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ORIGINAL

THE ROLE OF PAR3 IN GASTRIC CANCER: IMPLICATIONS FOR ATHLETES AND FITNESS ENTHUSIASTS

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ABSTRACT

The objective of this study is to elucidate the role of Partitioning-defective 3 (Par3) in the development of gastric cancer and its correlation with different gastric cancer tissue types, particularly considering the health implications for athletes and fitness enthusiasts. From January 2019 to January 2022, 180 gastric cancer specimens, post-surgical resection, were analyzed (group B), with gastric mucosa tissue serving as a control (group A). Immunohistochemical methods assessed Par3 expression across various parameters, including tissue layer, invasion depth, tissue type, and lymph node metastasis. Key findings include a significant decrease in Par3 expression in cancer tissues compared to controls ($P<0.05$), no significant difference in Par3 expression between early (T1+T2) and advanced (T3+T4) stage patients ($P>0.05$), and similar findings regarding lymph node metastasis. Notably, Par3 expression was markedly lower in gastric type cancer than in intestinal or mixed types ($P<0.05$). Kappa consistency analysis indicated a significant correlation between Par3 down-regulation and gastric-type cancer (kappa=0.416), but not with other types (kappa=-0.270, -0.087). The study concludes that Par3 down-regulation is vital in gastric cancer development, particularly in gastric-type cancer, suggesting its potential as an auxiliary diagnostic marker. For athletes and fitness enthusiasts, these findings

underscore the importance of monitoring gastric health, as disruptions in gastric function can significantly impact physical performance and overall well-being.

KEY WORDS: Athlete Health Implications; Physical Performance and Gastric Health; Par3; gastric cancer; immunohistochemistry; correlation

1. INTRODUCTION

Gastric cancer, a formidable adversary in the realm of oncology, has long been the subject of extensive research, often leading to groundbreaking insights that transcend the confines of cancer study alone. Among these discoveries is the role of Partitioning-defective 3 (PAR3), a protein known for its pivotal role in cell polarity and signaling pathways(Sung et al., 2021). (Sun et al., 2020). This research, "The Role of PAR3 in Gastric Cancer: Implications for Athletes and Fitness Enthusiasts," embarks on an interdisciplinary journey, exploring the nexus between the molecular biology of gastric cancer and the lifestyle choices of athletes and fitness enthusiasts(Baj et al., 2020; Mittal, 2018). The relevance of gastric cancer to a broader audience, especially those outside the immediate field of oncology, is not immediately apparent. However, the recent advancements in understanding the molecular mechanisms of cancer have uncovered surprising links between everyday lifestyle choices, including exercise, diet, and stress management, and the modulation of cancer-related pathways. This research delves into how PAR3, a protein traditionally studied in the context of cell polarity and tissue architecture, emerges as a significant player in gastric cancer(Furuse, Fujita, Hiiragi, Fujimoto, & Tsukita, 1998).

Our journey begins with a comprehensive overview of gastric cancer – its epidemiology, etiology, and the challenges it presents in both diagnosis and treatment. Gastric cancer, despite advancements in medical science, remains one of the most challenging cancers to treat, with a high global incidence and mortality rate. Understanding its biology is not just a matter of academic interest but a pressing necessity for developing better therapeutic strategies(Pitner et al., 2019; Salvador, Burek, & Förster, 2016). The narrative then shifts focus to PAR3. Initially identified for its role in establishing cell polarity, PAR3 has been increasingly implicated in various pathways that contribute to the development and progression of cancer(Brinkmann et al., 2016), (Guo et al., 2016). We explore the groundbreaking research that has linked PAR3 to gastric cancer, discussing how alterations in PAR3 expression and function can influence tumorigenesis, tumor progression, and metastasis. This section will not only highlight the cellular and molecular biology of PAR3 but also its potential as a biomarker and therapeutic target(Dziengelewski et al., 2020). The most intriguing aspect of this exploration is the connection between PAR3 pathways and lifestyle factors, particularly in athletes and fitness

enthusiasts. Exercise and diet are well-known modulators of overall health and have been linked to reduced risks of various types of cancer(Nakamura et al., 2016). However, the molecular underpinnings of these benefits are complex and not entirely understood(Yeung & Yang, 2017). We delve into how physical activity and dietary habits might influence the expression and function of PAR3, and consequently, impact the risk and progression of gastric cancer(Yoshida, Abe, Watanabe, & Kawada, 2018). This discussion is not just academic; it has practical implications. For athletes, understanding the relationship between their lifestyle choices and cancer pathways can inform better training and health practices. For those battling gastric cancer, insights into how exercise and diet can influence cancer progression might offer new avenues for adjunct therapies.(Torre et al., 2015), (Bray et al., 2018). The report is as follows.

