In the name of god

Topic :

Bacteria and bacterial derivatives as drug carriers for cancer therapy

Isfahan university of medical science

Presented by : nafise jafari kondori

Introduction

Cancer is considered a major public health problem, and is a leading cause of death, both in developed or developing countries.

Although tremendous efforts have been made to fight against cancer, millions of people die from cancer every year, and the mortality rate is increasing year by year.

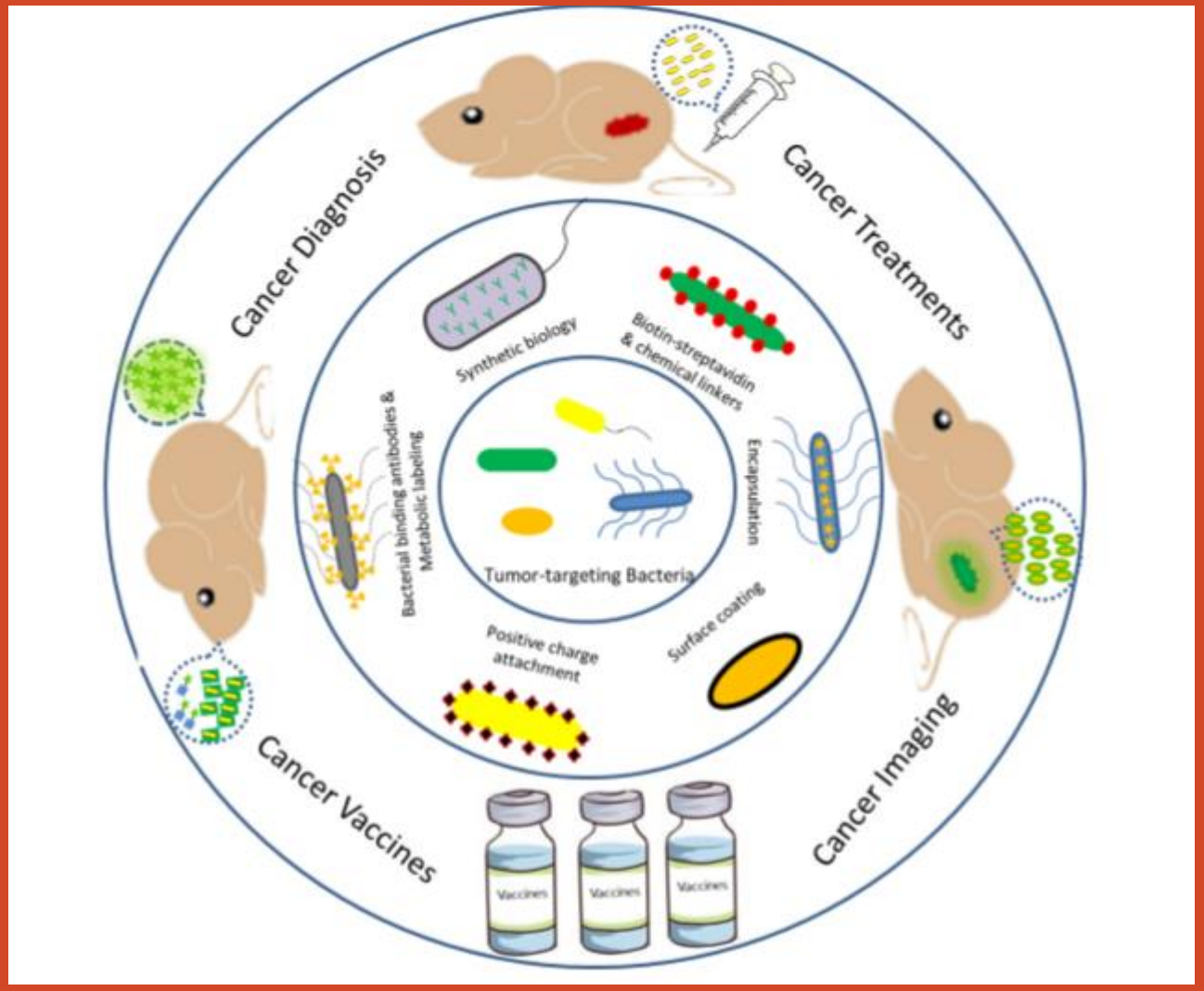
Conventional cancer treatment strategies

1. Surgery
2. Chemotherapy
3. Radiotherapy

Introduction

In recent years, scientists have been working on effective strategies of anticancer drug delivery.

Various systems for the delivery of therapeutic agents including micro/nanoparticles and liposomes have been designed and widely evaluated both in animal models and clinical trials ، as they have the potential to enhance the therapeutic efficacy by reducing toxic side effects, prolonging circulation time and improving tumor specificity.



Applications of bacteria as therapeutics, bioimaging and diagnostic agents for treating cancer.

Bacterial-mediated anticancer drug delivery

Since in the late 19th century, bacteria and bacteria-derived spores have been used as antitumor agents to delivery various therapeutic agents, such as toxic proteins and small molecular-weight drugs, into tumors, as the scientists discovered that bacteria were able to disperse into tumor tissues and inhibit their growth.

