Proceedings of ICBioMed 2024 Workshop: Workshop on Intelligent Medical Data Analysis for Precision Medicine
DOI: 10.54254/2753-8818/54/2024AU0117

The emerging role of cryogenesis in cancer treatment

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Abstract. Cancer is one of the most lethal chronic diseases in the world. In the United States alone, over 1.7 million diagnosed new cases of cancer cases was reported in 2022 and over half a million people died due to complication regarding cancer in that same year. The mutation that gives rise to cancer cells occurs in normal cells and causes them to proliferate uncontrollably, obstructing essential organs and making the body more vulnerable to deadly infectious infections. In modern society, the combination of a sedentary lifestyle and exposure to unsafe molecules around the public has drastically increased the mass's probability of mutation within their genetics and for cancer cells to proliferate. Cryogenesis therapy is the usage of cryogenic substances such as liquid nitrogen or argon gas to freeze and destroy the cancer cell. Cryogenesis generally involves the repetition of two steps: the freezing process and the thawing process. The freezing process is performed under extremely low temperatures and allows for the formation of ice crystals both on the inside and outside of the cell membrane, which in terms causes the rupture of the cell membrane. The thawing process is performed after the freezing process and allows the target cell to thaw; the thawing process is performed to induce osmotic shock and further induce the damage caused by the freezing process. The two cryogenesis cycles are repeated to reinforce the damage caused to the cancer cells. Compared with traditional therapies, cryogenesis therapy, as a non-invasive treatment, has The advantages of using cryogenesis are the therapy's non-invasive treatment methods, pinpoint precision and accuracy, reduced side effects after the therapy, and repeatability. Although the cryogenesis process is still new in under development, it has the potential to be effective against the most lethal cancer types, such as lung cancer and brain cancer. This review explores a new treatment for cancer, in cryogenesis, that have minimal side-effect and discusses its mechanism and application to different type of cancer and combination effect.

Keywords: Cryogenesis, cancer, treatment.

1. Introduction

Cancer cells are developed through the mutation within normal cells that causes uncontrollable proliferation, inhibiting the proper control and regulation. In 2021 1.9 million new cases of cancer were recorded and within nearly two million diagnoses, over 600 thousand people would succumb to the chronic disease [1,2]. Through technological advancement and development, however, the overall 5-year survival rate for all types of cancer combined in the United States is approximately 67%, a substantial increase from previous century where the survival rate was around 50% [3]. The lethal characteristic of tumor cell stems from the accumulation of cancer cells that can block the functions of vital organs. In addition, through the process of metastasis, cancer cells are also capable of relocating

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from one organ to another, blocking the other organ and hugely increasing the potential of blocking a vital organ, leading to total organ failure. Cancer cells can also serve as a catalyst for an infectious disease outbreak; the presence of cancer cells preoccupies the attention and effort of the immune system, which allows for the contagious disease to cause life-threatening damage.

With the emergence of technological advancement, modern society became substantially more likely to develop a sedentary lifestyle, drastically increasing exposure to unsafe molecules In addition, society's dependence on technology increases the public's exposure to radiation and unhealthy molecules in food molecules or technological devices. The combination of a sedentary lifestyle and over-exposure to unsafe conditions results in a substantial increase in mutations within genetic coding ,which directly increases the probability of developing tumors and cancer cells.

Cryogenesis is a cancer therapeutic technique that involves the freezing and thawing of target cells to induce the formation of ice crystals throughout the cancer cells, resulting in the cancer cells' cell membrane rupture. Cryogenesis uses cryogenic substances conditioned to be under -150 degrees Celsius to induce the freezing process within the cell and osmotic shock when the cell is thawed.4 The most successful cryogenic substances used in freezing have been proven to be liquid nitrogen and argon gas. The freezing cycle of cryogenesis involves injecting a specific cryogenic substance into the cancerous cells and allows for the cancerous cells to rupture in the process of necrosis. The thawing cycle of cryogenesis consists of the thawing of cancer cells from the freezing temperatures. The thawing cycle further damages cancer cycles as the transition from frigid temperatures causes osmotic shock, resulting in self-induced apoptosis. Cryogenesis is preferred over other cancer therapy sessions due to its non-invasive treatment, precision, lack of side effects and recovery time, and repeatability. Cryogenesis is generally performed through needles and probes through the skin, which is significantly less invasive than surgical removal but more precise than other treatments like chemotherapy in sparing normal cells. Due to its non-invasive treatment, patients experience fewer side effects and recovery time after the treatment.

