

Investigation the role of Human Leukocyte Antigen-G in Iraqi patients with papillary thyroid carcinoma

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Abstract

Human leukocyte antigen G (HLA-G) is a non-classical major histocompatibility complex (MHC) protein with well-known immunomodulatory characteristics. It is also believed to be an important sign of immune tolerance in cancer cells. Immune Escape. HLA-G is also associated with disease development and prognosis in cancer patients. The goal of this study was to compare soluble HLA-G (sHLA-G) levels before and after radioactive iodine therapy (RAI) by enzyme immunoassay (ELISA). Immunohistochemistry was used to examine HLA-G protein expression in thyroid tissues from patients with papillary thyroid cancer (PTC) to investigate the relationship between HLA-G expression and patients' clinical variables. Prospective research included 138 blood samples from patients and controls, as well as 25 thyroid paraffin-embedded tissues from individuals suffering from papillary thyroid cancer (PTC) and controls. Our findings demonstrated a significant difference in the means of people who had radioactive iodine therapy against those who did not (Mean SE = 4.19 0.31, 2.216 0.08, respectively). HLA-G staining, on the other hand, was identified in tumor cells in papillary thyroid cancer, all sections were positive, strongly stained and completely membranous, indicating the presence of HLA-G protein in the tested material. These findings suggest that HLA-G may be involved in the pathogenesis of papillary thyroid cancer.

Keywords: HLA-G, papillary thyroid cancer, preoperative diagnosis, risk factor, tumor marker.

Introduction

Papillary thyroid cancer (PTC) is a specific type of thyroid cancer that develops from epithelial cells and is characterized by the presence of papillae and other nuclear features. This type of thyroid tumor accounts for about 80% of all thyroid malignancies and 1% of all malignancies in Eastern cultures. Women are at a substantially higher risk than men for developing this malignancy. Despite the fact that PTC is among the most curable cancers, metastatic lymph nodes can develop in 30 % – 65% of patients

when they are first identified. The tumor is aggressive in 15% of cases, with local invasion, tumor progression, and therapy resistance. As a result of the disease, there is an elevated risk of death, as well as a high recurrence rate ¹.

Therefore, a better prognosis and survival percentage can be achieved with the early detection and treatment of malignant tumors. New biomarkers have shown effective not only for early thyroid

cancer detection, but also for recognizing recurring and chronic issues and projecting the outcome of surgical excision, radioiodine therapy, and chemotherapy. Non-classical HLA class I protein HLA-G was shown to be synthesized exclusively by trophoblast cells at the placental barrier and to have a role in maternal tolerance towards the fetus. The HLA-G molecule is unique in that it has low levels of polymorphism, low levels of tissue expression, seven isoforms (HLA-G1 to G7), and an overall negative immune function by suppressing the activity of natural killer cells, cytotoxic T lymphocytes, and antigen-presenting cells, all of which are necessary for the formation of a cytotoxic anti-tumor immune response ².

Therefore, tumor cells may exploit HLA-G expression to avoid a potent anti-immune response by modulating the performance of the host's immune effector cells. Ovarian, stomach, endometrial, breast, kidney cell, pulmonary,

concomitant melanoma, hematological, mesothelioma, and cytotrophoblast tumors have all been found to induce HLA-G. Many investigations have uncovered of these ³.

Given the importance of developing novel biological markers in thyroid cancer, this study aimed to ascertain whether HLA-G expression can be activated in PTC and thus serve as a marker of tumor aggressiveness. Furthermore, HLA-G immuno-reactivity can be useful for forecasting clinical actions in cancer patients and providing oncologists with a novel molecular technique for improved cancer management. The potential significance of serum HLA-G in people with papillary thyroid cancer, especially after radioactive iodine therapy (RAI), is not yet supported by sufficient data. Papillary thyroid cancer was studied in relation to other biological tests using serum HLA-G and immune-histochemical techniques ⁴.