Salmonella spp.,*Clostridium* spp., *Escherichia coli* and *Listeria* spp. havebeen attenuated by deleting their key virulence factor gene

Delivery of anticancer drugs mediated by bacteria

Bacterium	Therapeutic agent	Modification strategy	Type of treatment	Ref.
Salmonella typhimurium	Paclitaxel-loaded liposomes	Biotin-streptavidin	Chemotherapy	[56]
Salmonella typhimurium YS1646	Doxorubicin loaded-low-temperature sensitive liposome	Biotin-streptavidin	Chemo-immunotherapy	[57]
EcN	Doxorubicin	Acid-labile linkers of cisaconitic anhydride	Chemotherapy	[58]
Escherichia coli MG1655	Doxorubicin and Fe_3O_4 nanoparticles	Surface charge and noncovalent interactions	Chemotherapy	[16]
Escherichia coli MG1655	Doxorubicin and SPIONs loaded soft red blood cells	Biotin-avidin-biotin	Chemotherapy	[15]
Listeria monocytogenes	188-Rhenium	Listeria-binding antibodies	Radiotherapy	[65]
Listeria monocytogenes	32-Phosphorus	Metabolic labeling	Radiotherapy	[66]
Salmonella Typhimurium VNP20009	Polydopamine	Coating	Photothermal-therapy	[38]
Salmonella Typhimurium Ty21a	Gold nanoparticles	Encapsulation	Photothermal-therapy	[50]
Escherichia coli MG1655	Fe_3O_4 nanoparticles	Covalent linker	Photothermal-therapy	[73]
Salmonella typhimurium YB1	Indocyanine green	Biotic/abiotic cross-linker	Photothermal-therapy	[75]
Escherichia coli	CD47 nanobodies	Genetic modification	Immunotherapy	[44]
EcN	PD-L1 and CTLA-4 nanobodies	Genetic modification	Immunotherapy	[93]
Salmonella typhimurium	FlaB	Genetic modification	Immunotherapy	[55]
Salmonella typhimurium	NY-ESO-1	Genetic modification	Immunotherapy	[83]
Salmonella typhimurium	Cytolysin A	Genetic modification	Protein-based biotherapy	[81]
EcN	p53&Tum-5	Genetic modification	Protein-based biotherapy	[82]

Bacterial-mediated anticancer drug delivery

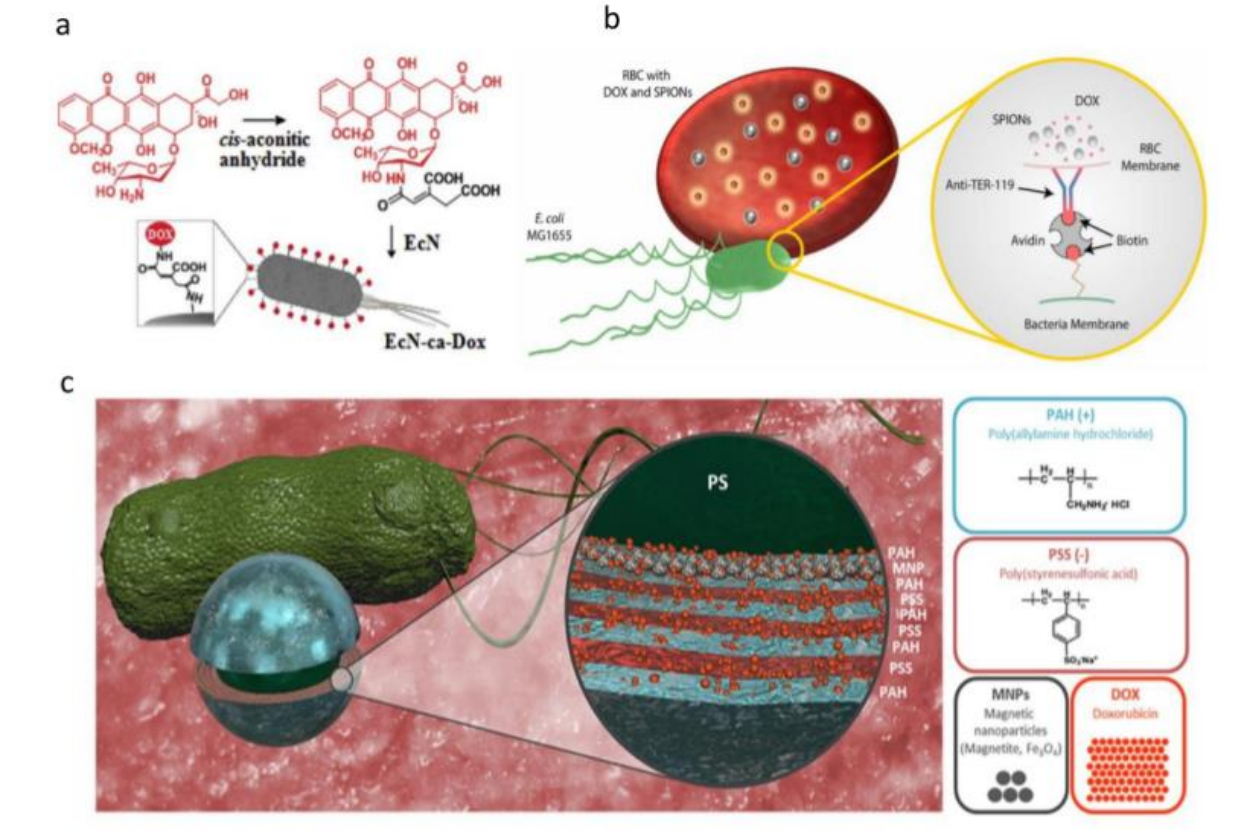
1. Chemo-therapeutic drugs
2. Radio-therapeutic drugs
3. Photothermal-therapeutic drugs
4. Immuno-therapeutic drugs

Chemo-therapeutic drugs

As a first-line therapy for cancer patients, chemotherapy has been widely performed to treat various cancers in the past few decade.