2. Cancer symptoms and mechanisms

Cancer cells are formed through the genetic mutations of normal cells. Several mutation locations yield for the uncontrollable reproduction of cells. The mutation of oncogenes within normal cells inhibits oncogenes' function, which regulates cell proliferation and cell division. When the specific gene sequence is mutated, the silenced oncogene leads to uncontrollable proliferation of cells. In addition, cancer cells with oncogene mutation inhibit enzymes, such as E-cadherin or β-catenin, that regulate contact inhibition [4]. Contact inhibition is the process that signals cells to cease the proliferation process as the population has reached the border. The silencing of the enzyme responsible for contact inhibition results in the pile-up of cancerous cells, forming a tumor [5].

Following the accumulation of cancer cells, the tumor cells may undergo further mutation for the property to metastasis and spread to other, potentially vital, areas within the host. Metastasis is the process in which cancer cells acquire the property to spread from the origin of cancer to other parts of the body by blood vessel transport. The common mutation process that allows for the mutation of cancer cells to metastasis is the Epithelial-Mesenchymal Transition (EMT) [6]. When cancer cells undergo the Epithelial-Mesenchymal Transition, the cell loses its inherent property for cell adhesion, which is the cell's property to be attached to another cells, and allows for the cell to gain mesenchymal properties in which increases mobility by allowing the cell to detach from the tumor cell and invade other areas of the host by blood vessel transport [7]. The ability for metastatic cancer cells to spread through blood vessels leads to multiple sites of concern as tumor cells accumulate within multiple sites of the host. Through traveling by blood vessels that circulate the entire body of the host, metastasis cancer cells may settle and proliferate at an organ within the body that is essential for the survival of the host [8]. The proliferation and accumulation of cancer cells may result in the blockage of the function of the organ or cut off any blood supplies to the vital organs. This may lead to total organ failure and may subjugate the host within critical conditions in need for life-support treatment.

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3. Cryogenesis

Cryogenesis or cryotherapy is a medical technique that uses cryogenic substances such as liquid nitrogen and argon gas, under extremely cold temperatures in order to destroy abnormal accumulation of cancer cells. Cryogenesis mechanism undergoes a series of complex processes that instigate a drastic change in temperature within the cancer cells, leading to the death of the abnormal cell [9]. The initial steps in the process of cryoablation describe the cooling phase of the therapy. The cooling phases of cryogenesis involves the introduction of cryogenic substances into the tumor tissues. A cryoprobe is inserted into the tumor tissues, while being guided by imaging techniques such as ultrasound and Magnetic Resonance Imaging (MRI) techniques, and cryogens, like liquid nitrogen, are introduced into both the interior and exterior of the cancer cells. Cryogens are maintained within an extremely cold temperature and are inserted within the cancer cells in often below -100 degrees Celsius. The extremely cold temperature induced by the cryogens initially form ice crystals within extracellular space, this rapid drop in temperature causes water to flush out of the cell due to osmosis, leading to hyper osmosis process and an increase in concentration of solute outside the cell. As temperature continues to drop, ice crystals begin to also form within the intracellular space, the ice formation within the cell disrupts the functions of protein, organelles and the stability of the cell membrane, which may cause the rupture of cell membrane leading to mechanical damages and deformation of the cell [10]. The cooling phase of the cryogenesis varies in duration from the size of the cancer cells and the location of tumor. Following the cooling phase, the introduction of cryogens stops and the cryoprobe is allowed to warm up through a warming agent and the initiation of the thawing process begins. The warmed up cryoprobe through a controlled warming agent mitigates the rate of thawing and regulates the gradual increase in temperature rising in the frozen tissue. This rise in temperature causes the ice crystals both within and outside the cell to melt proportional to the rate controlled by the warming agent [11]. As the extracellular space thaws and the ice crystals melts, the cancer cell experiences an osmotic shock as the melted ice crystal flushes back into the cell due to osmotic gradient from the cooling phase. This flux of water back into the cell causes the cell to swell under the pressure of hyperostosis and damage the already ruptured cell membrane and organelle stability. The combination of cooling and thawing processes is repeated multiple times to reinforce the pressure of osmosis shock and ensures that any surviving cancer cells are subjugated to additional freezing-thaw cycles. The repeated cycles of freezing and thawing ultimately leads to the lysis of cell membrane and the signaling for cell death.

