Analysis of the Impact of Aurora-A Expression on Postoperative Biochemical Cure in Medullary Carcinoma: Postprint

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Date: 2023-01-09T00:00:00+00:00

Abstract

Background The relationship between Aurora-A expression level in medullary thyroid carcinoma (MTC) tissues and the clinicopathological data of MTC patients, as well as biochemical cure, remains unclear.

Objective To analyze the relationship between Aurora-A expression in medullary thyroid tissues and patients' clinicopathological characteristics, further analyze the risk factors for biochemical cure, and clarify the correlation between Aurora-A expression and biochemical cure.

Methods A total of 90 patients with medullary carcinoma who were hospitalized and underwent surgery in the Department of Thyroid and Head and Neck Oncology, Tianjin Medical University Cancer Institute and Hospital from February 2011 to July 2019 were selected. Pathological specimens from 90 surgically resected medullary thyroid carcinoma patients were subjected to Aurora-A immunohistochemical staining, and complete clinical data were collected with follow-up conducted to analyze the relationship between Aurora-A expression levels and clinicopathological characteristics of patients, as well as the relationship with biochemical prognosis.

Results The positive expression rate of Aurora-A in medullary thyroid carcinoma tissues was 68.89%. Aurora-A expression in medullary carcinoma tissues was associated with patient gender, extrathyroidal invasion, tumor size, biochemical cure, TNM stage, clinical stage, and recurrence ($P < 0.05$). Whether medullary carcinoma patients achieved biochemical cure was associated with gender, number of lesions, extrathyroidal invasion, TNM stage, clinical stage, and high Aurora-A expression ($P < 0.05$). Multivariate analysis using Logistic regression revealed that high Aurora-A expression (HR 3.22, 95%CI 1.07-9.74, $P = 0.038$), multiple lesions (HR 3.18, 95%CI 1.01-9.97, $P = 0.047$), and T3/T4 vs

T1/T2 stage (HR 3.69, 95%CI 1.05-12.93, P = 0.042) were independent factors for failure to achieve biochemical cure in medullary carcinoma patients.

Conclusion High Aurora-A expression is associated with tumor invasion in medullary thyroid carcinoma, and the expression level of Aurora-A can influence whether medullary carcinoma patients achieve biochemical cure.

Full Text

Preamble

Effect of Aurora-A Expression on Biochemical Cure After Surgery for Medullary Thyroid Carcinoma

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Funding: National Natural Science Foundation of China (81872169, 82172821, 82103386); Tianjin Science and Technology Project (19JCYBJC27400); Beijing-Tianjin-Hebei Basic Research Cooperation Project (20JCZXJC00120)

Abstract

Background: The relationship between Aurora-A expression levels in medullary thyroid carcinoma (MTC) tissues and clinicopathological data, as well as biochemical cure in MTC patients, remains unclear.

Objective: To analyze the association between Aurora-A expression in medullary thyroid tissue and clinicopathological characteristics, to identify risk factors for biochemical cure, and to clarify the correlation between Aurora-A expression and biochemical cure.

Methods: We enrolled 90 patients with medullary carcinoma who underwent surgery in the Department of Thyroid, Head and Neck Oncology at Tianjin Medical University Cancer Hospital between February 2011 and July 2019. Pathological specimens from these 90 patients who underwent surgical resection for medullary thyroid cancer were subjected to Aurora-A immunohistochemical staining. Complete clinical data were collected, and patients were followed up to analyze the relationship between Aurora-A expression levels and clinicopathological features as well as biochemical prognosis.

Results: The positive expression rate of Aurora-A in medullary thyroid cancer tissues was 68.89%. Aurora-A expression in medullary carcinoma tissues was significantly associated with patient gender, extraglandular invasion, tumor size, biochemical cure, TNM stage, clinical stage, and recurrence ($P < 0.05$). Achievement of biochemical cure was associated with gender, number of lesions, extraglandular invasion, TNM stage, clinical stage, and high Aurora-A expression ($P < 0.05$). Multivariate logistic regression analysis revealed that high Aurora-A expression (HR 3.22, 95%CI 1.07-9.74, $P = 0.038$), multiple lesions (HR 3.18, 95%CI 1.01-9.97, $P = 0.047$), and T3/T4 versus T1/T2 stage (HR 3.69, 95%CI 1.05-12.93, $P = 0.042$) were independent factors preventing biochemical cure in medullary carcinoma patients.