A broad spectrum of effective anticancer chemo-therapeutic agents has been approved by the US FDA, including camptothecin, doxorubicin, colchicine, paclitaxel, cisplatin, and carboplatin.

Bacteria-mediated delivery of chemo-therapeutic drugs

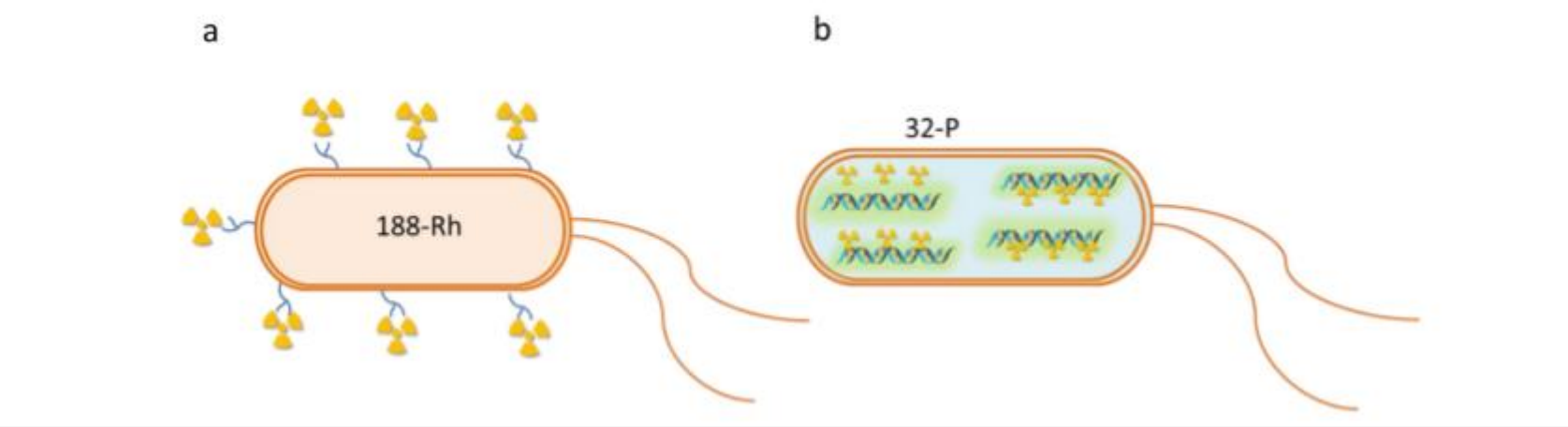


Radio-therapeutic drugs

Radiotherapy, first used to treat cancer over a century ago, is an effective physical strategy using high-energy rays to cure many different cancer.

Moreover, radiotherapy is able to modulate both the immunogenicity and adjuvanticity of tumors by triggering the release of pro-inflammatory (and anti-inflammatory) mediators, increasing tumor infiltrating immune-stimulatory (and immune-inhibitory) cells and enhancing the expression of neoantigens.

Bacterial-mediated tumor-targeting delivery of radio-therapeutics agents.

