CYTOLYTIC PEPTIDE OFFER A NEW HOPE IN CANCER TREATMENT

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ABSTRACT

Zubaidah Ningsih A., S. 2012. Cytolytic peptide offer a new hope in cancer treatment.

Research into effective cancer treatment has not yet discovered an entirely effective and universally accepted approach. A promising targeted anti-cancer agent, cytolytic peptides, which can be found in plants, animals and even human body, show high speed and selectiveness in targeting abnormal cells. Cytolytic peptides, which commonly are positively charged, selectively lyse the more negatively charged cancer cell membrane compared to the normal cell. In addition, the ability of cytolytic peptides to disrupt cell membrane within a millionth of a second can prohibit cancer cell resistance development. With these features, cytolytic peptides offer a new hope in cancer treatment.

Keywords: anti-cancer, cytolytic peptide, efectivity, selectivity

ABSTRAK

Zubaidah Ningsih A., S. 2012. Peptida sitolitik memberikan harapan baru pada perawatan kanker

Hingga saat ini pendekatan pengobatan kanker yang efektif dan diterima secara umum belumlah ditemukan. Peptida pembunuh sel *(Cytolytic peptide)* yang banyak ditemukan di tanaman, hewan bahkan di tubuh manusia ditengarai mempunyai potensi menjadi obat kanker yang efektif karena efektivitas dan selektivitasnya dalam membunuh sel kanker. Peptida pembunuh sel yang umumnya bermuatan positif secara selektif dapat menghancurkan dinding sel kanker yang bermuatan lebih negatif dibanding sel sehat. Selain itu kemampuan peptida ini dalam menghancurkan dinding sel dalam hitungan detik mampu mencegah timbulnya resistensi sel kanker terhadap obat anti-kanker. Dengan kemampuan ini peptida pembunuh sel menawarkan kemungkinan penemuan obat anti-kanker yang efektif.

Kata kunci : anti-kanker, peptida pembunuh sel, efektivitas, selektivitas

INTRODUCTION

Cancer is still included in the world's most deadly diseases. It caused approximately 7.6 million deaths in 2008 and is projected to cause 13.1 million deaths in 2030 (WHO, 2012). Meanwhile, research into effective cancer treatment has not yet discovered an entirely effective and universally accepted approach. Even though chemotherapy, which treats cancer by applying certain chemicals to the patient, is considered to be the most effective cancer treatment nowadays, many doubt its effectiveness since it fails to accurately attack cancerous lesions. Hence, treatment has been shifted to the targeted therapy in which the chemicals are designed specifically to destroy cancer cells. A promising targeted anti-cancer agent, cytolytic peptides, which are protein-class compounds having cell membrane destroying properties, show high speed and selectiveness in targeting abnormal cells (Leuschner & Hansel, 2004; Papo & Shai, 2005; Meyer & Harder, 2007). This essay will evaluate the features of cytolytic peptides which make it a better targeted anti-cancer agent compared to the drugs in current use. The first part of this essay will present the shift of chemotherapy to targeted therapy and is followed by the evaluation of cytolytic peptide features, specifically their selectiveness and effectiveness.

RESULTS AND DISCUSSIONS

The shift of chemotherapy to targeted therapy in cancer treatment

At the beginning of cancer treatment, most prominent chemicals used in chemotherapy were derived from an accident invention instead of a careful drug designing. Only in the 1950's did clinical trials start to investigate the exact mechanism of those chemicals. In the ensuing years, many scientists successfully designed anti-cancer agents which they then applied in chemotherapy. These chemicals are mainly alkylating agents, platinum compounds, antibiotics, alkaloids and other sorts of drugs which

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enable DNA structure modification, life-cycle perturbation or self killing initiation of cancer cells.

However, Gnewuch & Sosnovsky (2002) report that the failure to understand the exact mechanism of cancer cell initiation and drug delivery system might lead to a mistaken prediction of drug effect where apparently anti-cancer agents attack not only cancer but also normal cells. Since the drugs are administered intravenously, they spread uncontrollably which may lead to normal tissue destruction and the annihilation of abnormal cells. Moreover, a barrier consisting of capillaries networkwhich might prohibit the therapeutic agents in the blood permeating brain system, preventing the drugs from reaching the cancerous area (Braun, Pipkorn, & Waldeck, 2005). Thus, chemotherapy is often an ineffective treatment and causes cancer patients to vomit, lose immunity and easily feel weary.