Conclusion: High Aurora-A expression is associated with tumor invasion in medullary thyroid cancer and influences whether patients achieve biochemical cure.

Keywords: Medullary thyroid carcinoma; Aurora-A; biochemical cure; immunohistochemical staining

Introduction

Medullary thyroid carcinoma (MTC) is a relatively rare neuroendocrine tumor that originates from calcitonin-secreting thyroid parafollicular cells (C cells) [1]. Through aberrant signaling mediated by encoded proteins, MTC promotes tumor cell proliferation, invasion, and metastasis, resulting in a worse prognosis than differentiated thyroid cancer (DTC) [2]. Despite recent therapeutic advances, total thyroidectomy with central neck dissection remains the preferred treatment for operable MTC patients. In patients with complete tumor resection, postoperative calcitonin levels can drop below detectable limits, achieving biochemical cure. These patients have a favorable prognosis, with 10-year survival rates of 95–97% [3]. However, MTC is highly aggressive and prone to lymph node and distant metastasis. Among MTC patients presenting with palpable neck masses, 70% have cervical lymph node metastasis and 10% have distant metastasis [4]. MTC differs from the more common papillary thyroid carcinoma in its pathogenesis, diagnosis, and treatment, with a poorer prognosis that necessitates improved therapeutic strategies and identification of novel targets for adjuvant therapy and recurrence reduction.

Aurora-A, also known as BTAK, Aurora2, AIK1, STK15, STK6, or HsAIRK1, belongs to the Aurora kinase family. As a serine/threonine protein kinase that regulates centrosome and microtubule function, Aurora-A plays a crucial role in normal mitotic and meiotic progression [5]. Recent studies have demonstrated high Aurora-A expression in various tumor tissues, including head and neck cancers [6], breast cancer [7], non-small cell lung cancer [8], ovarian cancer [9], and gastric cancer [10]. This overexpression can influence multiple biological behaviors such as tumor cell proliferation, migration, and stemness main-

tenance [11], and is significantly associated with patient survival and prognosis. Compared with normal thyroid follicular cells and benign follicular adenomas, Aurora kinase family expression is significantly elevated in both papillary thyroid carcinoma and anaplastic carcinoma, suggesting that Aurora kinases may play important roles in malignant thyroid cancers. Furthermore, the Aurora-A inhibitor MLN8237 can significantly inhibit thyroid cancer proliferation [12], indicating that Aurora-A may serve as a novel therapeutic target for thyroid tumors.

Methods

1.1 Study Criteria

Inclusion criteria: (1) Complete clinicopathological data available; (2) No preoperative radiotherapy, chemotherapy, or other tumor-related treatments; (3) Postoperative pathological diagnosis of medullary carcinoma; (4) Sporadic medullary carcinoma.

Exclusion criteria: (1) Pediatric MTC and patients without lymph node dissection; (2) Failure to resect lesions surgically; (3) Concurrent other malignancies; (4) Patients with recurrent medullary carcinoma undergoing repeat surgery. All patients provided informed consent, and the study was approved by the Ethics Committee of Tianjin Medical University Cancer Hospital.

1.2 Patient Data

We selected 90 patients with medullary carcinoma who were admitted and underwent tumor resection in the Department of Thyroid, Head and Neck Oncology at Tianjin Medical University Cancer Hospital between February 2011 and July 2019. The cohort included 40 males and 50 females, aged 19–74 years (mean age 53 years). Tumor diameter was $ $2 cm in 55 patients and >2 cm in 35 patients. Clinical staging was I+II in 31 patients and III+IV in 59 patients. The normal reference range for serum calcitonin (CT) was 0–5 ng/L, with postoperative serum CT <5 ng/L defined as biochemical cure. Forty patients achieved biochemical cure. Recurrence was defined as cervical lymph node metastasis confirmed by pathology occurring more than 6 months postoperatively, with distant metastasis confirmed by chest/abdominal CT, ECT, or PET-CT. Eighteen patients experienced recurrence.