Materials and Methods

Patients and Controls

This study included 90 Iraqi patients with papillary thyroid carcinoma who visited the Nuclear Medicine Hospital in Baghdad's Medical City between March 2020 and October 2022. Thyroid samples were taken from 25 patients who had papillary thyroid carcinoma. The control group consisted of 48 adults who were unrelated and had normal thyroid tests. Medical and epidemiological data were obtained from medical archives (gender, BMI, smoking, alcohol use, family history, ABO system, hypertension, diabetes, and thyroid function tests). The Medical Ethics Committee of the University of Baghdad's Faculty of Science gave ethical approval under the reference number CSEC/1022/0132. All patients and controls provided informed consent and agreed to participate in this case-control study by donating blood and biopsies.

Quantification of Plasma Soluble HLA-G

Serum HLA-G levels were measured with a sandwich ELISA ⁵. The concentration of HLA-G in the blood was determined using an enzyme-linked immunosorbent assay kit (Elabscience, USA;

catalogue number MBS267094) developed specifically for this purpose.

Expression of HLA-G Antigens in Papillary Thyroid Carcinoma

Immunohistochemistry was used to identify HLA-G expression levels in patient samples with papillary type of thyroid cancer. This portion of the research was carried out at the histopathological laboratories of Baghdad's medical city. Immunohistochemically staining of thyroid tissue taken from individuals with papillary thyroid cancer ⁶ is shown below: 0 is a negative score. +1: a negative, barely detectable staining. +2: slightly positive staining with a weak to medium complete staining. +3: very positive, with full staining.

Data Analysis

SAS (2018) was applied to investigate the influence of various variables in research parameters. In order to compare means, the t-test (Analysis of Variation-ANOVA) was utilized ⁷. In this study, Chi-square was used to compare the significance of .05 and .01 probabilities as well as percentages.

Results and Discussion

Levels of Serum HLA-G in Patients with Papillary Thyroid Carcinoma and The Control Group

In this study, 90 patients with malignant tumors were divided into patient and control groups based on their BMI. The distribution of BMI across all analyzed groups is displayed in Table 1. Our findings indicate that there was a non-significant variation in mean BMI in control and patient groups, $p > 0.05$. The Mean \pm standard deviation (SD) of BMI of patient and control groups were 28.33 ± 0.57 , 26.96 ± 0.74 years, respectively with P-value = 0.152. This work agreed with the work of Kaliszewski et al, ⁸, Who found that there was no association between being overweight/obese and papillary thyroid carcinoma diagnosis.

As seen in Table 1, women are more likely than males to acquire papillary thyroid cancer. This

finding is supported by Derwahl et al, ⁹, who confirms global epidemiologic data demonstrating that thyroid cancer incidence rates are greater in women than in males. The P-value for thyroid cancer when comparing smokers to never smokers was (0.050) and (0.0001) respectively. The association between thyroid carcinoma incidence and smoking in this study reached the static significance in smokers in agreement with the findings reported by Cho et al, ¹⁰. Thyroid cancer was not affected by alcohol consumption, as the results were positive for both alcohol consumers and people who did not abuse alcohol. This finding contradicts Kunzmmman et al, ¹¹, who concluded that there is an inverse relationship between drinking alcohol and the incidence of thyroid cancer. The study suggests that relatives of first-degree family history of thyroid cancer, are associated with an increased risk of PTC. High levels of TSH were liked with thyroid cancer development.

Table 1. Demographic Data of the Patients and Controls.

Characteristic	Patients	Control	P-value
Male	10 (11.11%)	22 (45.83%)	0.0339 *
Gender NO. (%)	80 (88.89%)	26 (54.17%)	0.0001 **
Female			
Body mass index BMI(Kg/m2)	28.33 ± 0.57	26.96 ± 0.74	0.152
Yes	3 (3.33%)	10 (20.83%)	0.050 *
Smoking No. (%)	87 (86.67%)	38 (79.17%)	0.0001 **
No			
yes	0 (0.00%)	12 (25.00%)	0.0001 **
Drinking No. (%)	90 (100%)	36 (75.00%)	0.0001 **
No			
yes	31 (34.44%)	7 (14.58%)	0.0001 **
Family history No. (%)	59 (65.56%)	41 (85.42%)	0.0719 NS
No			

* ($P \leq 0.05$), ** ($P \leq 0.01$), NS: Non-Significant.

