

## EFFECT OF EXPRESSION OF TAFAZZIN (TAZ) ON THE DEVELOPMENT OF CERVICAL CARCINOMA

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**ABSTRACT :** Cervical cancer represents one of the possibly preventable cancer. The study was designed to find the possible correlation of Tafazzin on the progression of cervical carcinoma. Two groups of paraffinized blocks were included. The study group of 30 cervical tumors as well as 15 biopsies of healthy cervical tissues. After sectioning on a positive charge, immunohistochemical application (IHC) was performed to detect Tafazzin expression. Eighty percentage (27 out of 30) of the studies group showed positive overexpression as shown in with a significant association of the expression with cervical cancer with a significant association. There is a possible role of TAZ in hastening the development of cervical cancer through different mechanisms. Further studies with large samples are recommended.

**Key words :** Tafazzin, immunohistochemistry, cervical cancer.

### INTRODUCTION

Cervical cancer has a global impact on both morbidity and mortality among women and has a definite correlation with high-risk types of HPV. On the other hand, it can be a possibly preventable infection (Yim and Park, 2007; Khasman *et al*, 2019).

From the first utilization of Papanicolaou (Pap) in the screening of cervical malignancy and despite its great impact on the earlier diagnosis and prognosis of cervical cancer, which decreased the cancer mortality, the women worldwide still died because of metastasis, this opened the way for the investigation for different molecular signaling pathways to understand this cancer development (Lee and Shen, 2012; Khasman *et al*, 2019). Human papillomavirus (HPV) has been found associated with Cervical lesions were in patients with H-SIL biopsy revealed genotypes 16 and/or 18. The CH<sub>2</sub> technique is useful as a screening procedure, while PCR is interesting to identify HPV-HR genotypes (Hachim *et al*, 2020).

The gene tafazzin encodes for a human protein known as TAZ protein, which has anaphospholipid-lysophospholipid transacylase activity (Xu *et al*, 2009; Xu and Ren, 2006) that enables it to re-modulate cardiolipin glycerophospholipid located in the inner mitochondrial membrane that is important in the stabilization of mitochondrial respiratory chain cascades and triggering apoptosis (Pathak *et al*, 2014).

Different evidences pointed out that TAZ protein could be one of the casual links between mitochondrial dysfunction and different inflammatory illnesses (Acehan *et al*, 2011; Wilson *et al*, 2012).

Recently, the increased evidences of TAZ involvement in different cancers such as colon, thyroid and rectal cancers opened the window for researchers to investigate its role and mechanism in the tumorigenesis of different cancers such as in the squamous cell cervical carcinoma (Liu *et al*, 2018) and this make the rationale to study the possible impact of Tafazzin expression in some Iraqi cases with cervical carcinoma.

### MATERIALS AND METHODS

Two groups were used in this study, the apparently healthy group of fifteen archival blocks and the study group of thirty archival tissues of cervical cancer. All these samples were collected from different governmental and private laboratories in Baghdad.

For each block, two slides with 4 µm thickness were used, for routine hematoxylin and eosin staining and the other on a positively-charged slide for an immunohistochemical procedure using anti-Tafazzin from Santa Cruz Biotechnology Company and Mouse and Rabbit Specific HRP/DAB Detection from (ABCAM) company.

After dewaxing and rehydration, the endogenous

peroxidase activity and non-specific binding were blocked by incubation with peroxide block and protein block ready to use reagents, respectively. To remove the fixative effect, heat mediated antigen retrieving was used with citrate buffer pH 6 before commencing with IHC staining protocol. Slides were then incubated sequentially with diluted primary antibody for 1hour at 37°C and then secondary antibody was applied for 10 minutes at room temperature followed by incubation with Streptavidin-HRP for 10 minutes at 37°C. Diaminobenzidine hydrochloride (DAB) was used as the chromogen to visualize peroxidase activity. Sections were counterstained with Mayer's hematoxylin for 30 seconds, dehydrated and mounted (Khashman *et al*, 2018).

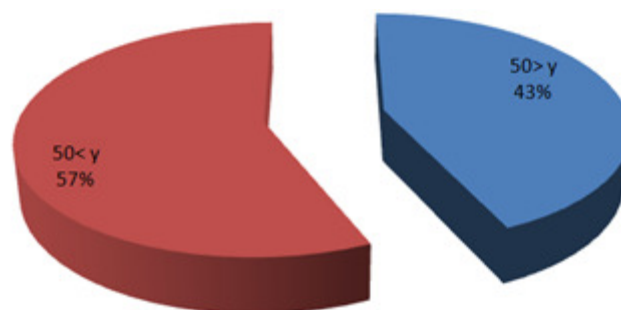
### Statistical analysis

In order to find out the association of EBV LMP1 expression with both cervical cancer and normal tissues, Fisher exact test was applied considering the P-value ( $<0.05$ ) as statistically significant (<http://www.socscistatistics.com>).

### RESULTS

Fifty four year is the mean age of the cervical cancer patients with a percentage of 57% for the patients with age above 50 years and 43% for those less than 50 years (Fig. 1).

