether invadopodia protein expression changes with tumor progression or in response to therapy.

Taken together, the correlated findings suggest that invadopodia proteins play a central role in MEC progression by orchestrating both cytoskeletal dynamics and proteolytic activity. Tks4 and Tks5 appear to function as scaffolds that facilitate cortactin-mediated actin polymerization, enabling the recruitment of MT1-MMP to invadopodia, where it activates downstream MMP-2/9 and promotes ECM degradation. Metallothionein further modulates this protease activity, amplifying the invasive potential of MEC cells. This integrated model, supported by both tissue and functional evidence, positions invadopodia-related proteins as potential biomarkers of aggressive MEC phenotypes. Clinically, their detection may complement histopathological grading in risk stratification. From a therapeutic perspective, targeting invadopodia scaffolds or proteases such as through MT1-MMP inhibition could represent novel strategies to mitigate MEC invasion, though such approaches remain exploratory.

Conclusion

This systematic review demonstrated that invadopodia-related proteins, including Tks4, Tks5, cortactin, MT1-MMP and associated proteolytic partners such as MMP-2/9 and metallothionein, are consistently expressed in mucoepidermoid carcinoma and play a functional role in its invasiveness. Evidence from tissue and in vitro studies supports their involvement in ECM degradation and tumor progression. However, the available data are limited by small sample sizes, methodological heterogeneity and the absence of clinical outcome analyses. Future multicenter studies with standardized protocols and integration of prognostic endpoints are essential to establish the clinical significance of these proteins and to explore their potential as biomarkers and therapeutic targets in MEC.

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Review Article

Competing interests

The authors declare no competing interests. No financial or personal relationships with other people or organizations have inappropriately influenced this work.

Availability of data, code and other materials

The following materials are publicly available upon reasonable request from the corresponding author: template data collection forms; data extracted from included studies (summarized in Tables 1 and 2); data used for all analyses (presented in the Results section). No analytic code was generated for this systematic review as no quantitative meta-analysis was performed. Other materials, including the PRISMA 2020 checklist and PROSPERO registration details, are available from the corresponding author. No public repository was used.

Author biographies

Dr. Karthik Shunmugavelu is an Oral and Maxillofacial Pathologist with multiple international fellowships and affiliations. He serves as Associate Faculty at the Faculty of Dental Trainers, Edinburgh and holds memberships with the Royal College of Surgeons of England and Glasgow. His research interests include salivary gland pathology, tumor invasion biology and systematic review methodology.

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Author contributions

Dr. Karthik Shunmugavelu: Conceptualization, methodology, formal analysis, investigation, data curation, writing – original draft, writing – review and editing, visualization, supervision, project administration.

Dr. Niraimathi Gnanasekaran: Investigation, data curation, writing – review and editing, validation, resources.

Both authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Informed consent

The requirement for informed consent was waived due to the retrospective nature of the included studies and the use of anonymized data, as approved by the relevant ethics committees of the respective original studies. No direct patient contact or primary data collection was performed in this systematic review.

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Review Article

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