1.3 Immunohistochemical Detection of Aurora-A Expression in Medullary Carcinoma

Aurora-A antibody was purchased from Abcam (catalog number ab1287). Paraffin-embedded medullary carcinoma tissues were sectioned. The experimental procedure strictly followed the immunohistochemistry kit instructions (Sangon, D601037-0020). Sections were deparaffinized, dehydrated in ethanol,

and subjected to antigen retrieval. Hydrogen peroxide was used to block peroxidase activity, followed by blocking with 5% BSA. Two hundred microliters of Aurora-A primary antibody mixture (1:200 dilution) was applied overnight. The primary antibody was recovered the next day, rabbit secondary antibody was added and incubated at room temperature for 2 hours, and after PBS washing, DAB chromogenic solution was applied. Sections were then rinsed with tap water, counterstained with hematoxylin, dehydrated in ethanol and xylene, air-dried, and mounted with neutral resin.

Result evaluation: Two senior pathologists guided specimen collection and slide interpretation. Aurora-A positive expression was localized to the nucleus. The final immunohistochemistry score was the product of staining intensity and proportion. Intensity scoring: (1) 0 points: negative; (2) 1 point: weak; (3) 2 points: moderate; (4) 3 points: strong. Positive cell frequency scoring: (1) 0 points: <25%; (2) 1 point: 26–50%; (3) 2 points: 51–75%; (4) 4 points: >75%. The two scores were summed, with 0–1 points defined as low Aurora-A expression and 2–6 points as high Aurora-A expression.

1.4 Statistical Methods

Statistical analysis was performed using SPSS 22.0 software. Count data were described as cases (%) and compared between groups using ^{2} test and Fisher' s exact test. Variables showing significant differences in univariate analysis were included in the logistic regression multivariate risk model. $P < 0.05$ was considered statistically significant (two-tailed).

Results

2.1 Aurora-A Protein Expression in Medullary Carcinoma Tissues

Aurora-A protein staining was primarily localized to the nuclei of medullary carcinoma cells (Figure 1). The positive expression rate of Aurora-A in medullary thyroid cancer tissues was 68.89%. Among immunohistochemical staining results, the percentage of Aurora-A-positive cells ranged from 26% to 90.2%. In the 90 medullary carcinoma patients, the Aurora-A protein positive rate was 68.89% (62/90).

[Figure 1: see original paper]. The expression and staining intensity of Aurora-A in medullary carcinoma tissues

2.2 Relationship Between Aurora-A Expression Level and Clinicopathological Features

There were no significant differences in age, unilateral/bilateral lesions, or number of lesions between patients with high and low Aurora-A expression ($P > 0.05$). However, significant differences were observed in gender, extraglandular

invasion, tumor size, T3/T4 stage, N stage, III/IV clinical stage, achievement of biochemical cure, and recurrence ($P < 0.05$, Table 1).

Table 1 Relationship between clinicopathological features and Aurora-A expression levels in 90 MTC patients

Clinicopathological Feature	Aurora-A Low Expression (n, %)	Aurora-A High Expression (n, %)	P-value
Age (years)	20 (71.4)	8 (28.6)	
Gender	17 (60.7)	11 (39.3)	<0.05
Extraglandular invasion	30 (48.4)	32 (51.6)	<0.05
Tumor size	25 (40.3)	37 (59.7)	<0.05
T1/T2 stage	27 (53.8)	35 (46.2)	<0.05
T3/T4 stage	21 (33.9)	11 (17.7)	<0.05
N0 stage	30 (48.4)	15 (3.8)	<0.05
N1 stage	47 (96.2)	20 (32.3)	<0.05
Clinical stage I/II	42 (67.7)	16 (25.8)	<0.05
Clinical stage III/IV	46 (74.2)	23 (85.2)	<0.05
Biochemical cure	4 (14.8)	21 (96.4)	<0.05
Recurrence	7 (3.6)	27 (96.4)	<0.05
Non-recurrence	1 (3.6)	22 (78.6)	<0.05

Aurora-A: Aurora kinase A; AJCC: American Joint Committee on Cancer

2.3 Relationship Between Biochemical Cure Achievement and Clinicopathological Features

No significant differences were found in age, unilateral/bilateral lesions, tumor size, or recurrence between patients who achieved and did not achieve biochemical cure ($P > 0.05$). However, significant differences were observed in gender, extraglandular invasion, number of lesions, Aurora-A expression level, T3/T4 stage, N stage, and III/IV clinical stage ($P < 0.05$, Table 2).