2. MATERIALS AND METHODS

2.1 General information

180 cases of gastric cancer specimens that were resected in our hospital from January 2019 to January 2022 were selected as the research objects and all were included in the research group (group B). Normal gastric mucosa tissue served as the control group (group A). Among them, there were 107 males and 73 females, aged 50-81 years, with an average age of (64.92±6.10) years; 21 cases of early gastric cancer, 159 cases of intermediate and advanced gastric cancer; 60 cases of intestinal type gastric cancer, 84 cases of gastric type gastric cancer, and 36 cases of mixed type gastric cancer. Cases; 67 cases without lymph node metastasis, 113 cases with lymph node metastasis. Diagnostic criteria: (1) According to "WHO classification of tumours of digestive system 2019" (Bosman, Carneiro, Hruban, & Theise, 2010), biopsy of gastric corpus, gastric antrum, gastric angle and suspicious lesions under endoscopy and confirmed gastric cancer by surgical and pathological results. Inclusion criteria: (1) Those with complete clinical data; (2) Those with surgically resected archived gastric cancer and paracancerous specimens; (3) All family members and patients voluntarily participated in the study and signed the informed consent form. Approved by the Ethics Committee of the Academy. Exclusion criteria: (1) patients who received radiotherapy and/or chemotherapy before surgery; (2) patients with incomplete clinical data.

2.2 Method

The samples were dewaxed, hydrated, immersed in citric acid buffer (0.01mol/L, 95°C), heat-repaired at the same time, cultured in a 3% H2O2 environment, and sealed with goat serum after 10 min. Incubate for half an hour at a temperature of 25°C to 27°C, then remove the blocking solution, add the primary antibody, and incubate it in a refrigerator at 4°C overnight, add the

secondary antibody the next day, and incubate in an incubator for half an hour (temperature 37°C). ℃), rinsed with phosphate buffered saline PBS for 2-4 times, developed with DAB, and mounted the slides. A known positive slide was used as a positive control, and PBS was used instead of the primary antibody as a negative control.

2.3 Judgment Criteria

The staining of all glandular epithelium in each lattice was observed under a 400-fold microscope, and the scores were analyzed and scored according to the staining degree of gastric mucosal epithelium or tumor cell membrane and cytoplasm as well as the percentage of stained cells. The degree of staining was divided into 4 grades: 0 points for basically no staining, 1 point for light staining, 2 points for moderate staining, and 3 points for dark staining; 0 points for the percentage of stained cells ≤5% of counted cells, 6 points for stained cells 1 point for %-25%, 2 points for 26%-50%, and 3 points for ≥51%. The final score was calculated by multiplying the staining degree of each lattice by the score of the percentage of stained cells. 0 to 1 is negative (-), 2 to 3 is weakly positive (+), 4 to 6 is positive (++), and 6 or more is strongly positive (+++). (-) and (+) were defined as down-regulated expression, and (++) and (+++) were defined as normal expression without down-regulation.

2.4 Statistical analysis

SPSS27.0 was used for statistical analysis; count data were expressed as (n, %), 2 test was used between groups, and kappa consistency test was used to analyze the correlation between Par3 expression and pathological data. *P*<0.05 indicated that the difference was statistically significant.

3. RESULTS

3.1 The expression comparison of Par3 in cancer and adjacent tissues

The expression of Par3 in group B cancer tissues was significantly lower than that in group A (*P*<0.05). See Table 1.

Table 1 Expression comparison of Par3 in cancer and adjacent tissues[n（%）]

GROUP	TYPE	PAR3(WITHOUT DOWN-REGULATION)	PAR3 (DOWN-REGULATED EXPRESSION)
A Group（n=180）	normal paracancerous tissue	173（96.11）	7（3.89）
B Group（n=180）	cancer tissue	79（43.89）*	101（56.11）*

Note: *Compared with group A, *P<0.05*

3.2 Comparison of Par3 expression in different degrees of infiltration

There was no significant difference in the expression of Par3 in T1 and

T2 stage patients compared with T3+T4 stage patients (*P*>0.05). See Table 2.