Moreover, Gnewuch and Sosnovsky (2002) states that chemotherapy using alkylating agents often faces failure due to the development of resistant cancer cells. At early stage of the treatment, akylating agents which are capable of adding functional groups to cancer cell's DNA structure, induce DNA structure modification and form mutated DNA. As a result of the mutation, cancer cells fail to replicate themselves. Consequently, the spread of cancer cells is stopped. However, cancer cells gradually produce particular enzyme which makes the cells no longer susceptible to the alkylating agents. These enzyme, such as GAT (O6-alkylguanine-DNA transferase) are likely to prevent cancer cells division for they disallows the alkylation of DNA by cancer drugs. Given that alkylation of DNA can be avoided,cancer cells become insensitive to the drugs. Therefore, cancer cells resist alkylating agents and the drugs fail to cure cancer.

As a result of drugs failure in healing cancer, chemotherapy has become less popular. It has been asserted by Braun, Pipkorn and Waldeck (2005) that "targeted cancer therapy", which is a cancer treatment involving therapeutic agents that precisely attack cancer cells, is a new way of improving the efficiency of chemotherapy. In addition,targeted cancer therapy reduces the destruction of normal tissue or adjacent organs since it attacks cancer cells accurately. Furthermore, an exact amount of drugs could be delivered to the specific target which minimizes overdose risk as well as drug toxicity. Cytolytic peptides are one of the compounds which are known to have potency as targeted anti-cancer agent.

Cytolytic peptides

Since their discovery, cytolytic peptides, which mainly are positively charged, have shown high affinity towards negatively charged microbial cell membranes (Brogden, 2005). Research has since discovered that they also show preference to cancerous cells. While the membrane of normal cells is neutral, membrane of cancerous cells contains 3-7 times more phosphatidylserine (PS) than the normal cells. PS is commonly known as a negatively charged compound (Leuschner & Hansel, 2004). Therefore, cytolytic peptides could accurately discern cancer to normal cells which gives it extremely high potential as a targeted anti-cancer agent.

Cytolytic peptides can be found in many organisms such as plants, animals and also human. Size, charge, sequence, conformation, hydrophobicity and amphipathicity of cytolytic peptides determine the biological activity and toxicity of cytolytic peptides. By 2005, 880 cytolytic peptides have been identified (Brogden, 2005). Further to these findings, research has been conducted to explore cytolytic peptides toxicity towards cancer cells. Meyer & Harder (2007) claim that defensins, one of cytolytic peptides which are derived from human granulocytes, are able to surpress oral cancer growth. In addition, Leuschner & Hansel (2004) report that crecopins, which are the cytolytic peptide isolated from silk moth, and magainins and dermaseptin, which are the class of cytolytic peptide taken from frog skin, show capability to lyse tumor cells selectively. Another class of cytolytic peptide, melittin, which is extracted from bee venom, also exhibits toxicity to cancer cells (Soman, Baldwin, Hu, Marsh, & Lanza, 2009). This data support the idea that indeed cytolytic peptides show promise in cancer treatment.

Cytolytic peptide selectiveness in disrupting cancer cells

Whereas it is believed that cytolytic peptides are a breakthrough in finding an effective targeted anti-cancer agents, nonetheless many scientists are uncertain about its selectiveness (Gnewuch & Sosnovsky, 2002; Kuhn-Nentwig, 2003; Leuschner & Hansel, 2004; Meyer & Harder, 2007). Some cytolytic peptides such as magainins, crecopins and dermaseptin indeed have capability of killing bacterial and tumoric cells only, yet melittin is unable to do so. Melittin disrupts bacterial, tumoric as well as mammalian normal cells which lead to low selectiveness (Leuschner & Hansel, 2004). As described previously, positively charged cytolytic peptides tend to bind to negatively charged cancerous cells. However, melittin, which carries 6+ charges,

fails to selectively attack abnormal cells. This implies that a particular cytolytic peptide with a specific structure performs differently from one to another even though they share similar main features.

Moreover, Leuschner and Hansel (2004) maintain the urgency of research regarding the cytolytic peptides structure which influences its effect to cancer cells. The lack of exact understanding in regards to cytolytic peptides killing mechanism is considered as an obstacle in predicting the drugs effect when administered into human body (Gnewuch & Sosnovsky, 2002). Several cell-killing mechanisms which have been proposed to describe the phenomena, signify the need of further investigation (Leuschner & Hansel, 2004). Thus, it can be argued that the effectiveness of cytolytic peptides application is debatable.