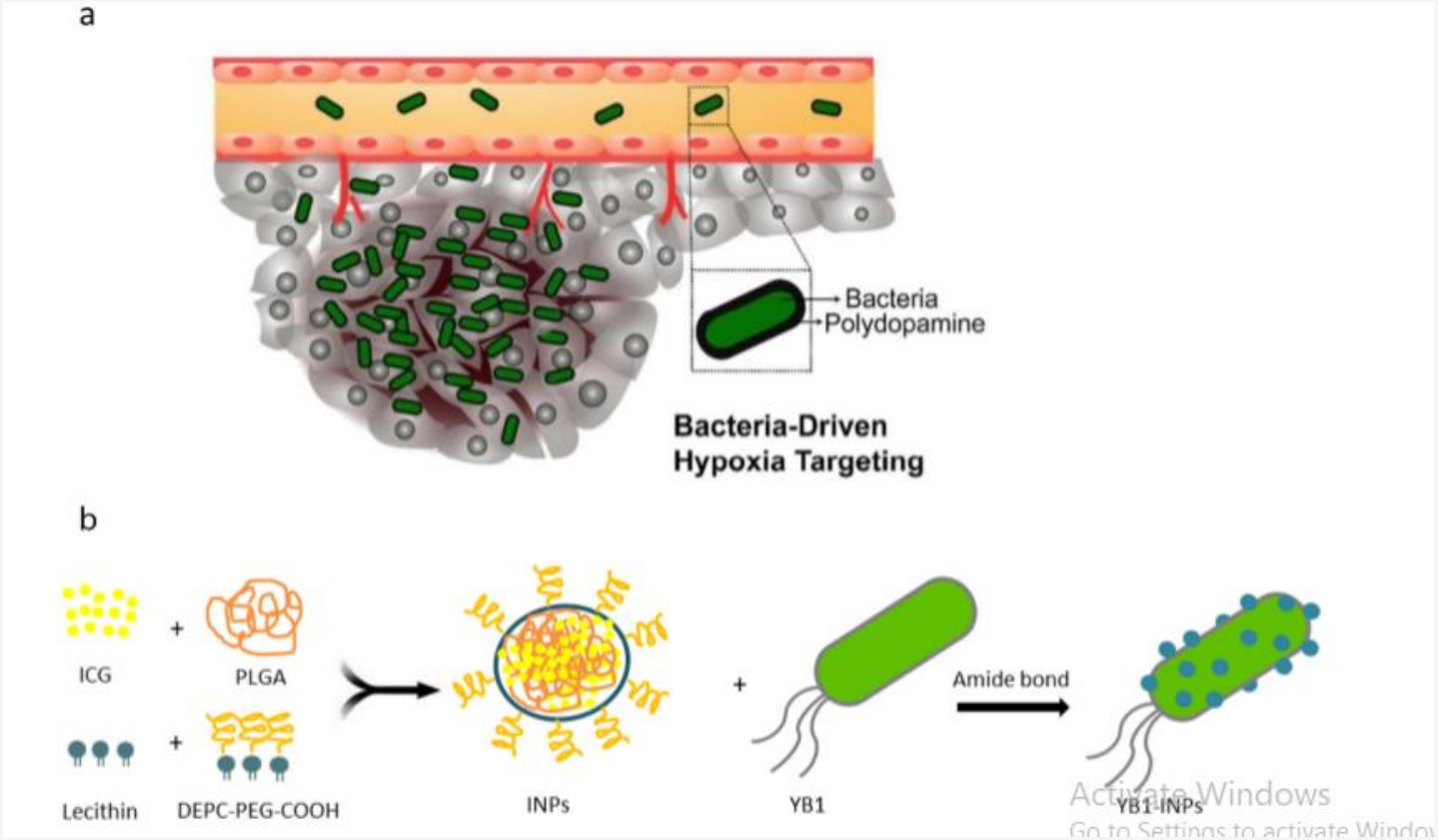


Photothermal-therapeutic drugs

With the development of bacterial mediated anticancer research, a number of works have focused on combination therapy, as the efficiency of a single treatment is often limited.

In addition to chemotherapy and radiotherapy, bacterial mediated photothermal-therapy is another important and effective strategy for treating various types of cancer.

