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Review

Radio frequency responsive nano-biomaterials for cancer therapy

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ABSTRACT

Radiofrequency (RF)-assisted cancer therapy is well-known in the medical field as it is non-hazardous and can penetrate tissues, enabling a deeply rooted cancer treatment. However, the current treatment regimen is non-specific and invasive, making it difficult for patients to undergo the RF ablation procedure. Recently, there has been tremendous attention given on replacing RF probes (through which the RF current passes into the tumors) with metallic nanoparticles (NPs) such as gold and iron oxide. These metallic NPs can be combined with stimuli responsive polymers to have a simultaneous drug delivery to tumors and better thermal ablation. This review will give a brief overview on the various nanobiomaterials based on metals and polymers and their composites in RF-assisted cancer therapy. Special attention has been given on RF responsive composite nanomaterials. Besides these, the importance of RF-assisted drug delivery using the nanobiomaterials for cancer therapy, as well as the advantages and future perspectives of these materials are discussed in detail.

Contents

1. Introduction

"Cancer" remains as incurable deadly disease that has been afflicting many lives all around the globe. Precisely, cancer is a collective term for a large group of diseases that can be affected by any part of the body [1–3]. Recently, there have been many changes in cancer treatment modalities, especially in advanced radiation therapy. Among which, radiofrequency (RF) ablation (RFA) has got enormous attention, as it is a non-hazardous treatment [4–6]. RF-assisted cancer therapy that utilizes RF current with a frequency ranging from 10 kHz and 900 MHz has been established in the biomedical field to ablate cancer cells [7]. Unlike the

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conventional treatment regimens such as radiation and laser treatments, the RF waves have high penetration capability. This power is influenced by the electromagnetic wave frequency, tissue permeability, and its conductivity [8–10].

Deep rooted cancers such as liver cancer can be well-treated with RFA since they are completely non-ionizing and cause no harm to humans, making it one of the most ideal cancer treatment modalities. The Food and Drug Administration (FDA) has already approved RFA for hepatic carcinoma treatment. RFA can generate heat induced thermal disruption via the friction created by the ionic collisions of the molecules when they align under the alternating current as it flows within the tissue.

RFA started gaining importance in the early 1990s as a proposed treatment for unresectable, malignant hepatic carcinomas [11,12]. Further experiments on animal models and human trials were successful enough to prove potential safety of RFA in treatment of hepatic carcinoma [13]. The current RFA therapy has many limitations in terms of painful procedure of needle insertion, précised image-guidance, tumor size, and damage to non-tumorous regions and surrounding tissues.

It is a well-known fact that most of hepatic carcinoma victims cannot undergo surgery at the time of diagnosis. On the other hand, traditional RFA has invasive procedures which hinder patient compliance, and sometimes resulted in severe side effects. Thus it is highly recommended to have a non-invasive procedure in which the RF current can produce heat energy with the help of certain nanoparticles (NPs), and would be used for ablating tumor cells. In a typical RF-assisted treatment, the patient has to undergo surgery, followed by RF probe insertion squarely in the affected area, as shown in Fig. 1.

In clinical practice, the RF electrode is directly connected to the RF generator. The heating is due to the ionic agitation around the RF electrode as a result of RF wave oscillations. Due to the high potency of this technique, FDA has already approved the clinical usage of RFA against hepatic carcinoma [14–22]. RFA involves the use of electric current that can pass through a targeted area of hepatic carcinoma with the help of an RF electrode. Heat is produced by the electric current, which kills cancer cells at the site of the tumor. The approved procedure utilizes traditional imaging methods (such as ultrasound, a computerized tomography (CT) scan, or magnetic resonance imaging (MRI)) to guide the physician in achieving the correct needle insertion of the probe into the cancer tissue. The cancer tissue can be processed with RF probe (through which RF current is produced at the tissue). Then, cancer cells are heated by the electrical current from the RF probe creating irreversible tumor tissue destruction [23–25].

In general, the conventional treatment regimens have many drawbacks, including non-specific action (which affects the normal healthy cells surrounding the tumor or adjacent to the tumor cells) and invasive mode of treatment. Thus, the major challenge in this area is to achieve a non-invasive mode of treatment, where the RF probe could be replaced with "RF responsive nanobiomaterials". These nanomaterials could heat up the tissues when an external RF source is applied [26,27].

