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Expression of FOXP3, OCT4 and SOX2 Proteins in Cervical Cancer

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Abstract

Cervical cancer is one of the most common oncologic disease of reproductive system which is the leading cause of cancer-related death for women in countries with low and middle income. High mortality rates are due to the diagnosis at late stages, ineffective treatment options for advanced disease and lack of effective biomarkers for disease monitoring. The importance of biomarkers is obvious in case of cervical cancer treatment resistance and recurrence. We expect that both phenomena are linked with the presence and activation of cancer stem cells. The last ones are subpopulation of cancer cells with stem cells specific morphologic, biochemical and physiologic features due to the expression of specific proteins. FOXP3, OCT4 and SOX2 proteins belong to the group of such kind of proteins. The present study aimed determination of FOXP3, OCT4 and SOX2 proteins expression by ELISA method in collected plasma samples of patients with diagnosed cervical cancer and CIN in comparison with control group. The high expression of FOXP3 has been revealed in plasma samples of cervical cancer patients. OCT4 and SOX2 showed high expression plasma samples of patients with CIN, this was the case of proteins co-expression. We assume, that the FOXP3, OCT4 and SOX2 proteins are important biomarkers for cervical cancer. Our research data suggest the necessity of further investigation into FOXP3, OCT4 and SOX2 in cervical cancer.

Keywords: Cervical Cancer; Cervical Intraepithelial Lesion; FOXP3; OCT4; SOX2

Introduction

Oncology diseases, their screening, treatment and monitoring are the top actual healthcare issues. The available data are underestimating the true cancer incidence and cancer-related mortality [1]. One of the most common oncologic disease of reproductive system is cervical cancer. It is a leading cause of cancer-related death for women in countries with low and middle income [2-4]. High mortality rates are related with diagnosis at late stages, ineffective treatment options for advanced disease and lack of effective biomarkers for monitoring of treatment and advanced disease. The last option is of utmost importance in case of treatment (i.e., radiation therapy) resistance and cervical cancer recurrence. We expect that both phenomena are linked with the presence and activation of Cancer Stem Cells (CSCs). These cells are subpopulation of cancer cells with stem cells specific morphologic, biochemical and physiologic features. CSCs have the unique ability to differentiate into multiple cellular types. In case of cervical cancer treatment (i.e., radiation or chemical therapy) is targeted on cancer cells, but some neoplastic cells can survive and acquire resistance to the used treatment. The elimination of such cells with the properties of CSCs is very difficult [5-8].

The background of CSCs unique features is the expression of specific proteins. One of such proteins is FOXP3. It is coded by Foxp3 gene located in the short arm of X chromosome. The stimulation of T cells by antigen-presenting cells ensures expression of FOXP3 and "activation" of suppressor function [9]. The mechanism is important for cancer cells escape from immune response [10]. Among CSC specific markers are octamer-binding transcription factor 4 (OCT4) and sex determining region Y-box 2 (SOX2). Both proteins are transcriptional factors, OCT4 is a member of POU (Pit-Oct-Unc) transcriptional factor family. The expression of this protein is important for pluripotency specific to stem cell and differentiation process by which the type and fate of embryonic stem cells will be determined. Expression of OCT4 in CSCs correlates with self-renewal and tumorigenesis. Furthermore, it has been experimentally shown that OCT4 expression is linked with low differentiation of tumor cells and metastasis development [5]. SOX2 is a transcription factor, which belongs to SRY-related HMG-box (SOX) family. It is involved in stimulation of the adult cells reprogramming into induced pluripotent stem cells and maintenance of stem cell-like properties in cancer. SOX2 is highly expressed in premalignant lesions (i.e., lung squamous dysplasia and carcinoma in situ in lung) [5].

Although prior studies provide some data on FOXP3, OCT4 and SOX2 proteins expression during tumorigenesis, but the prognostic importance of these proteins as well as their biomarker role in monitoring of oncologic diseases aren't clearly defined. In this study we investigated the cervical cancer and cervical intraepithelial neoplasia specific fate of FOXP3, OCT4 and SOX2 proteins expression in comparison with control group.

Materials and Methods

The present study was conducted in frames of Petre Shotadze Tbilisi Medical Academy Funding program for Development and Support of Scientific Research Projects - "Expression of FOXP3 gene

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as the risk factor of metastasis development". It was approved and monitored by the Bioethics and Granting-Research Committees of Petre Shotadze Tbilisi Medical Academy (Tbilisi, Georgia). All procedures performed in the present study were in accordance with the Helsinki Declaration of 1975, as revised in 2000.

The study aimed performance of ELISA analysis to determine the expression of FOXP3, OCT4 and SOX2 proteins in collected plasma samples. The ELISA kits produced by the company "MyBioSource" have been used. The kits were for research use only. The ELISA analysis have been performed in the research-educational laboratory of Petre Shotadze Tbilisi Medical Academy accordingly with the provided, kit specific manuals. The ELISA analysis results were read at 450 nm wavelength by usage of Huma Reader.