Bacteria-based tumor-targeting delivery of photothermal-therapeutic agents

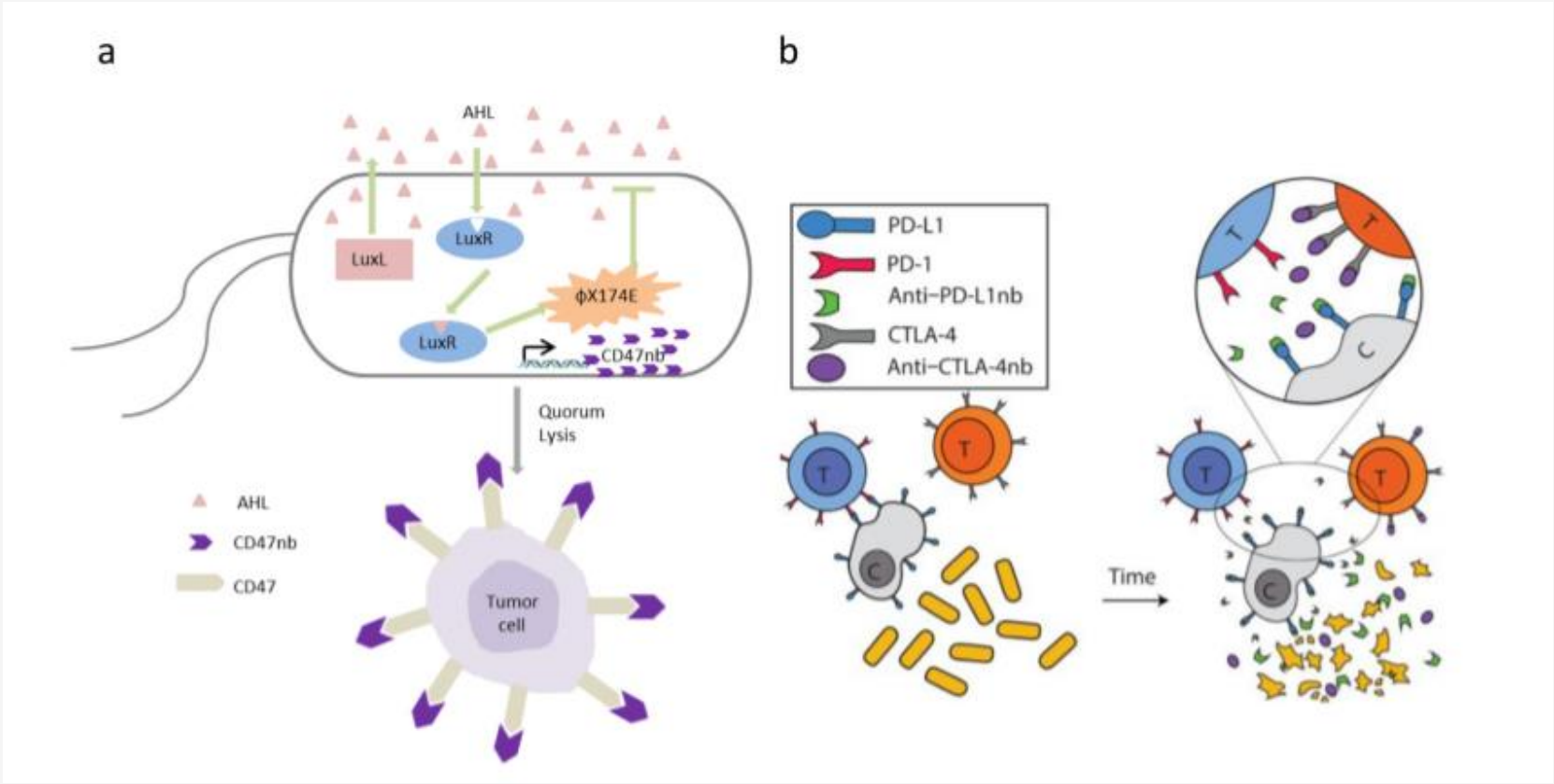


Immuno-therapeutic drugs

Cancer immunotherapy is a tumor treatment mode that stimulates or boosts the body's immune system, particularly, to enhance the antitumor immunity of the tumor microenvironment to inhibit and kill tumor cells.

Although numbers of recent studies have demonstrated that the combination of anticancer bacteria and immune checkpoint inhibitors significantly improves the efficacy of cancer elimination.

Bacteria-assisted tumor-targeting delivery of immuno-therapeutic agents

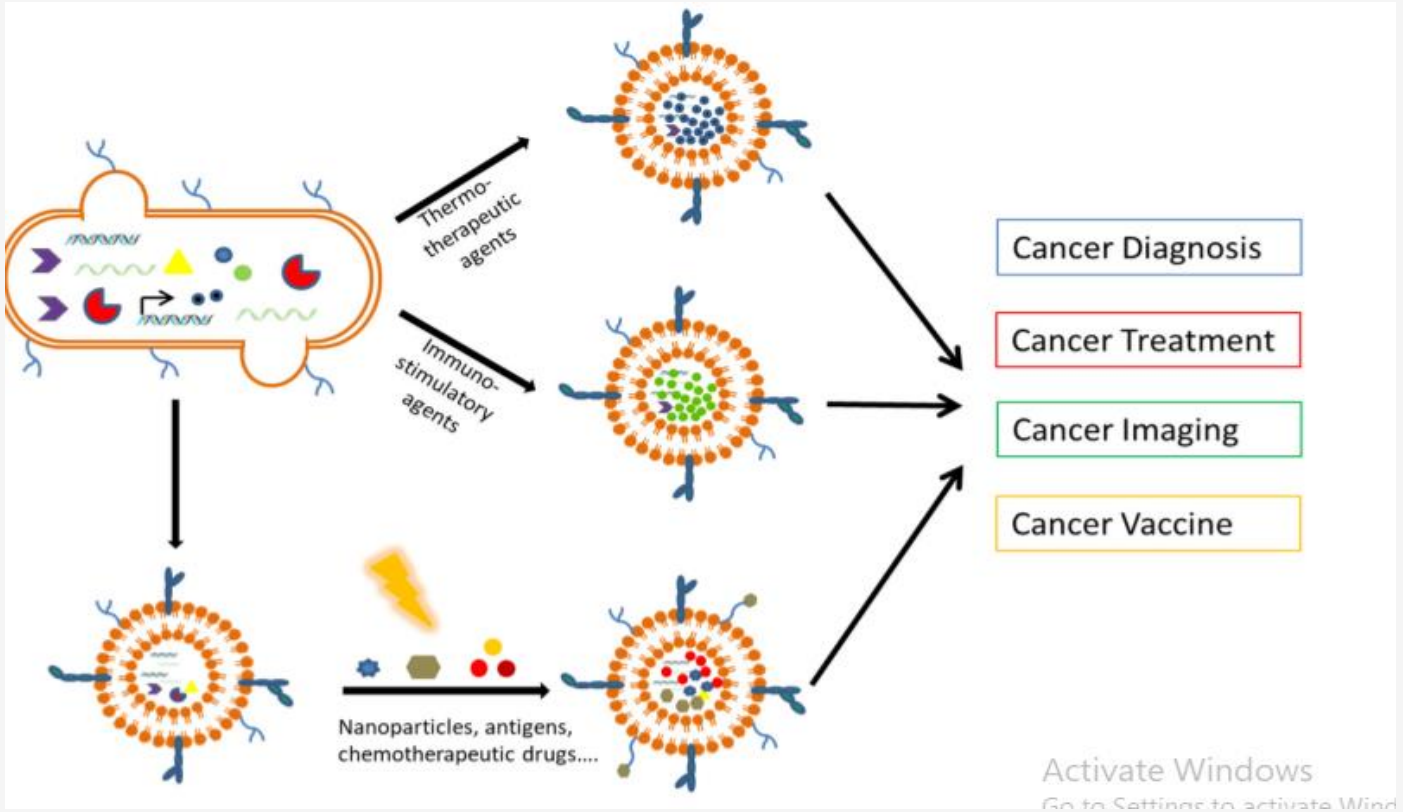


Bacterial derivative-mediated anticancer drug delivery

MVs released from bacteria are double lipid layered nanoparticles at the size of 20–400 nm in diameter that are naturally secreted during bacterial growth through controlled membrane blebbing.