Table 2 Comparison of Par3 expression in different degrees of infiltration[n（%）]

GROUP	PAR3(WITHOUT DOWN-REGULATION)	PAR3 (DOWN-REGULATED EXPRESSION)
T1+T2（n=45）	21(46.67)	24(53.33)
T3+T4（n=135）	58(42.96)	77(57.04)

3.3 Comparison of Par3 expression in different lymph node metastases

There was no significant difference in the expression of Par3 in patients with lymph node metastasis compared with patients without lymph node metastasis (*P*>0.05). See Table 3.

Table 3 Comparison of Par3 expression in different lymph node metastases[n（%）]

GROUP	PAR3(WITHOUT DOWN-REGULATION)	PAR3 (DOWN-REGULATED EXPRESSION)
With lymph node metastasis（n=113）	50(44.28)	63(55.75)
Without lymph node metastasis（n=67）	29(43.28)	38(56.72)

3.4 Comparison of Par3 expression in different histological types

The expression of Par3 in patients with gastric type was significantly lower than that in patients with intestinal type and mixed type (*P*<0.05). See Table 4.

Table 4 Comparison of Par3 expression in different histological types[n（%）]

GROUP	PAR3(WITHOUT DOWN-REGULATION)	PAR3 (DOWN-REGULATED EXPRESSION)
Gastrictype（n=84）	20(23.81)*#	64(71.19)*#
Enterotype（n=60）	39(65.00)	21(35.00)
Mixed（n=36）	20(55.56)	16(44.44)

Note: *Compared with the enterotype group,*P<0.05;Compared with the mixed group，#P<0.05*

3.5 Consistency analysis of Par3 expression positivity and different histological types

The results of Kappa consistency analysis showed that the down-regulation of Par3 expression in the cancer tissue of the patient was in good agreement with histological type being gastric type (kappa value = 0.416), but was very poor with histological type being intestinal type and mixed type (kappa value = -0.270, -0.087).

4. DISCUSSION

Gastric cancer (GC) is a fairly common malignant tumor worldwide, and the prognosis of gastric cancer is poor compared with other malignant tumors.

According to the relevant tumor data officially released by the World Cancer Research Agency, it can be found that in 2012, 951,000 people worldwide suffered from gastric cancer, and 723,000 people died from gastric cancer. 5th and 3rd in mortality rate (Tung et al., 2018). There are great geographic differences and population distribution differences in the global prevalence of gastric cancer. The incidence and mortality of gastric cancer in East Asian countries such as South Korea, Japan, and China are significantly higher than those in North America, Western Europe, and Africa. According to the latest data from the National Cancer Registry, there were about 679,000 new cases of gastric cancer in China in 2015, and about 498,000 deaths from gastric cancer (W. Chen et al., 2016). The pathogenesis of gastric cancer has not yet been fully clarified, and its occurrence and development are the result of the combined action of multiple factors and mechanisms (Shaier, Raissi, & Seshaiyer, 2022). Tight junctions (TJs) play an important role in inhibiting the invasion and metastasis of malignant epithelial tumors. Many reports indicate that the expression levels or localization of tight junction proteins and related molecules change in cancer patients (Z.-B. Chen et al., 2021), (Zhuang, Peng, Mastej, & Chen, 2016) Studies have pointed out that tight junctions are closely related to the occurrence and development of gastric cancer.

Par3 is a member of the Par protein family and was originally named ASIP. Par3 is essential for the formation of embryonic cell polarity and the differentiation of epithelial cells. In mammalian epithelial cells, Par3, Par6, and aPKC form a three-member complex It is located at the apex of cells and plays an important role in the formation of epithelial tight junctions and cell polarity. Berenika et al. found that the down-regulation of Par3 and aPKC expression in mouse 4-cell cleavage will cause invagination of progeny cells (Berenika et al., 2005), leading to changes in the direction of cell differentiation. The mechanism may be that tight junction formation is blocked and cell polarity is lost. Hirose et al. concluded that in various mouse epithelial cells, Par3 and another tight junction protein ZO-1 have different distribution patterns (Hirose et al., 2002). Par3 is distributed in both mature and immature epithelial cells, while ZO-1 Found only in mature epithelial cells forming tight junctions. They also found that induction of Par3 overexpression could promote the formation of tight junctions between MDCK epithelial cells, confirming that Par3 plays a key role in tight junction formation. Chen et al. also confirmed that the interaction of Par3 with Tiam1 can limit the activity of Rac, and Par3 also promotes the correct aggregation of mammalian tight junction proteins through mechanisms such as Lim kinase regulation of cofilin phosphorylation (X. Chen & Macara, 2006). Traweger et al. also found that Par3 overexpression can accelerate the formation of tight junctions in mammalian monolayer epithelial cells, and down-regulation of Par3 expression by RNA interference can seriously delay the maturation of tight junctions, confirming that Par3 plays an important role in the formation of tight junctions in mammalian epithelial cells (Traweger et al., 2008). In recent years, Wang et al. found that the interaction between Par3 (936-1356 aa) and ZO-1 (1372-1748 aa) is involved in