Regarding TAZ expression, 90% (27 out of 30) of the studies group showed positive overexpression as shown in Table 1 with a significant association of the expression with cervical cancer.



**Fig. 1 :** The distribution of age groups of the studied samples.

**Table 1 :** The expression of TAZ in the studied groups.

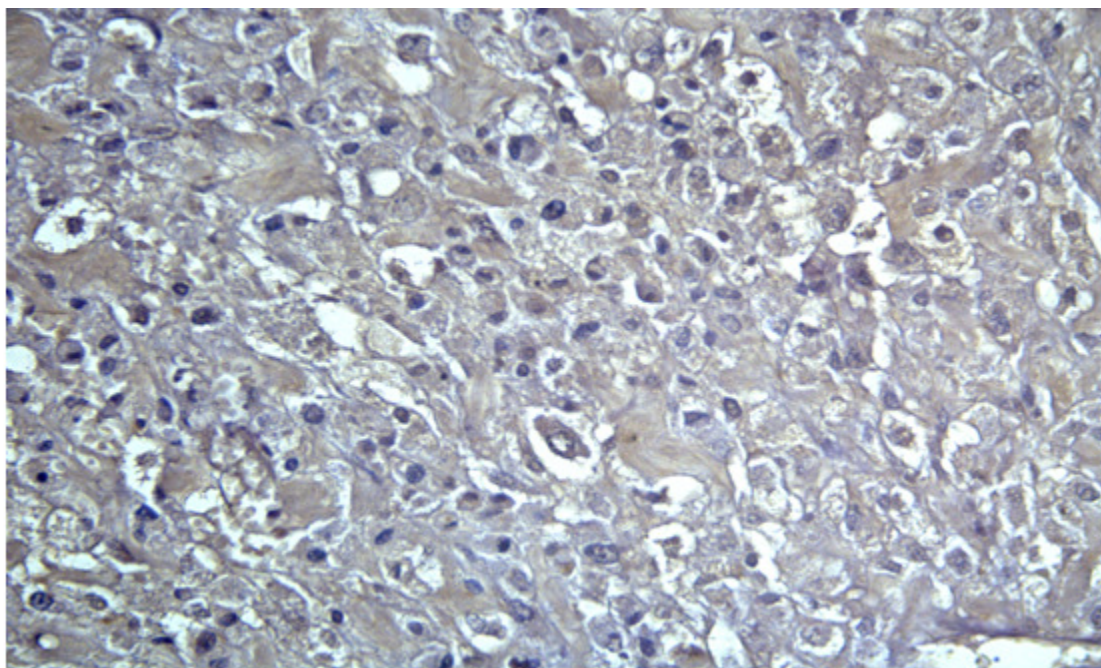
IHC expression	Cervical cancer	Normal tissue	Marginal Row Totals
TAZ Positive	27	5	32
TAZ Negative	3	10	13
Total	30	15	45

\*P= 0.0002.

### DISCUSSION

From the first essential research in the 1920s done by Warburg, extensive scientific researches were published on the matter of Otto Warburg theory highlighted the emerging role of defects occurs during mitochondrial respiration, which re-defined cancer as a metabolic disease (Kiebish *et al*, 2008).

Moreover; tafazzin is an important enzyme for cardiolipin-remodeling and maintains the mitochondrial cardiolipin and hence has its importance in mitochondrial energy production and apoptosis and as a result in the cellular metabolism (Chen *et al*, 2017). The hypothesis



**Fig. 2 :** Immunohistochemistry positive expression of TAZ results in cervical cancer (40x). The DAB produce (Brown) signal, Harris Hematoxylin (the counter stain) produce (purple) color.

of the current study suggests the role of TAZ in the progression of cervical cancer and in this regards, the output of our study revealed that the vast majority of the studied cases 90% (27 out of 30) showed overexpression of Tafazzin and this coincides with the findings of Chen *et al* (2017) both *in vivo* and *in vitro* which confirm this role of the Tafazzin protein in enhancing the carcinogenesis of cervical carcinoma and inhibitions of cervical cells programmed cell death. Notably, the cellular localization of TAZ expression in the current study (Fig. 2) refers to its role in cancer development and metastasis which comes in parallel with the theory of Liu *et al* (2018.)

The major role of the TAZ during cardiolipin remodeling and its localization of Tafazzin in the membrane of the mitochondria enables it to induce carcinogenesis through mitochondrial pathway in different strategies, like decreasing cleavage of caspases (Houtkooper *et al*, 2009). Furthermore, some researchers pointed out the importance of TAZ oncoprotein in both cell proliferation and Epithelial–Mesenchymal transition which were crucial in the carcinogenesis (Ibeanu, 2011) and the cellular localization can prognose the possible role of the tafazzin if it acts as an oncogene (nuclear localization) downstream of the PI3K/AKT pathway or a tumor suppressor protein (Debaugnies *et al*, 2018).

## CONCLUSION

There is a possible impact of TAZ in hastening the development of cervical cancer through different mechanisms. Studying the TAZ role in the initiation and development of different cancers and its potency as a therapeutic target is a burgeoning field and extensive further studies are required to fulfill this unmet medical part.

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