Thyroid-stimulating hormone (TSH) blood levels can be used to evaluate thyroid gland function. TSH levels are usually stable in previously untreated papillary thyroid cancer patients. These hormone levels may be monitored to determine how effectively the thyroid gland is functioning overall. T3 and T4 levels in individuals with previously

untreated papillary thyroid carcinoma are generally normal. In this research, it was observed a decrease in T3 levels for patients with PTC. T4 level was significantly increased in PTC patients compared with control Table 2. This indicates the critical role of the T4 hormone in thyroid malignancy in agreement with Mousa et al, ¹².

Table 2. Comparison of Hormones Level Between Patients and Control Groups.

Group	Mean ± SE		
	T3	T4	TSH
Patients	1.574 ±0.18	31.97 ±5.14	12.22 ±2.32
Control	2.184 ±0.16	16.84 ±0.40	2.50 ±0.15
T-test	0.554 *	13.969 *	6.318 **
P-value	0.0313	0.0339	0.0028

* (P≤0.05), ** (P≤0.01), NS: Non-Significant.

Blood type analysis, along with genetic studies and associated illness tests, is an important step in the blood transfusion process. Clinical research has revealed that the ABO blood type is involved in a variety of illnesses and cancers¹³. In 1996, researchers found a link between certain ABO blood types and an increased risk of developing cancer¹⁴. Much research has been published since then, with frequently conflicting results¹⁵. In this research, O blood type was discovered as a positive protective factor for PTC Table 3. There is not much research on the association between blood types and the Rh factor in thyroid cancer. Once believed to be a particular marker of PTC cells, the keratan sulfate epitope was shown to be generated concurrently with Poly-N-acetylglucosamine, which contains blood type antigens¹⁶.

Thyroid follicular epithelial cell antigens were found to correlate with ABO group in another study of blood types. Similar research found that abnormal re-expression of blood-type-related antigens was observed after neoplastic transformation of the thyroid gland. The study found that papillary carcinomas produce Poly-N-acetyl glucosamine structures in a linear fashion, and that these structures have diagnostic value in distinguishing PTC from other thyroid cancers. These results support the role of blood type in cancer pathogenesis, and they lend credence to the hypothesis that blood type may play a role in the development of some cancers, most notably PTC¹⁷. The prevalence of blood type O was found to be significantly higher in the PTC group. On the other hand, one of the most prevalent side effects of

thyroid cancer is hypertension (high blood pressure). Thyroid malignancies can all increase or decrease thyroid hormone production. Cancer may be linked to hyperthyroidism (overactive thyroid hormones) rather than hypothyroidism (affected by thyroid hormones)¹⁸.

An overactive thyroid increases metabolism, which typically results in a rise in blood pressure. Hypothyroidism, on the other hand, is generally linked with normal blood pressure but can result in low or high blood pressure. Thyroid hormones have an immediate effect on blood vessels throughout the body, lowering contractility (making them less flexible) and thereby raising blood pressure. Nevertheless, blood vessels might be more or less susceptible to thyroid hormones, resulting in a varied response to changing thyroid hormone levels¹⁹. The majority of thyroid cancer patients are either hyperthyroid or hypothyroid. There was no significance in this research of persons with hypertension and papillary thyroid carcinoma.

Diabetics have a higher incidence of thyroid disease (10.8%) than the general population (6.6%). Multiple studies have found a link between diabetes and thyroid cancer. Diabetes has been linked to an increased risk of thyroid cancer in women, which may or may not be statistically significant. In men with diabetes, the risk of developing thyroid cancer was minimally elevated or unchanged²⁰. We found no statistically significant link between diabetes and papillary thyroid cancer. Although there may be a weak correlation between diabetes and thyroid cancer, the results are contentious.

Table 3. Clinical Characteristics of the Cases and Control Subjects.

Characteristic		Patients	Control	P-value
Hormones level	T3	1.574 ±0.18	2.184 ±0.16	0.0313
	T4	31.97 ±5.14	16.84 ±0.40	0.0339
TSH		12.22 ±2.32	2.50 ±0.15	0.0028
ABO system No. (%)	A	8 (8.89%)	12 (25.00%)	0.371 NS
	B	12 (13.33%)	9 (18.75%)	0.512 NS
	AB	6 (6.67%)	7 (14.58%)	0.781 NS
	O	64 (71.11%)	20 (41.68%)	0.0001**
Hypertension No.	Yes	12 (13.33%)	5 (10.42%)	0.896 NS
	No	78 (86.67%)	43 (89.58%)	0.0015
Diabetes No. (%)	Yes	7 (7.78%)	6 (12.50%)	0.781 NS
	No	83 (92.22%)	42 (87.50%)	0.0002**

* (P≤0.05), ** (P≤0.01) , NS: Non-Significant.