MVs play important roles in various bacterial biological processes, such as virulence, phage infection, horizontal gene transfer, cellular metabolites export and cell communication.

Bacteria-derived membrane vesicles as carriers the delivery of diagnosis, treatment, imaging and vaccine agents for cancer therapy



Delivery of anticancer drugs mediated by bacterial MVs.

Delivery of anticancer drugs mediated by bacterial MVs.

Parent bacterium of MVs	Therapeutic agent	Type of therapy	Type of cancer	Ref.
Salmonella typhimurium	Tegafur	Chemo-immunotherapy	Melanoma	[110]
Salmonella typhimurium	Doxorubicin	Chemotherapy	Brain tumor	[111]
Salmonella typhimurium	Paclitaxel	Chemotherapy	Breast, bladder, pancreatic, prostate and lung tumors	[112]
Salmonella typhimurium	Doxorubicin	Chemo-immunotherapy	Glioblastoma, colon cancer (CT26)	[114]
Salmonella typhimurium	Doxorubicin	Chemotherapy	Neuroblastoma	[115]
Salmonella typhimurium	Doxorubicin	Chemotherapy	Recurrent glioblastoma	[117]
EcN	Doxorubicin	Chemotherapy	Breast cancer (4T1)	[100]
Salmonella typhimurium	Melanin	Photothermal therapy	Breast cancer (4T1)	[119]
Salmonella typhimurium *SL1344*	Ovalbumin fragment	Immunotherapy	n/s	[106]
Salmonella typhimurium	Ovalbumin fragment	Immunotherapy	n/s	[125]
Escherichia coli	Basic fibroblast growth factor molecule	Immunotherapy	Melanoma (B16)	[107]
Salmonella typhimurium	Melanoma cytomembrane vesicles, PLGA-ICG nanoparticles	Photothermal and Immunotherapy	Breast cancer (4T1)	[108]

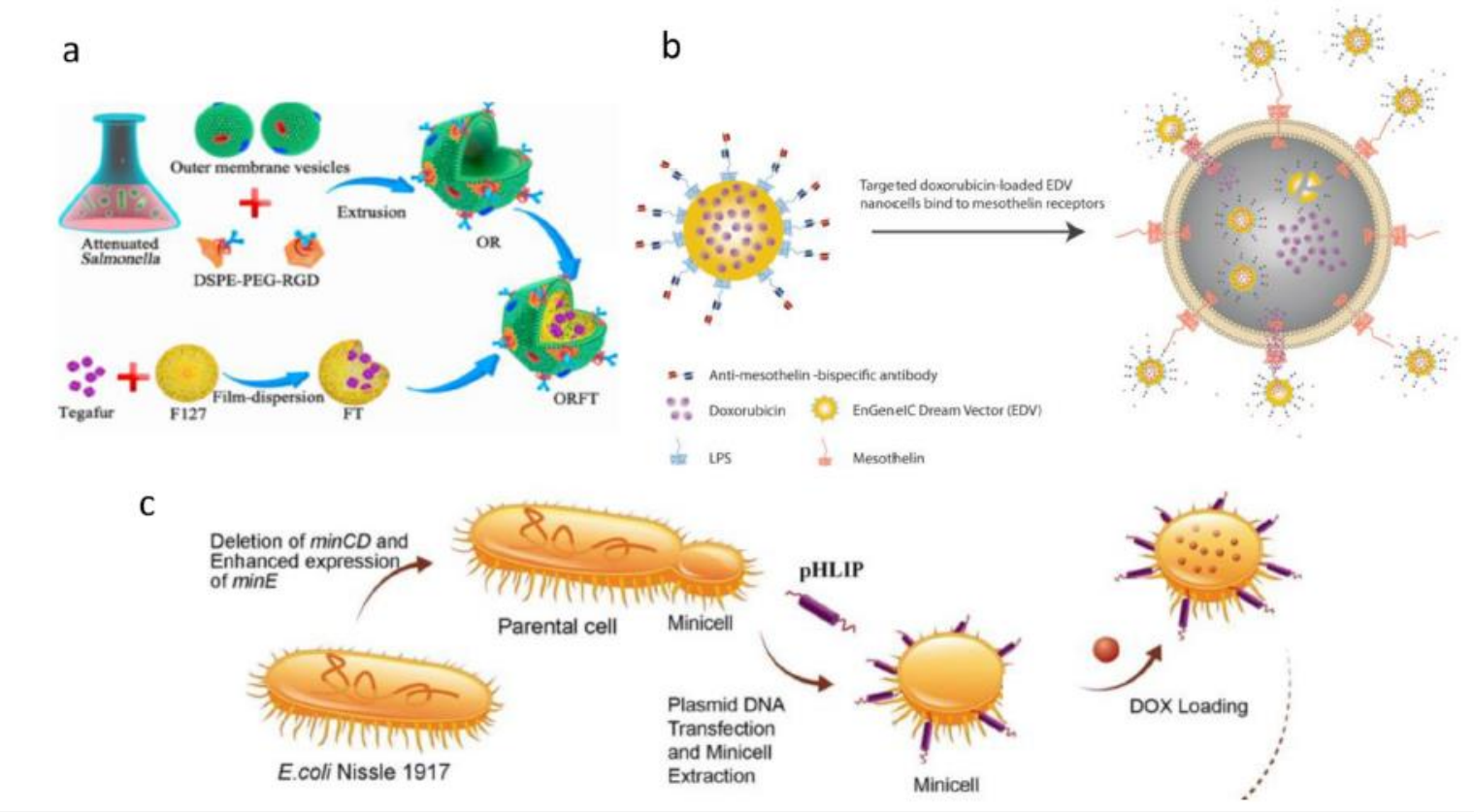
Bacterial derivative-mediated anticancer drug delivery