2. Potential RF responsive nanobiomaterials for cancer therapy

A nanobiomaterial becomes RF responsive only when it attains the ability to heat up in the RF field. Metallic NPs, such as gold (Au-NPs), iron oxide, cobalt, carbon-based nanomaterials, and QDs have been reported to have significant RF responsive heating in the *in vitro* experimental conditions (Fig. 2). The basic principle behind RF heating is Joule heating or magnetic heating. Even though there are no optimum RF conditions for effective heating, most of the reported research work have different RF exposures in their experiments. It has a range of 40 to 800 W.

3. Gold as a potential nanobiomaterial for RF-assisted cancer therapy

It has been well-known that Au-NPs can image tumor vasculature [28] and can act as a potential diagnostic marker for specific aiming and boosting up the intratumoral localization of therapeutics to many cancer cells [29]. Additionally, there has been many recent studies on RF-assisted cancer treatment using Au-NPs [30–32]. As far as the reported results are concerned, there have been many similar results regarding the RF heating ability of Au-NPs [26,33–41]. The basic principle behind background heating from Au-NPs arises due to the excess ionic contents developed during the Au-NPs preparation time [41]. Majority of the reported synthesis of Au-NPs entails NaOH to adjust the pH, leading to unnecessary heating under RF than the Au-NPs. This issue has to be considered. To avoid this, it is better to adjust the pH using tris-buffer so that the resulting Au-NPs would not have any extra heating from ionic counterparts.

The idea of RF-assisted heating using Au-NPs was first introduced by John S. Kanzius, an American inventor and amateur radio operator from Erie, Pennsylvania [42]. Though there are many studies using Au-NPs for NIR-assisted cancer therapy at the *in vitro* and *in vivo* levels, NIR has

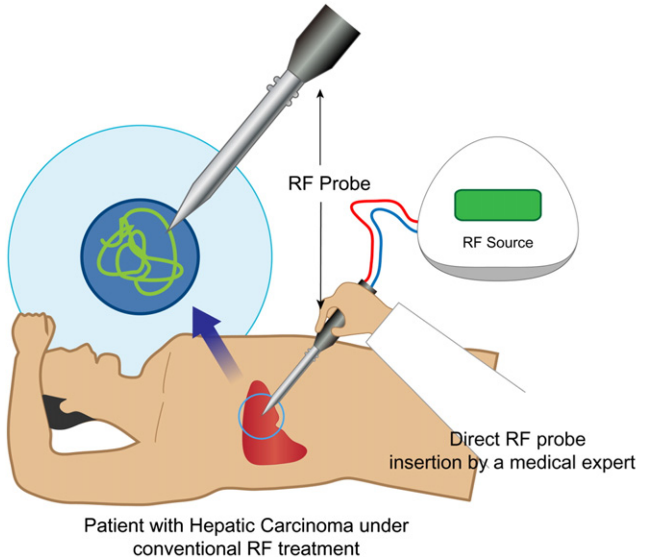

Fig. 1. Schematic illustration of insertion of RF probe into the hepatic carcinoma for RFA based tumor destruction. The electrode is connected to the RF regenerator. The heating results due to the ionic agitation around the RF electrode as RF waves oscillate during attempts to reach its grounds (grounding pad is not shown on the patient's back here).

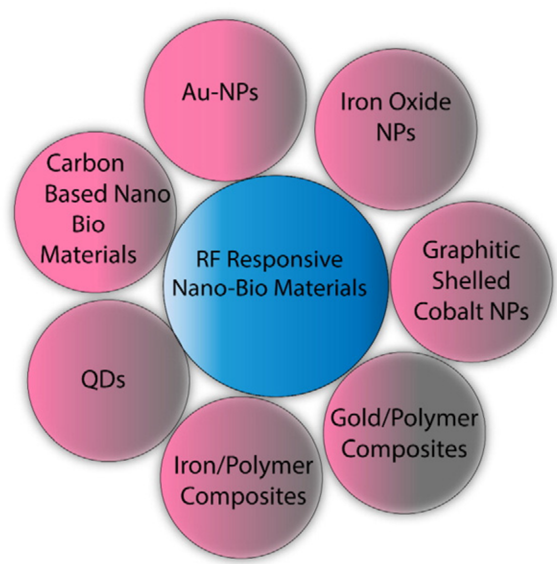

Fig. 2. Major RF responsive nanobiomaterials in the current medical research field.