Medical Hypotheses 100 (2017) 78–81

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

In pursuit of cancer metastasis therapy by bacteria and its biofilms: History or future

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ARTICLE INFO

Article history:
Received 22 August 2016
Accepted 26 January 2017

Keywords:
Biofilms
Metastasis
Anti-metastasis phenotypes
Coley's toxin
Bacteria mediated cancer therapy

ABSTRACT

The 20th century observation of increasing comprehensive load of cancer, advanced cancer prevention strategies, creative hypotheses and control procedures by research communities are being traversed and stimulated in multiple facets. Inference of genetically modified non-pathogenic and natural bacterial species as potential anti-tumor agents is one such original perspective. Live, genetically modified non-pathogenic or attenuated bacterial species are able to form biofilms by multiplying selectively or non-selectively on cancer cells, which will lead to metastasis disruption. However, the appearance of gene-directed prodrug therapy and recombinant DNA technology has invigorated the notice in range of applications employing bacteria and bacterial therapy and have been carried out. The most possible and promising upcoming strategies are bacteria mediated cancer treatment. Significant efficacy in pre-clinical studies have been demonstrated and some are presently under clinical investigation. The theorem is that cancer metastasis can either be blunt by opponent bacterial biofilm infection or serve as model vectors for delivering therapeutic proteins to tumors or generation of the new phenotypes during the SOS reaction incite by anticancer drugs.

Background

Over a century ago, attempts were made to control cancer growth using live bacteria [1]. Microorganisms are one of the known causative agents of cancer. Examples includes gastric cancer in humans and animals caused by *Helicobacter pylori* [2], and crown gall disease in plants caused by *Agrobacterium tumefaciens* [3]. However, the utilization of microbes and microbial extracts for the treatment of cancer is less commonly known. The most cited case of the function of bacteria in cancer therapy was recognized almost 100 years back by the physician and surgeon William B. Coley (active career 1891–1936) of Memorial Sloan-Kettering Hospital, which was previously named as Memorial Hospital in New York City. He experimentally proved that, when his several patients with different stages of cancer had their tumors regressed, when they were infected with a mixture of variety of bacterial pathogens [4,5]. It allowed the cancer to return, when he started the treatment to eradicate the infections instead of reducing it [4,6]. In the late 1800's, he then developed a risk-free and safe vaccine, which was later described as Coley's toxin. It was composed of *Serratia marcescens* and *Streptococcus pyogenes*, the two killed bacterial species. This mixture of *Serratia* and *Streptococcus* was able to simulate an infection with fever in addition without the risk of an real infection, and helped his patients by reducing/shrinking the tumors [7–9]. At that time, his vaccine was extensively used to treat carcinomas, sarcomas, melanomas, lymphomas, and myelomas successfully [10,6]. Afterward, numerous strains of bacteria have been used in the past, in an endeavor to trim down the size or growth rate of tumors. Presently, the well-known example, is the treatment of bladder cancer with the use of *Mycobacterium bovis*, the vaccine strain (BCG) [11]. Achievement of Coley's toxin provided the argument for recent advances in this field. This review appraise the history of these hard work and presents a dialogue to compare present day immunotherapy, and how can we bond with past for healthy future.

Introduction

Cancer is a disease characterized by unobstructed and invasive multiplication of cells. This may metastasize to other parts of the body from where it started (the primary site) [12]. Despite the per-

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http://dx.doi.org/10.1016/j.mehy.2017.01.018
0306-9877/

sistent incorporation of novel drugs and therapies into the oncological pool, metastasis still is the major cause of morbidity and mortality throughout the world, because dealing with small non-necrotic metastases of large main tumors is the only and most difficult problem. Sarcomas in patients was regressed with acute *Streptococcal* infections, a nineteenth century remarked study, that has in present, enthused the research communities in many-facets; one of them is metastasis [5,7,13].

During the past couple of years, exhaustive studies has been done for the treatment of tumors, whether it's by surgical resection, radiotherapy, chemotherapy, gene-directed enzyme prodrug therapy or by biofilms. The most regular type of tumor treatment, is an effective conventional chemotherapy against actively proliferating tumor cells. However, in the process of treating cancer cells, this therapy can damage other types of fast-growing, healthy normal cells. This will also induce various adverse reactions, or side effects. Scientists are developing a new treatment for cancer that will be more efficient and less harmful than chemotherapy: bacteria as cancer fighting microbot [14]. It has been recently discovered that iron oxide nanowires obtained from biofilm waste by bacteria *Mariprofundus ferrooxydans* are demonstrated as new multifunctional drug carriers for triggered therapeutics release and cancer hyperthermia applications [15]. Here, we will discuss the future of cancer metastasis and oncolytic potential of bacterial biofilms in specific facet. Few studies recently tried this year to reveal the potential of biofilms and somehow tried to show the utility of biofilms in treatment of cancer or even as a marker of colon neoplasia [15–17]. The dilemma has been approached in the following way: (a) Whether the method has a therapeutic value or not: Is there plenty experimental and clinical evidence available to validate this statement (b) If so, what components control the success or failure? (c) Why did this technique still didn't attain recognition? (d) If the conclusions to the above enquiry necessitate advance study, what can be done to make the biofilms or bacterial derivatives consistently effective?