1. Delivery of chemo-therapeutic drugs
2. Delivery of thermo-therapeutic drugs
3. Delivery of immuno-stimulatory agents

Delivery of chemo-therapeutic drugs

MVs-mediated delivery of chemo-therapeutic drugs that selectively targets tumor cells is a promising approach to enhance therapeutic efficacy and also reduce toxicity caused by systemic treatment.

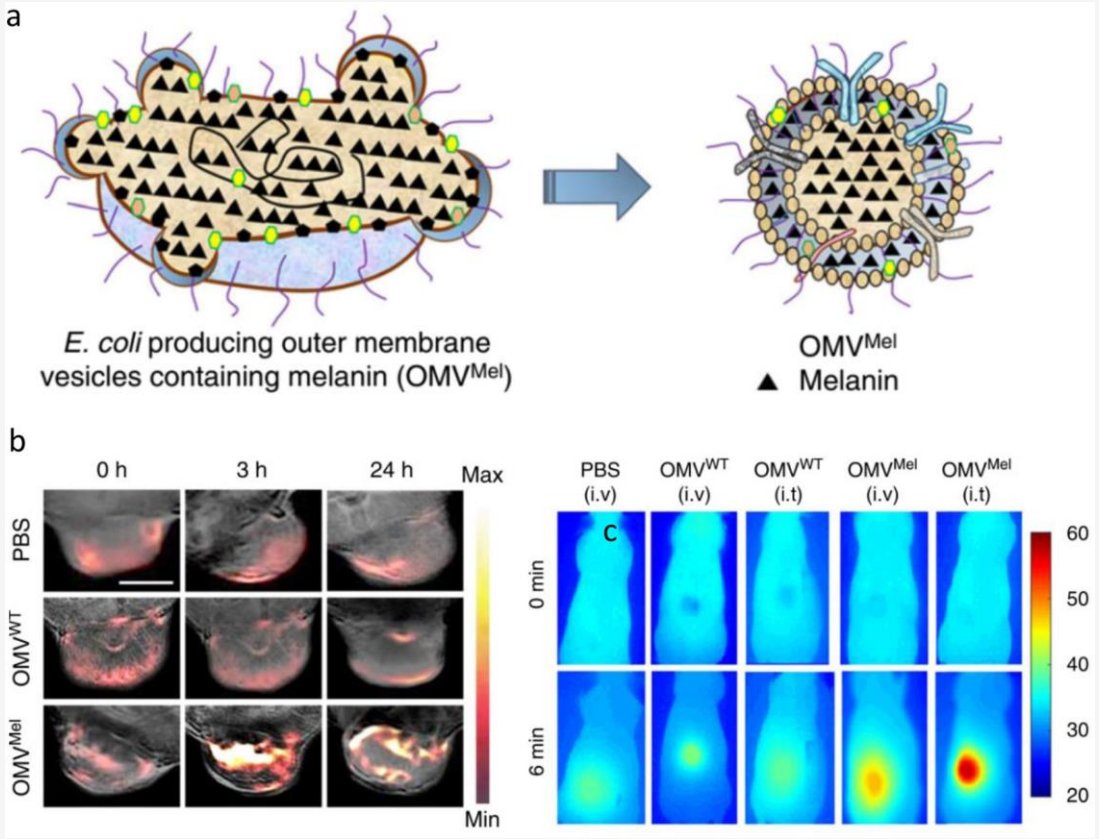
Bacteria-derived MVs for the delivery of chemo-therapeutic drugs.



Delivery of thermo-therapeutic drugs

Similar to bacteria, bacterial derived nano-vesicles have been explored for photothermal therapy, although there are fewer examples reported. For example, bacterial MVs packed with melanin were used for optoacoustic imaging and thermal therapy.

Delivery of thermo-therapeutic drugs mediated by bacteria-derived MVs.