For the study in May-August 2019 a total 100 plasma samples have been collected from the patients of the Research Institute of Clinical Medicine (Tbilisi, Georgia). 90 plasma samples were collected from patients with cervical cancer and Cervical Intraepithelial Neoplasia (CIN); amongst the mentioned 90 plasma samples 34 plasma samples were collected from the patients with cervical cancer and 56 plasma samples from the patients with diagnosed CIN. 10 plasma samples of patients those were negative for intraepithelial lesion or malignancy were used as control group in the frames of our study. Communication with patients as well as collection and labeling of plasma samples has been performed by the responsible medical personnel of the Research Institute of Clinical Medicine. Plasma samples have been provided to our research group anonymously, by labeling it wasn't possible to determine the sample category (i.e., patient with diagnosed cervical cancer/patient with diagnosed CIN/control group).

Statistical analysis has been performed by using SPSS v.21.0 software (SPSS Inc., Chicago, IL). A value of $p<0.05$ was considered as statistically significant.

Results and Discussion

As it was mentioned above, the present study aimed determination of FOXP3, OCT4 and SOX2 proteins expression by ELISA method in collected plasma samples of patients with diagnosed cervical cancer and CIN in comparison with control group (Table 1). It has been revealed, that the rates of FOXP3, OCT4 and SOX2 proteins expression in plasma samples of control group are low. The high rates of FOXP3 expression are detected in plasma samples of patients with cervical cancer diagnosis as well as CIN; it is more obvious in plasma samples of patients with cervical cancer. The high rates as well as co-expression of OCT4 and SOX2 has been revealed in plasma samples of patients with CIN. In case of cervical cancer, the expression of OCT4 is reduced, but SOX2 is still highly expressed.

It has been determined by our study that FOXP3 is of great importance for cervical cancer progression. FOXP3 may affect regulation of proliferation, reduce the apoptosis, promote cell cycle progression, increase the invasion of cervical cancer cells and enhance their malignancy. The growth, infiltration and metastasis of cancers are performed with involvement of multiple signaling pathways and a lot of factors [11]. Additional studies are required to determine the role of FOXP3 in cervical cancer development as well as the expression of FOXP3 protein in case of human papillomavirus infection.

Table 1: Expression of FOXP3, OCT4 and SOX2 proteins determined by ELISA method.

Protein	Detection range accordingly with the ELISA kit	Plasma samples - cervical cancer group	Plasma samples-CIN group	Plasma samples-control group
FOXP3	0.31-20 ng/ml	18.7 (p=0.013)	13.2 (p=0.020)	0.01 (p=0.010)
OCT4	0.16-10 ng/ml	4.4 (p=0.021)	9.8 (p=0.032)	0.03 (p=0.017)
SOX2	0.156-10 ng/ml	9.2 (p=0.019)	7.9 (p=0.029)	0.02 (p=0.010)

As it was stated above, OCT4 and SOX2 are important transcriptional factors essential for pluripotency and self-renewal of CSCs. The preliminary data on these proteins altered expression during progression of different cancers have been reported [12-14]. The role of SOX2 in cell cycle regulation, DNA repair and stem cells self-renewal has been reported too [15]. It has been revealed that high expression of SOX2 is associated with low rates of cellular differentiation and can contribute to invasion of cancer cell lines [16]. The results of the present study demonstrated, that the expression of OCT4 and SOX2 is increased in cervical cancer and CIN cases in comparison to control group. Notably, OCT4 and SOX2 expression has been obviously increased in CIN cases, but the expression of OCT4 protein in cervical cancer cases isn't so high. The absence of correlation between OCT4 and SOX2 proteins expression in cervical cancer cases is confusing, because OCT4 and SOX2 are cooperatively acting and self-regulate themselves via OCT4/SOX2 complex in embryonic stem cells [17,18]. We expect that OCT4 and SOX2 might function independently, or activity of one or both proteins can be inhibited and their functional connection can be lost during tumor progression. Further study is required to clarify this question and determine the link between OCT4 and SOX with other biomarkers (i.e., CEA, TP53 and etc.) and human papillomavirus infection.

Conclusion

The study investigated the expression of FOXP3, OCT4 and SOX2 proteins by ELISA method in plasma samples of patients with diagnosed cervical cancer and CIN in comparison with control group. The high expression of FOXP3 has been revealed in plasma samples of cervical cancer patients. OCT4 and SOX2 showed high expression in plasma samples of patients with CIN, this was the case of proteins co-expression. We assume, that FOXP3, OCT4 and SOX2 proteins are important biomarkers for cervical cancer. Our research data suggest the necessity of further investigation into FOXP3, OCT4 and SOX2 and their role in cervical cancer.

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