Cryogenesis offers several advantages in treatment against cancer, mainly in terms of the therapies non-invasive treatment, precision in targeting tumors. Cryogenesis offers a non-invasive treatment method against cancer through the usage of a percutaneous approach, similar to injections [12]. Cryotherapy often involves the usage of cryoprobe which functions similar to needles through its insertion into the skin by small incision or simply puncturing the skin. The non-invasive treatment generally involves localized anesthesia and minimal permanent damage to the patient by the therapy which minimizes the physical trauma experienced by the patient and results in quicker recovery time. The non-invasive and minimal side effect advantages offered by cryogenesis makes the therapy an attractive alternative option compared to surgical procedures within its invasive techniques and up to months of recovery time. In addition, cryogenesis offers precise targeting of tumor cells in order to minimize the damage caused to nearby cells. Cryogenics treatments are often guided by real-time imaging techniques such as MRI and ultrasound in order to localize and present a precise visualization of the tumor and surrounding tissues during the therapy session. In addition, the advanced cryoprobes acts as a vector for precise and controllable injection of cryogens, the flexibility of the cryoprobes also allows for the targeting of tumor cells in various location and sizes, which further assures the precise injection of the cryogenic molecules into cancerous cells with minimal side effects to the surrounding tissues [13].

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4. Cryogenesis application in cancer treatment

4.1. Cryogenesis application in combination therapy

Cryogenesis may serve in combination with other therapy to ensure treatment in multiple conditions, synergizing the advantages in multiple therapies. Cryochemotherapy is a treatment approach that combines the freezing and thawing cycles within cryoablation with chemotherapy to enhance the efficacy of cancer treatment [14]. In terms of cryogenics contribution within the treatment, the insertion of cryoprobe in the execution of freezing and thawing cycles leads to permanent mechanical damages and cell lysis in the disruption of cell membrane as well as vascular damages leading to ischemia and further enhances cell death. Chemotherapy functions by administering chemotherapeutic substances either systemically or locally to kill cancerous cells. The combination of the two therapy increases efficacy of cell death and overcomes the resistances of each therapy. In terms of the synergize effect when combined, recent study propose in comparison to normal chemotherapeutic session, the experimental group with the addition of cryogenics application prior to the chemotherapy session yielded for improvement in autonomic symptoms such as dizziness and low blood pressure, in addition, the experimental group was found to be effect against small fiber neuropathy, preventing patients any chance of developing neurological disorder after the cancer therapy [15]. Cryotherapy disrupts the cancerous cell membrane which in terms increases the cancer cells' permeability for chemotherapeutic agents. The weakening of the cell membrane through repeated cycles of freezing and thawing lead to greater susceptibility for chemotherapeutic agents. In addition, cryotherapy may help overcome chemotherapy resistance in establishing a favorable tumor microenvironment which further weakens the cancer cells vulnerability to chemotherapeutic agents [16]. Cryotherapy damages the blood vessels surrounding the tumor masses in freezing and formation of ice crystals, in addition the reduction of blood vessels also results in the reduction of blood supplies. This may lead to hypoxia and nutrient deprivation, further increasing the cancer cells' permeability for chemotherapy agents. Through clinical trials, the application of cryotherapy with chemotherapy has yielded positive results in terms of an overall increase in 1-year survival rate. Specific studies in which an experimental trial combined the application of cryotherapy with chemotherapy is paired against control trials only distributing chemotherapy yielded for a higher overall 1-year survival rate with an average survival rate of 89% compared to the control group's approximately 76% survival rate [17].

