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Review

Photodynamic therapy in colorectal cancer treatment—The state of the art in preclinical research

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ABSTRACT

Background: Photodynamic therapy (PDT) is used in many different oncologic fields. Also in gastroenterology, where have been a few attempts to treat both the premalignant lesion and advanced colorectal cancer (CRC). This review aims to give a general overview of preclinical photodynamic studies related to CRC cells and animal studies of photodynamic effects related to CRC treatment to emphasize their potential in study of PDT mechanism, safety and efficiency to translate these results into clinical benefit in CRC treatment.
Materials and method: Literature on *in vitro* preclinical photodynamic studies related to CRC cells and animal studies of photodynamic effects related to CRC treatment with the fallowing medical subject headings search terms: colorectal cancer, photodynamic therapy, photosensitizer(s), in vitro, cell culture(s), *in vivo*, animal experiment(s). The articles were selected by their relevance to the topic.
Results: The majority of preclinical studies concerning possibility of PDT application in colon and rectal cancer is focused on phototoxic action of photosensitizers toward cultured colorectal tumor cells *in vitro*. The purposes of animal experiments are usually elucidation of mechanisms of observed photodynamic effects in scale of organism, estimation of PDT safety and efficiency and translation of these results into clinical benefit.
Concluding remarks: In vitro photodynamic studies and animal experiments can be useful for studies of mechanisms and efficiency of photodynamic method as a start point on PDT clinical research. The primary disadvantage of *in vitro* experiments is a risk of over-interpretation of their results during extrapolation to the entire CRC.

Contents

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1. Introduction

Colorectal cancer (CRC) is the third most common cancer in men (10.0% of the total incidences) and the second in women (9.2%, respectively) worldwide. About 750,000 deaths from CRC are predicted in 2015 globally, accounting for 8.5% of all cancer deaths predicted in this year, which makes CRC the fourth most common cause of death from cancer [1–3]. According to the data from 2011, approximately 20–25% of patients with CRC already have metastases at the time of diagnosis and 50–60% of the remainder will develop metastases [4]. The treatment options and prognosis for patients with CRC have improved through the development of novel drugs and treatment regimens. [5–9]. However, the increasing resistance of tumor cells toward chemotherapeutic and biologic drugs used in CRC [6,8,10–12] as well as non-specific toxicity of these drugs on healthy tissues [13–15] creates a necessity to find other methods of CRC therapy. One of these methods is photodynamic therapy (PDT) [16–18] involving interaction between light, photosensitizer and oxygen to destruct tumor tissue through direct oxidative damage, vascular shutdown and activation of immune response against cancer cells [19–21]. The advantages of PDT over conventional chemotherapy are: higher tumor selectivity, lack of cross-resistance which enables the use of PDT in cases of recurrent tumors, wide range of total light and drug dose, allowing multiple application of PDT toward the same tumor as well as very good cosmetic effect with small or no scarring [22].

In this review, the results of *in vitro* preclinical photodynamic studies related to CRC cells and animal studies of photodynamic effects related to CRC treatment performed during the past few decades were presented. Over 100 abstracts and articles contained in NCBI, Excerpta Medica and Chemical Abstracts data bases which described experiments concerning photodynamic effects on CRC cells cultures, were analyzed. The keywords of searching were: "colorectal cancer", "photodynamic therapy", "photosensitizer(s)", "*in vitro*", "cell culture(s)" "*in vivo*", "animal experiment(s)".

2. *In vitro* cell research

The majority of preclinical studies concerning possibility of PDT application in colon and rectal cancer is focused on phototoxic action of photosensitizers toward cultured colorectal tumor cells *in vitro*. The *in vitro* research simplifies the system under study comparing to living organism so that investigator can focus on the limited number of cell components and interactions between them [23]. This is important in studies of photodynamic effects toward cancer cells due to complexity of these processes, Another advantage of *in vitro* methods is that they enable direct use of human cells. Thus, no translation from animal to human is necessary in this case [24]. Furthermore, *in vitro* methods are amenable to miniaturization and automation yielding high throughput screening methods for testing phototoxic effects [25–27].

A key component of the PDT is a photosensitizer (PS) and selection of an appropriate one depends upon the type of cancer. Therefore, studies comparing the photodynamic effect of different PS under the same treatment conditions for a certain type of cancer cells are very important. In most of available articles, the photodynamic action of tetrapyrollic PS such as porphyrins, chlorins, bacteriochlorins and phthalocyanines was examined. The collected data are presented in Table 1.

2.1. Porphyrin-mediated photodynamic action toward CRC cells

2.1.1. Effect on molecular regulatory factors

The longer PDT is under investigation, the more experience aims to explain the mechanisms of its action, taking into account factors affecting regulation at the molecular level. Hanlon et al. evaluated expression of mitochondrial heat shock protein (Hsp60) following phototoxic effect mediated by Photofrin® at a concentration of 2.5–10 mg/l by human CRC cell line HT29 and its resistant to Photofrin®. Basal levels of Hsp60 which is involved in apoptosis regulation in the tumor cells were similar in the murine cell lines while in the human model the resistant HT29-P14 cell line presented a small increase in basal levels comparing to its parental population. Hsp60 levels were determined with flow cytometry. A significant increase in Hsp60 concentration was noticed in all analyzed cell lines, both after incubation with Photofrin® only or after photosensitization. Maximum concentration of Hsp60 were detected 6–8 h post irradiation, when, Hsp60 induction was considerably greater in the resistant variants of studied cells. Beside timedependent also photosensitizer dose-dependent relationship for PDT was observed. Obtained results indicate that Photofrin®-mediated phototoxic effect can induce Hsp60. The differences in secretory activity of Hsp60, between the tested cell lines with varying degrees of resistance, implicated Hsp60 as a factor which may contribute to the resistance to therapy observed in the induced resistant cell lines [28].

He et al. showed that CRC cell line CT-26 pretreated with hematoporphyrin methyl ester (HMME) induced photosensitization in combination with hyperthermia (41 °C for last third hours of HMME incubation) after injection to tumor-bearing mice. Cells were irradiated with 630 nm light *via* semi-conductor laser at a light dose of 5 J/cm^2 for 20 min. CT-26 cells are characterized by a relatively low baseline expression of Hsp70 that is an analogue of Hsp50, and also HMME was a photosensitizer which induced less Hsp70 expression than other kinds of photosensitizers but had an influence on its surface localization. Therefore, the authors designed a combined of hyperthermia with HMME-mediated treatment to achieve both higher expression of Hsp70 and its enhanced