On the other hand, evidence against the idea that cytolytic peptides are unfeasible to be an effective targeted anti-cancer agent comes from Soman et al (2009). They have found that the integration of less specific cytolytic peptide into certain nanoparticles increases the capability of the peptide to target cancer cells. By including melittin into perfluorocarbon nanoparticle structure, a sufficient amount of melittin is successfully transmitted into the multiple targeted areas such as murine cancer cells and other lesions. Surprisingly, melittin also significantly reduces tumor growth without normal cell rupture. Even though at this level melittin render hemifusion rather than complete cell fusion, still it has a lethal effect on abnormal cells. Hence, Soman et al (2009) argue that "molecularly targeted nanovehicles" offer a way to optimize the usage of cytolytic peptides as an effective anti-cancer agent.

In addition, the treatment using multi-drugs, whether it is all targeted anti-cancer agents or combination between targeted anti-cancer agents and traditional drugs, is considered to be a complementary method to overcome anti-cancer agent's non-selectivity as well as treatment failure due to various cancer patient conditions. Since each drug has its own preference in weakening cancer cells and different patients suffer different cell anomalies, multi-drug treatment is asserted to be the most suitable treatment method. This is supported by the fact that researchers at The Sarah Cannon Cancer Centre in Nashville, Tennessee, have successfully improved targeted anti-cancer agents performance against kidney cancer when it is combined (The Economist, 2004). Even though some people infer that the combination treatment effectiveness is vague, still, this new approach offers a new way of improving cytolytic peptides selectivity.

Moreover, in the last few decades, research to elucidate cell-killing mechanism of cytolytic peptides has rapidly increased (Leuschner & Hansel, 2004). Inventions of how cytolytic peptides disrupt the cell membrane have significantly contributed to the revelation of cytolytic peptides activity as well as their effect inside human body. Consequently, it is easier to predict the effect of cytolytic peptides and to manipulate their structure in a way that suitable to our needs in fighting cancer. Proving that there are ways to overcome the shortages of cytolytic peptides together with more discoveries on the exact mechanism of cytolytic peptides cell-killing mechanism, cytolytic peptides offers a beneficial features as a new selective anti-cancer agent.

Cytolytic peptides effectiveness in killing cancer cells and inhibiting resistance

Having cell membrane disruption properties, cytolytic peptides rapidly destroy cancer cells within a millionth of a second (Leuschner & Hansel, 2004). However, it is not only cytolytic peptides which are capable of performing this action. Currently used drugs also lead to the death of cancer cells as fast as cytolytic peptides due to their high toxicity. Furthermore, Gnewuch & Sosnovsky, (2002) reported that cancer cells' resistance to the alkylating agents can be diminished by adding a certain compound. The addition of certain compound prior to alkylating agent administration to a cancer patient has successfully sensitized cancer cells. Based on this reasoning, many people have questioned cytolytic peptide effectiveness since the currently used drugs could perform as good as cytolytic peptides.

Meanwhile, other approaches have also been proposed to fight cancer. Many new targeted anti-cancer agents with different mechanisms have been introduced. For example, Gleevec and Ilressa, which play a significant role in replacing certain enzyme causing cancer cells division, have shown to be potential. Another example is Herceptin, which is included in antibodies class, are capable of attacking cancer cells for it is recognized as an invader in human body. Viruses, surprisingly, are also agents which can be employed to destroy cancer cells which are specifically different from normal cells. Adenovirus, for instance, is now being tested to cure brain cancer (The Economist, 2004).

Despite the fact that many approaches might offer the same chance of finding an entirely effective and universally accepted approach, I personally believe that cytolytic peptide still show the most potential agent for cancer treatment. The reason for this is that cytolytic peptides rapidly disrupt the

abnormal cell membrane so the organization of the cell is destroyed. This action causes permanent damage to the cell organization, leaving no chance for the cell to develop its resistance. In contrast, other anti-cancer agents tend to permeate into the cell attacking the DNA or other cell components without damaging the cell membrane allowing the development of cell resistance and this will eventually reduce drug's effectiveness.

CONCLUSIONS

After weighing up the evidence, it is can be concluded that cytolytic peptides offer a new solution to answer the controversy of finding the most effective approach in fighting cancer. Cytolytic peptides are likely to be the most effective anti-cancer agents since they are capable of selectively attack abnormal cells membrane in a very short period inhibiting cells resistance development. To optimize this potency, I strongly support further research in designing cytolytic peptides based targeted anti-cancer agents.

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