In addition, Cryotherapy may also work in conjunction with therapeutic cancer vaccines in the identification of antigens and release of damage-associated molecular patterns (DAMPs) which assist in the stimulation of the immune system. As cancer cells succumb to the effects of the cryotherapy, the tumor cells undergoing apoptosis and necrosis releases a variety of intracellular antigens into the surrounding tissues. These antigens can be identified and used in the priming of cancer vaccines and subsequent stimulation of the immune system. The cancer vaccine uses the antigens provided by cryotherapy to develop a vaccine to target the specific antigen and allows for the immune system to produce antibodies against cancer cells [18]. In addition, cryotherapy may also cause the release of DAMPs proteins which may initiate an immune response. After a cancer vaccine has collected and processed the specific antigen for the cancer cells, cryotherapy can be used to stimulate the immune system by initiating the release of DAMPs factors. The combination of cancer vaccine and stimulated immune system through the release of DAMP factors as a result of cryotherapy synergizes more efficient immune system response. While clinical trials vary in success rate in terms of the type of cancer and stage of cancer the combination treatment is used for, through laboratory results, the experiment trial has seen an increase in immune system effectiveness compared to the control trial with only administering cancer vaccine [19].

4.2. Cryogenics Application to different type of cancer cells

Cryotherapy is an emerging treatment option for localized lung cancer, specifically for patients who are not candidates for surgical removal of the cancer cells. In terms of patient selection, cryotherapy generally favors patients with small and localized lung cancer or metastatic lung cancer cells stimulated from a different origin of cancer, for patients who fits the criteria, cryogenesis serves as a powerful alternative for cancer therapy [20]. For cancer cells accessible through the airway, cryotherapy takes an alternative approach in guiding the cryoprobe to the location of the cancer accumulation. Rather than using ultrasound and MRI, the cryoprobe uses a bronchoscope to guide the cryoprobe to the tumor site and delivers cryogens to freeze the tumor cells. Alternatively, if the cancer cells are found within the peripheral lung, cryotherapy takes a traditional approach in using imaging technique to guide the cryoprobe and insert the vector through the skin and into the lung cancer tissue. The cryogenics therapy then subjected cycles of cooling and thawing phases in order to promote osmotic shock to the cancer cells. The success rate for the application of cryogenics varies in terms of the stage or development of the cancer cells and overall has shown survival rate comparable to other non-invasive treatment plans such as radiofrequency ablation [21]. In terms of some shortcoming by cryogenics in the treatment for lung cancer, the treatment may cause pneumothorax, which is collapsed lung due to the osmotic shock and freezing extracellular space induced by the initial process of cooling phase.

In addition, cryogenesis has shown great promise in the treatment against brain cancer. Similar to the patient selection of lung cancer, cryotherapy favors patients with small and localized cancer cells and also for patients that are not great candidates for the surgical removal of tumor masses. In accordance with the conventional methods for cryogenesis, precise imaging guidance is required for the placement of cryoprobe into the brain. The placement and precision of the imaging guidance of cryoprobe must be exceptionally paramount due to the critical natures of the soft brain tissue. As such, stereotactic techniques, in which a three-dimensional coordinate system is used for the precise insertion of the cryoprobe into the target tumor area [22]. The cryogenics therapy then subjected cycles of cooling and thawing phases in order to promote osmotic shock to the cancer cells. Due to cryotherapy being a relatively new therapeutic method, a limited amount of data can be drawn on the success rate against brain cancer, however a limited case report has shown that cryotherapy can be effective in reducing the tumor size. Some limitations in terms of cryotherapy's application to brain cancer result from the therapy's challenge when interacting with the highly sensitive nature of brain tissues.

5. Conclusion

Cryogenesis, or cryoablation therapy, represents a groundbreaking approach in the fight against cancer, offering a minimally invasive method that harnesses the power of extreme cold to destroy cancer cells. By leveraging the precise application of cryogenic substances like liquid nitrogen or argon gas, cryogenesis effectively induces necrosis and apoptosis in cancer cells through repeated cycles of freezing and thawing. This innovative technique provides numerous benefits, including pinpoint accuracy, reduced side effects, and the ability to be repeated as necessary, making it a promising option for treating some of the most lethal cancer types, such as lung and brain cancer. While still in the developmental stages, the potential of cryogenesis to offer rapid and effective cancer treatment with minimal side effects positions it as a valuable addition to modern oncological therapies. Further research and clinical trials will be essential to fully realize and optimize its therapeutic potential.

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