Table 2 Relationship between clinicopathological features and biochemical cure in 90 MTC patients

Clinicopathological Feature	Biochemical Cure (n, %)	No Biochemical Cure (n, %)	P-value
Age (years)	27 (67.5)	13 (32.5)	>0.05
Gender	17 (42.5)	23 (57.5)	<0.05
Extraglandular invasion	23 (46.0)	27 (54.0)	<0.05
Number of lesions	25 (50.0)	25 (50.0)	<0.05

Clinicopathological Feature	Biochemical Cure (n, %)	No Biochemical Cure (n, %)	P-value
Tumor size $ $2 cm	41 (85.4)	7 (14.6)	>0.05
Tumor size >2 cm	30 (60.0)	20 (40.0)	<0.05
T1/T2 stage	22 (44.9)	27 (55.1)	<0.05
T3/T4 stage	27 (54.0)	23 (46.0)	<0.05
N0 stage	20 (40.0)	30 (60.0)	<0.05
N1 stage	15 (30.0)	10 (20.0)	<0.05
Clinical stage I/II	25 (50.0)	12 (24.0)	<0.05
Clinical stage III/IV	38 (76.0)	8 (16.0)	<0.05
Aurora-A high expression	42 (84.0)	37 (74.0)	<0.05
Recurrence	13 (26.0)	37 (92.5)	>0.05

2.4 Logistic Regression Multivariate Analysis

Logistic regression multivariate analysis showed that high Aurora-A expression (HR 3.22, 95%CI 1.07-9.74, P = 0.038), multiple lesions (HR 3.18, 95%CI 1.01-9.97, P = 0.047), and T3/T4 versus T1/T2 stage (HR 3.69, 95%CI 1.05-12.93, P = 0.042) were independent factors associated with failure to achieve biochemical cure in MTC patients (Table 3).

Table 3 Logistic regression multivariate analysis of clinicopathological features and biochemical cure achievement

Variable	HR	95.0% CI	P-value
Gender (female vs male)			
Number of lesions (multiple vs single)	3.18	1.01-9.97	0.047
Aurora-A high expression	3.22	1.07-9.74	0.038
T stage (T3/T4 vs T1/T2)	3.69	1.05-12.93	0.042
N stage			
N1a vs N0			
N1b vs N0			
Clinical stage (III/IV vs I/II)			

Discussion

Medullary thyroid carcinoma is a highly malignant thyroid tumor that is insensitive to radiotherapy and chemotherapy, and ineffective for I-131 treatment. Currently, surgery is the only effective treatment modality for MTC. The high recurrence rate of MTC, along with its propensity for lymph node and distant metastasis, represents the main cause of poor prognosis [13]. In a retrospective study by Zhang et al. [14], the 5-, 10-, and 15-year cumulative survival rates for

MTC patients were 87.4%, 74.6%, and 54.2%, respectively. Multiple factors affect MTC prognosis, including age, gender, tumor size, lymph node metastasis, clinical stage, and biochemical cure. However, clinically, MTC patients at the same clinical stage often have different outcomes, making it crucial to identify factors that influence MTC prognosis.

AURKA kinase is a protein kinase associated with centrosome separation and closely related to mitosis, and has been implicated in the development and progression of numerous solid tumors [15]. Beyond its role in mitosis, increasing evidence demonstrates that AURKA can activate multiple signaling pathways, including PI3K/Akt, mTOR, β-catenin/Wnt, and NF- B, which interact to drive tumorigenesis [16-19]. Literature reports indicate that Aurora-A kinase inhibitors (MLN8237, MK0457) can inhibit the proliferation of the medullary carcinoma cell line TT and trigger apoptosis, demonstrating the therapeutic potential of Aurora-A kinase inhibitors in MTC [20]. Another study found that tumor diameter correlates with both lymph node and distant metastasis, with primary tumor length >2.5 cm significantly affecting survival [21]. In the present study, we used 2 cm tumor diameter as a grouping criterion and found through immunohistochemistry and clinical data analysis that high Aurora-A expression was associated with maximum tumor diameter >2 cm.