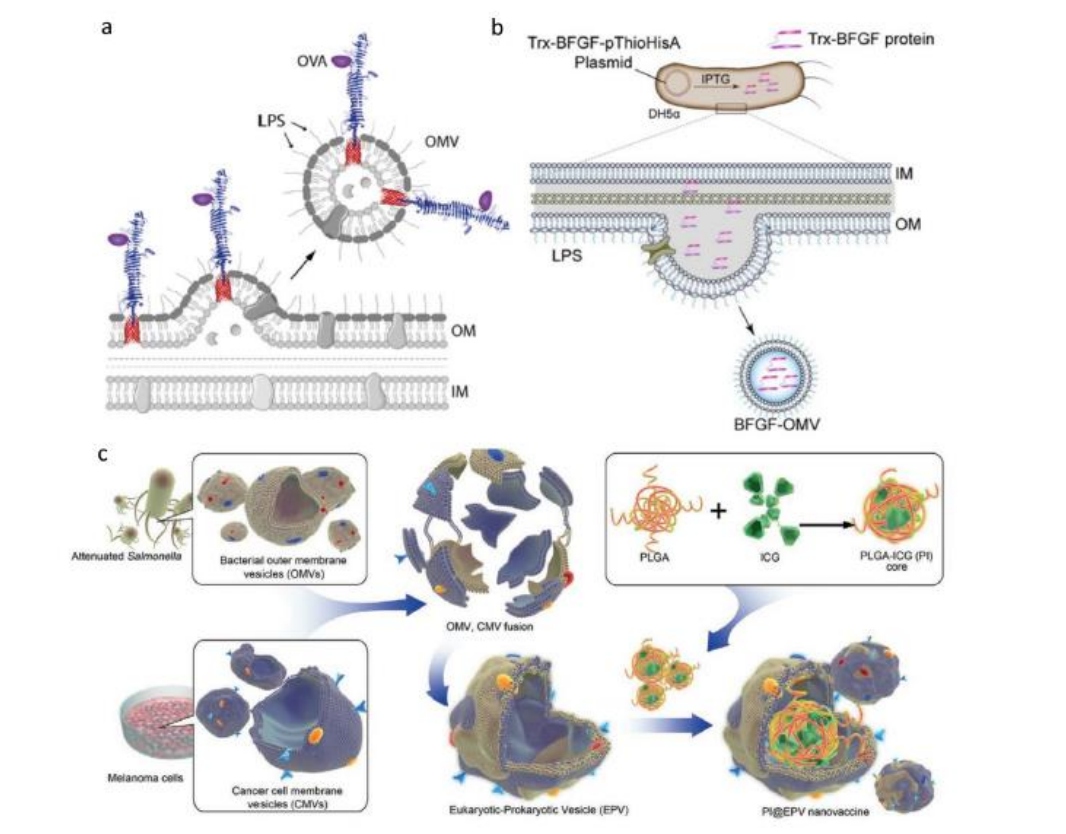


Delivery of immuno-stimulatory agents

Bacterial MVs have also been exploited for immuno-stimulatory agent delivery to act as vaccines and therapeutic agents for cancer immunotherapy treatments.

As they are released from outer membrane of bacteria, MVs contain numbers of surface adjuvants with natural immunogenicity, including lipopolysaccharides, peptidoglycan and flagellin, which could be used to initiate strong immune reactions against antigens existed on MVs and make MVs ideal vaccines against their pathogens.

Bacteria-derived MVs for the delivery of immuno-stimulatory agents.



Conclusion

In this article, we have briefly introduced the current progress in the development of bacteria and their outer membrane vesicles as drug carriers for cancer therapy.

Bacteria and their derivatives have the natural characteristics of tumor targeting, easy modification with unlimited gene packaging capability, and immune response activation.

With these advantages, tumor-targeting bacteria and their MVs are consequently ideal for controlled release and targeted delivery of chemo-therapeutic, radio-therapeutic, photothermal-therapeutic, and immuno-therapeutic agents.

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Bacteria and bacterial derivatives as drug carriers for cancer therapy

Zhenping Cao, Jinyao Liu*

Shanghai Key Laboratory for Nucleic Acid Chemistry and Nanomedicine, Institute of Molecular Medicine, State Key Laboratory of Oncogenes and Related Genes, Shanghai Cancer Institute, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200127, China

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ABSTRACT

The application of bacteria and bacteria-derived membrane vesicles (MVs) has promising potential to make a great impact on the development of controllable targeted drug delivery for combatting cancer. Comparing to most other traditional drug delivery systems, bacteria and their MVs have unique capabilities as drug carriers for cancer treatment. They can overcome physical barriers to target and accumulate in tumor tissues and initiate antitumor immune responses. Furtherly, they are able to be modified both genetically and chemically, to produce and transport anticancer agents into tumor tissues with improved safety and efficacy of cancer treatment but decreased cytotoxic effects to normal cells. In this review, we present some examples of tumor-targeting bacteria and bacteria-derived MVs for the delivery of anticancer drugs, including chemo-therapeutic, radiotherapeutic, photothermal-therapeutic, and immuno-therapeutic agents. We also discuss the advantages as well as the limitations of these tumor-targeting bacteria and their MVs used as platforms for controlled delivery of anticancer therapeutic agents, and further highlight their great potential on clinical translation.

Thank you for attention

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