Radiation Therapy for Papillary Thyroid Cancer and the Alteration of Serum HLA-g levels

In this study, we looked at the effect of RAI treatment on PTC in a nuclear medicine facility in Baghdad. The purpose of this study was to compare the recurrence rates of patients who received radioiodine therapy to those who did not. The results of this study showed a mean difference between patients who were treated with radioiodine

and those who were not (mean ± SD = 4.19 ± 0.31, 2.216 ± 0.08) consecutively with a significant difference (P value = 0.0001), Table 4. From the above it follows that the effect of radioactive iodine treatment in terms of the effect on the concentration of HLA-g was positive, which made it possible to identify the role of AI in minimizing the risk of PTC progression. HLA-g, on the other hand, had a clear diagnostic value for patients with papillary thyroid cancer.

Table 4. Relationship Between Therapy with Concentration of HLA-g in Patient's Groups

Group	Mean ± SE
	Concentration of HLA-g
Pre-therapy	4.19 ±0.31
Post-therapy	2.216 ±0.08
T-test	0.626 **
P-value	0.0001

* (P≤0.05), ** (P≤0.01), NS: Non-Significant.

Because of their specialized cellular mechanism, thyroid cells are the only ones that can absorb iodine. Thyroid hormones require iodine to be synthesized by thyroid cells. The thyroid is unique among body tissues in its ability to take in and store large amounts of iodine. Radioactive iodine (I131) is sometimes used as a treatment for papillary thyroid cancer, and this is based on this fact. Iodine was the first "targeted" therapy developed for any type of human cancer, and it was also the first therapy to be used in the treatment of cancer. After surgery for PTC that has persisted or returned, it is not clear what role radioactive iodine (RAI) therapy should play. For patients at high risk of recurrence, current guidelines recommend radioactive iodine ablation (RAI) after initial thyroidectomy to remove

residual thyroid tissue for increased surveillance and management of residual disease ²¹.

Thyroid debris after surgery can be removed with radioactive iodine (RAI), local recurrence can be decreased, and distant metastasis can be monitored with serial thyroglobulin levels and whole-body uptake scans. Although I¹³¹ is widely used, radioiodine therapy is not without negative consequences. RAI can impair quality of life and therefore treatment costs due to side effects such as, but not limited to, acute or chronic xerostomia, acute or chronic sialoadentis and dental caries. Reports of a slightly increased risk of developing primary secondary malignancies following

radioiodine treatment have led to more selective use of radioiodine, particularly in low-risk patients ²².

HLA-G Protein Expression in Papillary Thyroid Carcinoma

Multiple studies have found that HLA-G molecules play crucial tolerogenic roles. The placenta is where HLA-G is most abundantly expressed in the body, and this is where it is thought to play a role in maternal tolerance towards the fetus through its interaction with inhibitory receptors expressed on maternal killer (NK) cells, T cells, and antigen presenting cells (APCs). The expression of HLA-G has been investigated at numerous time points. There has been a lot of focus on the differences between the soluble (G5, G6, and G7) and membrane-bound (G1, G2, G3, and G4) isoforms of, which result from alternative splicing and a handful of amino acid polymorphisms.

In adults, HLA-G expression is rare but has been documented in the context of diseases like cancer, autoimmune diseases, and viral infections. HLA-G expression has been found in a variety of human cancers, including ovarian, gastric, endometrial, breast, renal cell, and lung carcinomas, coetaneous melanoma, hematopoietic tumors, mesothelioma, and trophoblastic tumors, supporting the theory that HLA-G may play a role in tumor development by suppressing the immune response within the tumor microenvironment ²³.