Bacteria commonly grow as an densely packed assemblage known as biofilms, community of cells embedded in a extracellular polymeric substance matrix [18,19]. This speculated hypothesis is affirmed by various findings. One study revealed the biofilm-like properties by *Pseudomonas aeruginosa* during growth within airway epithelial cells [20], not only this acquired by *Pseudomonas*, but it can also attach and penetrates into the epithelial cells resultant from a human bronchus alveolar carcinoma of human lungs [21]. Specific attachment of bacteria to cancer cells is required in order to invade to acquire nutrients and to hinder with other cellular functions and cancer metastasis. This will also allow the bacteria to grow on the surface of cancer cells [13]. Another study also indicates the usefulness and provided with a hope that the *Streptococcus agalactiae* polysaccharides can be used as a cancer metastasis inhibitors [22].

Process behind the sarcoma regression is uncertain, so we put forward the theory that metastasis can be hindered during the treatment with a specific type of anticancer drugs (DNA replication inhibitors) by bacterial macromolecules, antagonist bacterial infections [13] or SOS response triggered formation of new phenotypes and biofilm production on cancer cell surface. In addition, released proteins and DNA are certainly thought to be possible countermeasures against cancer [4,23]. Recently, it has been hypothesized, that treatment with anti-cancer drugs, stimulate bacterial adhesion and induce the bacterial SOS response (Fig. 1), leads to the formation of biofilms [1]. For example, hydroxyurea, an anti-proliferative drug for tumor treatment can induce the formation of bacterial biofilms and hypothesis predicts that they can form on cancer cells leading to metastasis disruption [6,24]. In the presence of the replication inhibitors and in order to escape the drug attack, bacteria growing with cancer cells undergo the SOS response. This will lead to the development and evolution of new and beneficial phenotypes, which acquire the capacity to attack/penetrate the cancer cells [25]. As a result, under the drug stress, diversity of bacterial mutants can be generated, and unique phenotypes are possibly be selected [1]. Moreover, the new phenotypes could be engineered for bacteria mediated gene-directed prodrug therapy and for selective damage of tumors [23]; in fact, biofilms are usually restricted to a particular site and involve a lesser amount of host damage than the acute infections caused by free-living bacteria. Plausibly, it can be said that, cancer cells encaged by bacterial biofilms, free floating bacteria itself and their macromolecules, shouldn't be able to metastasized and colonized to other parts of the body.

Bacteria emerging under antagonism and drug pressure are very likely to develop novel phenotypes against cancer (Fig. 1). In other words, attention will be on the use of bacterial products like peptidoglycans, lipopolysaccharides (LPS), epothilones, lipotechoic acid and or derivatives/macromolecules, which have been reported to acquire anti-cancer activity [26]. These derivatives/macromolecules released from the bacteria treated with the anti-cancer drug can coat cancer cells to block the metastasis and can mediate biofilm formation. This hypothesis is testable. Systematic identification and quantification of bacterial proteins can be simply identified by proteomic analysis, which are required for formation of biofilms and for specific bacterial adherence/attachment on tumor surface. The impact is thoughtful in control and treatment of cancer, as metastasis leads to major deaths from solid tumors [13,27]. Additional and advance research is required to associate these phenotypes as novel bacterial anti-metastasis regimens. Though, bacteria have shown capable and noteworthy effectiveness in eliminating recognized tumors found in pre-clinical tumor models of mouse [28]. However, the successful transformation to perform these pre-clinical approach into clinical practice will rely on results of clinical trials [29,30].

Targeted agents are now a day's been used against bacterial communication to fight bacterial infections. For example, Tuberculosis is treated with antibiotics, that interfere the quorum sensing of *Mycobacterium tuberculosis* [31]. Disrupting the code of cancer communication (e.g., hampering with cell navigation during metastatic spread) may give way to novel cancer-fighting drugs, that will target stromal cells and/or can slow down its ability to bind stromal cells [28,32]. In another instance, cancer cells somehow also generate microenvironments by binding with our gut microbiota to hide out of sight and thrive in there [33]. Therefore, disrupting the system of cross talk between commensal bacteria and cancer cells, can serve in the advancement of those drugs, which can avoid cancer from gaining the benefits from gut bacteria [34]. Another example of the wellness of microbiota of rhizosphere depends on its efficient interaction with its surrounding environments; this equivalent and comparable situation definitely holds for a cancer and commensal bacteria [34]. Combining probiotics and prebiotics in a form of synergism (symbiotic therapy) can also be the future in anaerobic bacteria vector-mediated cancer therapy. But symbiotic therapy, is still in its infancy stage and some promising signs are starting to emerge in colon cancer treatment [35,36].

Conclusion

The function of bacteria in cancer is quite vague. Formation of biofilms over cancer cells and disrupting metastasis can be an excellent start, which may somehow guide towards the effectual treatment/prevention of cancer. Relationship between certain species of bacteria and carcinogenesis have been indicated in numerous scientific findings [2]. Many other studies also have revealed