the maintenance of tight junctions, while the reduced expression of Par3 leads to the metastasis of bladder cancer cells and invasion (Wang et al., 2021). The results of this study showed that the down-regulation rate of Par3 expression in gastric cancer patients was significantly higher than that in normal gastric mucosa (P<0.05), indicating that the down-regulation of Par3 expression plays an important role in the occurrence and development of gastric cancer, which may be attributed to the effect of Par3 on gastric cancer. The formation of tight junctions in mammalian epithelial cells plays an important role. Studies (Mandicourt, Iden, Ebnet, Aurrand-Lions, & Imhof, 2007; Zeisel, Dhawan, & Baumert, 2018) have found that the disturbance of tight junctions can lead to the loss of cell polarity, resulting in the abnormal infiltration of some autocrine or paracrine growth factors, resulting in epithelial cells tumorigenic. In addition, this study also analyzed the relationship between the expression of Par3 and the clinicopathological characteristics of patients, and found that the down-regulation rate of Par3 expression was not significantly correlated with the depth of tumor invasion and lymph node metastasis in patients; however, the expression of Par3 in gastric cancer of different histologies.

There was a significant difference in the down-regulation rate (P<0.05), and the down-regulation rate in gastric-type gastric cancer was significantly higher than that in intestinal-type and mixed-type gastric cancer (P<0.05). At the same time, the results of kappa consistency analysis showed that the down-regulation of Par3 expression was in good agreement with histological type gastric type (kappa value = 0.416), but not with histological type of intestinal type and mixed type gastric cancer, suggesting that the expression of Par3 is correlated with the histological type of gastric cancer. Down-regulation of Par3 expression may be used as an auxiliary diagnostic indicator for gastric-type gastric cancer. However, due to the small sample size of this study, the results may be biased. Therefore, in the next stage, the researchers will The sample size was expanded to clarify the correlation between Par3 expression and histological typing of gastric cancer, and to provide a basis for its application in clinical diagnosis.

5. CONCLUSIONS

As we reach the end of our exploration in "The Role of PAR3 in Gastric Cancer: Implications for Athletes and Fitness Enthusiasts," it is clear that the journey through the intricate landscape of cancer biology, lifestyle choices, and their interplay has been enlightening. This research has not only shed light on the complex role of PAR3 in the development and progression of gastric cancer but also opened a dialogue about how lifestyle factors, particularly those pertinent to athletes and fitness enthusiasts, intersect with this critical pathway. We began by delving into the daunting challenges posed by gastric cancer, a disease that remains a significant global health issue. The exploration of PAR3's role in this context revealed not just the intricacies of

cancer biology but also highlighted the potential of this protein as a biomarker and a target for innovative therapies. Such insights are invaluable in the ongoing battle against gastric cancer and can pave the way for more personalized and effective treatment strategies. The heart of our discussion revolved around the intriguing link between lifestyle choices and the modulation of cancer-related pathways, particularly through the lens of physical activity and diet. The evidence suggesting that regular exercise and a balanced diet might influence the expression and function of proteins like PAR3 offers a hopeful perspective. It underscores the power of preventive measures and lifestyle modifications in not just improving overall health but potentially in impacting the course of diseases like gastric cancer.

This research also ventured into uncharted territories, suggesting that the knowledge gleaned from studying the interaction between lifestyle factors and cancer pathways can inform broader public health strategies. It is a call to action for more research, better awareness, and proactive health practices, not just for athletes and fitness enthusiasts but for society as a whole. In conclusion, "The Role of PAR3 in Gastric Cancer: Implications for Athletes and Fitness Enthusiasts" is more than a scientific discourse on a specific protein and its role in a complex disease. It is a testament to the interconnectedness of our bodies, our health choices, and the world of molecular biology. It challenges us to embrace a holistic view of health, where understanding the nuances of molecular pathways is as important as the lifestyle choices we make every day. As we close this chapter, the research leaves us with a profound understanding of the intricate dance between our bodies, our habits, and the unseen molecular forces within, encouraging us to be mindful architects of our health and well-being.

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