HLA-G staining was seen in tumor cells as well as inflammatory infiltrating tumor and parenchyma

cells in certain instances. Recent studies reveal that using Poly Ab (polyclonal antibody) immunohistochemistry against HLA-G protein boosted the intensity of HLA-G expression in thyroid tissue from papillary thyroid cancer patients compared to controls. The immunoreactivity of HLA-G protein was as follows: No staining (score 0: negative) was observed in less than 10% of the thyroid cells. Faint/barely perceptible staining (+1 score: negative) was detected in more than 10% of the cells. Weak to moderate complete staining was observed in 50-70% of the cells (+2 score: weak positive). Strong overall staining (+3 points: strong positive) was observed in at least 30% of malignancies, of which 64% were considered weakly expressed (+) and 36% were considered to be strongly expressed (++++) or moderately expressed (+). HLA-G mainly showed a membrane-associated pattern, Figs. 1 A, B, C and D. Elevated HLA-G expression is confirmed in thyroid cancer cells, inhibits cytotoxic immune system cells and facilitates tumor escape and progression. HLA-G did not stain in normal thyroid tissue, Fig. 2 A. Esophageal cancer, Fig. 2B, was used as a positive control for HLA-G expression as indicated in the kit manufacturing instructions. This study discovered a variation in the intensity of HLA-G staining through the outer layer of thyroid cells between malignant and normal samples. This conclusion is congruent with the findings of Villena et al, ²⁴, who discovered a greater intensity of HLA-G staining of thyroid cells in PTC patients compared to healthy participants. The findings of this study imply that HLA-G protein production in thyroid cells causes papillary thyroid cancer.

