

TOPIC

INNOVATIVE THERAPIES

Response to radiation in tumor biopsies from colorectal cancer patients

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Introduction

Radiotherapy plays an important role in colorectal cancer treatment. It has been shown that the scheme of chemoradiotherapy followed by surgery is the optimal way, to date, to treat rectal cancer in stages II and III mainly (locally advanced). The advantages provided by radiotherapy in this tumor are numerous, such as reduction in tumor size and stage, decrease in locoregional recurrence, increase in overall survival, and a higher rate of preservation of the anal sphincter. The latter is essential for a better quality of life for patients after surgery. However, the appearance of radiation-resistant cells can lead to treatment failure.

Objectives

The aim of this work is to study the response to radiation of colorectal cancer cells from patients' biopsies in order to analyze the resistance mechanisms involved and the definition of new molecular markers for innovative therapies and precision medicine.

Methods

A PubMed search was performed using the keywords “colorectal neoplasms”, “radiotherapy” and “resistance”. Articles published from 2014 related to studies performed in tumor biopsy samples were included. The exclusion criteria included animal studies, cultured tumor cells, and cancer stem cells.

Results

Various authors have obtained biopsies from patients with colorectal adenocarcinoma and, in some cases, from healthy tissues adjacent to the tumor. In these samples, markers that predicted the response to radiotherapy were studied. In addition, it was verified whether the radioresistance mechanisms previously analysed in vitro appeared also in vivo. Wang et al. (2014) report that high levels of CEA are associated with a lower response to radiotherapy, mainly in terms of reducing the tumor stage. The study of Gnosá et al. (2014) relates the overexpression of the AEG-1 oncogene to a higher risk of distant tumor recurrence and lower disease-free survival in patients treated with radiotherapy. Lastly, Yao et al. (2014) investigated HER-2 as a marker of response to treatment without conclusive results.

Regarding the mechanisms of radioresistance that were previously analysed in cultured cells, we found that overexpression of the CREB-KDM4B-STAT3 axis, epigenetic suppression of the BEX1 gene and under-expression of BTG3 mediated by hypoxia, correlate with the results obtained in patient samples. In addition, comparing the samples of tumor tissue with those of normal tissue, a significant increase in the expression of the RAD50 gene was observed in neoplastic cells, being even greater in cells with greater resistance to radiotherapy. For this reason, Chen et al. (2018) proposed it as a radioresistance biomarker. In addition, Wu et al. (2014) found that IGF-1R overexpression is related to an increase in DNA repair and a decrease in apoptosis, all of which leads to greater resistance to treatment with ionizing radiation.

Conclusions

Analysis of the response to radiation of tumor biopsies can provide very valuable information about the possible resistance of colorectal cancer to treatment. Resistance mechanisms involve overexpression of the CREB-KDM4B-STAT3 axis, as well as alterations in the expression of BEX1 and BTG3. It is important to highlight the increase in DNA repair and decrease in apoptosis by RAD50 and IGF-1R.

New therapies based on the use of molecular response markers and new therapeutic targets that address radiation resistance would be very useful for the individualization of treatments and precision medicine.