Medullary thyroid carcinoma is an endocrine tumor that synthesizes various biological substances, including calcitonin, adrenocorticotropic hormone, histamine, carcinoembryonic antigen, and vasoactive peptides. Calcitonin, a polypeptide hormone secreted by thyroid parafollicular cells, serves as a specific tumor marker for MTC and closely correlates with tumor burden [22]. Calcitonin levels are also important indicators for postoperative monitoring of recurrence, metastasis, and tumor burden. However, the optimal cutoff value and timing for calcitonin monitoring remain undetermined, and the cutoff value defining biochemical cure varies across studies [23,24]. One meta-analysis of 11 studies including 1,094 MTC patients reported that patients with postoperative biochemical recurrence had higher structural recurrence and mortality rates than those with normal postoperative calcitonin levels [25]. Machens et al. [24] analyzed 1,026 MTC patients and found that the number of positive lymph nodes (LNR) determined the likelihood of biochemical cure. Jes Sloth Mathiesen et al. [26] reached similar conclusions in a 17-year follow-up study, finding that distant metastasis predicted worse prognosis, while absence of cervical lymph node metastasis suggested potential for biochemical cure. A 30-year follow-up study identified failure to achieve complete biochemical remission within 6 months postoperatively (calcitonin <10 pg/ml without anatomic recurrence) as the most significant factor affecting MTC recurrence [27]. In our study, we collected serum calcitonin data at 6 months postoperatively, defining biochemical cure as restoration of calcitonin to normal or undetectable levels, and found that high Aurora-A expression was an independent factor affecting biochemical cure in MTC patients.

Different study populations also influence postoperative serum calcitonin levels

in MTC patients. Proper understanding of calcitonin requires long-term follow-up of multi-center, large-sample populations. Previous studies have found that preoperative serum calcitonin levels affect recurrence and metastasis in MTC patients. Machens' study [28] of 1,026 MTC patients showed that when preoperative calcitonin levels were 500 pg/mL, only 50% of patients achieved biochemical cure; when calcitonin levels exceeded 10,000 pg/ml, no patients achieved biochemical cure. All distant metastases occurred in patients with calcitonin $ $500 pg/mL. However, our study did not find high Aurora-A expression to be an independent factor for preoperative calcitonin levels. This may be because calcitonin production in MTC patients is a complex process with multiple causes for elevation, and high Aurora-A expression may only play a partial role. Additionally, the relatively small sample size in this study necessitates larger sample sizes for deeper investigation. We did not conduct survival follow-up in this study, so the correlation between high Aurora-A expression and disease-free survival (DFS) was not obtained. Given these limitations, we look forward to conducting multi-center, large-sample, prospective clinical trials.

In summary, medullary carcinoma is a highly malignant thyroid cancer prone to recurrence and metastasis. Aurora-A protein is highly expressed in MTC, and its overexpression correlates with extraglandular invasion, tumor size, biochemical cure, TNM stage, clinical stage, and recurrence. High Aurora-A expression is an independent factor for failure to achieve biochemical cure in MTC patients, suggesting that Aurora-A protein may serve as a biomarker for evaluating postoperative recurrence in medullary thyroid carcinoma. The specific molecular mechanisms of Aurora-A in MTC require further investigation.

Author Contributions

Zewei Zhao was responsible for literature search, study design, and manuscript writing. Ning Kang and Zhongyu Wang performed data collection and acquisition. Fengli Guo conducted data cleaning and statistical analysis and was responsible for figure and table preparation. Xiangqian Zheng critically reviewed the intellectual content, provided material support, performed quality control and review of the manuscript, and takes overall responsibility for the article. All authors approved the final manuscript.

Conflict of Interest

No conflict of interest.

Ethics Statement

This study was approved by the Ethics Committee of Tianjin Medical University.

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Note: Figure translations are in progress. See original paper for figures.