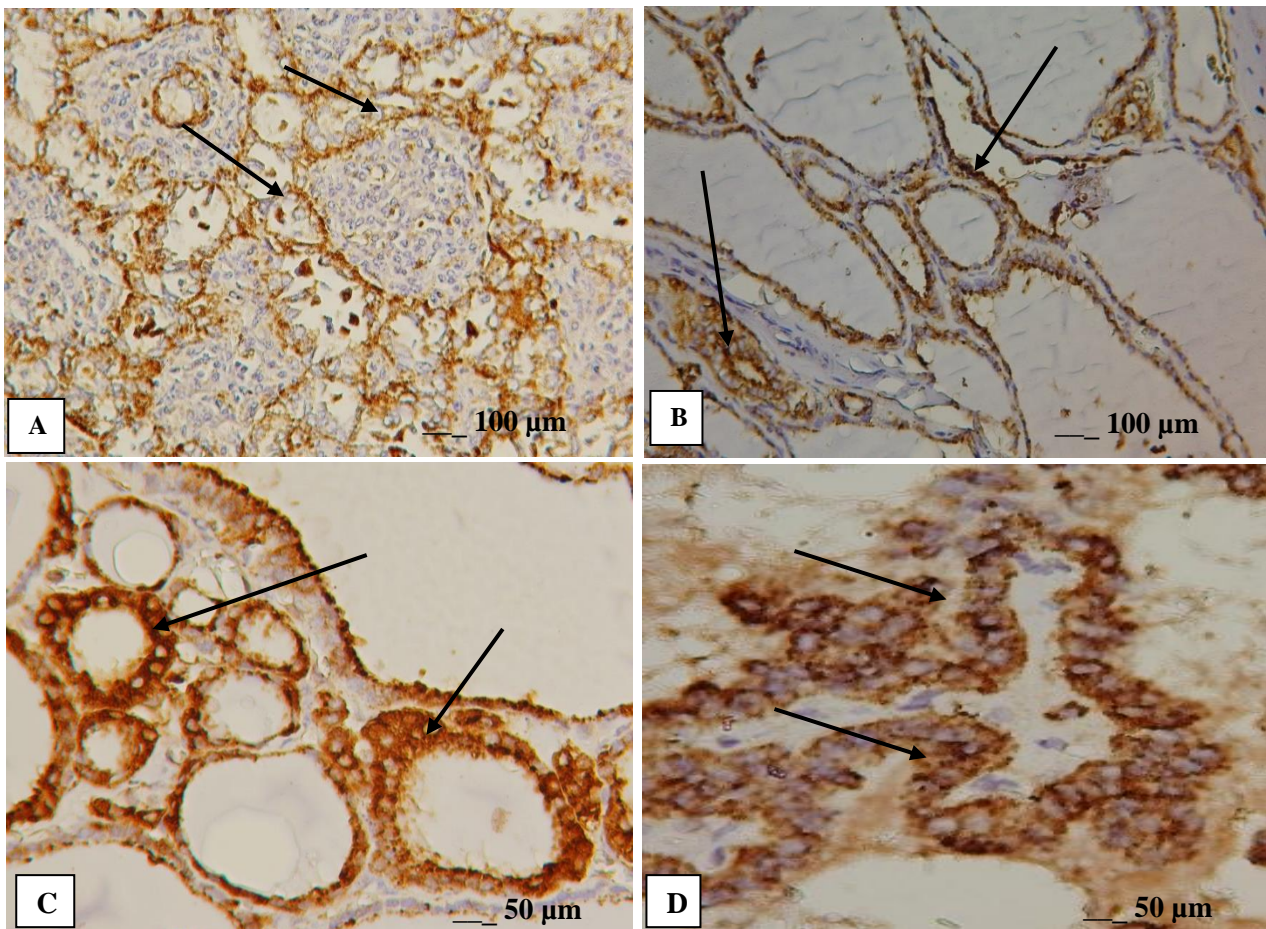


Figure 1. Cross sections in papillary thyroid cancer tissue, IHC, illustrated the positive expression of (HLA-G). cell membrane stained in brown color (arrows), IHC. (A, B) scale bar 100 μ m, 10X, (C, D) scale bar 50 μ m, 40 X, IHC.

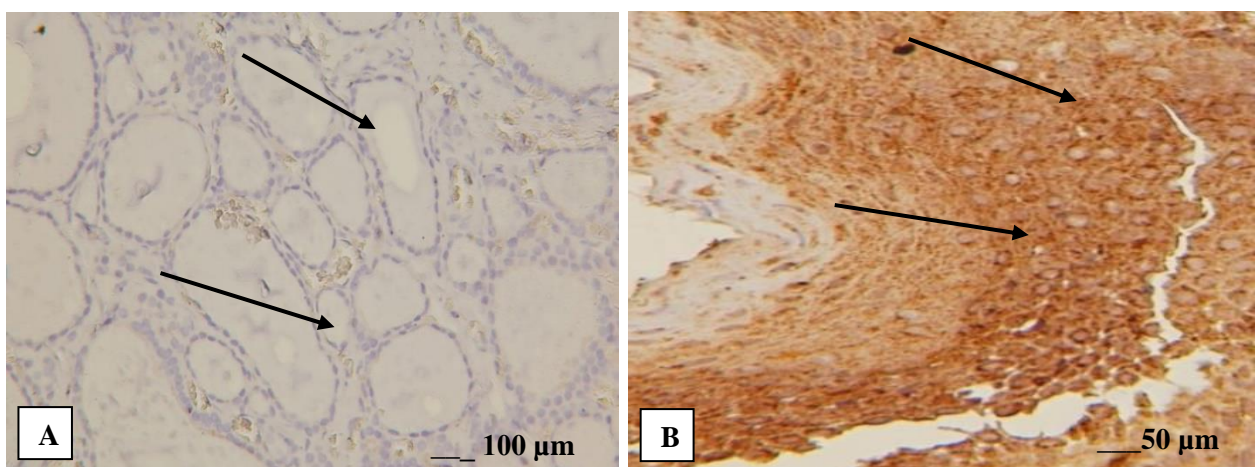


Figure 2. (A) Cross section in normal thyroid tissue, illustrated the negative expression of (HLA-G) represents the negative control, Scale bar 100 μ m, 10X (B) Cross section in esophagus cancer tissue illustrated the positive control of (HLA-G), cell membrane stained in brown color (arrow), Scale bar 50 μ m, 40 X, IHC.

Mononuclear cells with a morphology similar to lymphocytes were found to have infiltrated the PTC parenchyma during the inflammatory response, constituting the HLA-G+ cells. Lefebvre and coworkers found the same thing in 1960. Higher levels of HLA-G expression were observed in high-grade inflammatory breast tumor lesions, suggesting that inflammatory responses may activate HLA-G expression to inhibit host leukocytes' anti-tumor immune response. In many types of solid malignancies, the inflammatory response is taken as an indicator of success because it is based on the type of cell that infiltrates the tumor.

In addition, it was found that HLA-G expression was lost by these inflammatory cells once they were removed from the tumor invasion front. The process of trogocytosis, which involves the transport of membrane vesicles, may provide an explanation for

Conclusion

In this study, HLA-G was found to be associated with the development of papillary thyroid cancer. This marker showed a significant difference ($p \leq 0.05$), therefore it can be considered as a risk

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Authors' Declaration

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are ours. Furthermore, any Figures and images, that are not ours, have been included with the necessary permission for

Authors' Contribution Statement

The work was done in collaboration between the authors. N. H. B. collected the blood samples, biopsies, doing the practical work, analysis of data

this phenomenon. Thus, during trogocytosis, all molecules contained within a particular membrane region are transferred, including those that do not participate in cell-to-cell crosstalk and therefore transfer non-specifically. Temporary membrane uptake that occurs without maturation. By transferring HLA-G from tumor cells to activated cytotoxic NK cells, Caumartin et al.²⁵ demonstrated for the first time that HLA-G-negative tumor cells can evade the immune system by reprogramming effector cells to act as suppressors via a protein that they do not express. To effectively inhibit target destruction via the trogocytosis pathway, only a small number of cells expressing HLA-G are needed. That is to say, an HLA-G positive cell can protect an entire population of cells that are not positive.

factor for papillary thyroid cancer in the Iraqi population and used as a biomarker in the diagnosis of this disease.

re-publication, which is attached to the manuscript.

- Authors sign on ethical consideration's approval.
- Ethical Clearance: The project was approved by the local ethical committee at University of Baghdad.

and wrote of manuscript. R. M. A. read and approved final manuscript.

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التحقق من دور مستضد كريات الدم البيضاء البشرية نوع (ج) في مرضى عراقيين مصابين بسرطان الغدة الدرقية الحليمي

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قسم التقنيات الاحيائية، كلية العلوم، جامعة بغداد، بغداد، العراق.

الخلاصة

مستضد كريات الدم البيضاء البشرية-ج (HLA-G) هو جزيء معقد غير تقليدي للتوافق النسيجي الرئيسي ذو خصائص مناعية مميزة. يعتبر أيضاً علامة مهمة على التحمل المناعي في التهرب المناعي للخلايا السرطانية. يرتبط HLA-G أيضاً ارتباطاً وثيقاً بتطور المرض والتشخيص لمرضى السرطان. الهدف من هذه الدراسة هو مقارنة تراكيز (sHLA-G) القابلة للذوبان قبل وبعد العلاج باليود المشع (RAI) وأيضاً الكشف عن تعبير البروتين HLA-G في أنسجة الغدة الدرقية في المرضى الذين يعانون من سرطان الغدة الدرقية الحليمي (PTC) لدراسة العلاقة بين تعبير HLA-G والحالة السريرية للمريض. تضمن البحث 138 عينة دم من المرضى وعينات السيطرة، بالإضافة إلى 25 خزعة من الغدة الدرقية المحفوظة بشمع البارافين من مرضى سرطان الغدة الدرقية الحليمي (PTC) ومجموعات السيطرة. أظهرت النتائج فروقات معنوية في الأشخاص الذين عولجوا باليود المشع مقارنة بالذين لم يخضعوا للعلاج ($SE = 4.19 \ 0.3, \ 0.08 \ 2.216$) على التوالي. من ناحية أخرى، تمت دراسة تعبير HLA-G في الخلايا السرطانية في سرطان الغدة الدرقية الحليمي، أظهرت النتائج تعبير إيجابي للبروتين المذكور بدرجة قوية في كل العينات المفحوصة. بالنسبة لنمط التصبغ كان واضحاً في أغشية الخلايا أكثر من السائتوبلازم دليل على وجود بروتين HLA-G في الأنسجة المذكورة. تشير هذه النتائج إلى أن HLA-G قد يكون له دور في حدوث سرطان الغدة الدرقية الحليمي.

الكلمات المفتاحية: التشخيص المبكر، سرطان الغدة الدرقية الحليمي، عامل خطورة، مستضد كريات الدم البيضاء-ج، مؤشرات الورم.