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Research Article

A New Strategy to Assist Macromolecular Drug Therapy and its Potential Application on the Precision Medicine

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Abstract

Macromolecular drugs refer to the drugs whose active pharmaceutical ingredients are large molecules, including peptides, proteins, antibodies, polysaccharides and nucleic acids. Although these drugs have been applied to treat carcinoma, AIDS, cardiovascular disorders, genetic diseases and neurodegenerative disorders, generally speaking, the macromolecular therapeutics are still in the initiation stage. Theoretically, macromolecular drugs have huge potentials to be the best therapy for personalized precision medicine. For example, a cancer patient who is caused by the deficiency of a specific tumor suppressor can be easily treated by giving the exactly same tumor suppressors through the macromolecular therapy. This kind of application is out of scope of any small molecular drugs. The future of macromolecular therapy is promising, though there are obstacles to overcome. To date, none of the macromolecular therapeutics are produced by original normal human cells. Most of them are produced by non-human cell lines, transgenetic chicken (eggs), and immortalized human cell lines which made to actively proliferate via mutation. High-dose of macromolecular drugs have negative effects, while low-dose is hard to achieve therapeutic effects. Moreover, the current macromolecular drug delivery methods are not highly efficient, and the cost for high dose is also a concern. For example, the macromolecular drug treating the lethal disease of LAL deficiency is costing 0.6 million USD per patient per year. In another word, it costs a house to allow a patient to live for each extra year. People die because of non-affordability. Hereby, we are developing a new strategy to enhance the effects of macromolecular drugs. This strategy is named as the Sun Strategy in Drug Development, which applies one or several enhancers that enhance the macromolecular drug's efficacy while minimizing the dose of these external macromolecular molecules. It is noteworthy that such an enhancer could be a food supplement (active food component/nutraceutical), an herbal medicine, a pleasant music (music therapy) or a small molecule specifically designed by the rational drug design, or an optimized combination of these. In another word, one plus one is more than two; one plus one plus one is far more than 3; at least, one plus 0.5 is more than 1 – here by the "0.5" referring the reduced dose of the macromolecular drug that is either out of affordability or with strong negative side effects. By minimizing the doses of macromolecular drugs, this strategy saves or extends human lives.

Keywords: Personalized Medicine; Precision Medicine; Macromolecular Drug Design; Tumor Suppressor; Sun Strategy in Drug Development; Nutraceuticals; Music Therapy

Introduction

Macromolecular drugs refer to the drugs whose active pharmaceutical ingredients are large molecules, including peptides, proteins, antibodies, polysaccharides and nucleic acids. Although these drugs have been applied to treat carcinoma, acquired immunodeficiency syndrome (AIDS), genetic diseases, cardiovascular disorders and neurodegenerative disorders, generally speaking, the macromolecular therapeutics are still in the infant stage.

To date, none of the macromolecular therapeutics are produced by the original normal human cells. Most of them are produced by non-human cell lines, transgenetic chicken (eggs), and immortalized human cell lines which are engineered to actively proliferate via mutation. High-dose of macromolecular drugs have negative effects, while low-dose is hard to achieve the therapeutic effects. Moreover, the current macromolecular delivery methods are not highly efficient, and the cost for high dose is also a concern. For example, the macromolecular drug treating the life-threatening lethal disease of LAL-D (lysosomal acid lipase deficiency) is costing more than million dollars per patient per year. In another word, it costs a house to allow a patient to live for each extra year. People die because of non-affordability and poverty, which have raised the concerns of social fairness that are demanding a solution. Hereby, we propose a new strategy to enhance the effects of macromolecular drugs. This strategy is named as the Sun Strategy in Drug Development, which administers an enhancer that enhances the macromolecular drug's efficacy while minimizing the dose of these external macromolecular molecules.

The Sun Strategy is first proposed by the senior author Dr. Sun in one of previous studies [1]. This article will give more details about this strategy. It is worthy of mentioning that the above-mentioned enhancer could be a food supplement (active food component/nutraceutical), an herbal medicine, a pleasant music (music therapy) or a small molecule designed by rigorous rational drug design, or an optimized combination of these. By minimizing the doses of macromolecular drugs, this strategy saves or extends human lives. It is noteworthy that the above-mentioned Sun Strategy in Drug Development is not only limited to the macromolecular therapeutic development, but also applicable to a broad range of drug discoveries: in best scenarios, one plus one is more than two; one plus one plus one is far more than 3. At least, one plus 0.5 is more than 1 – hereby the "0.5" referring the reduced dose of the therapeutic drug that is either out of affordability or with strong side effects.

Although there are boundaries to break, the future is promising. Macromolecular drugs have huge potentials to be the best therapy for personalized precision medicine. For example, a cancer patient who is caused by the deficiency of a specific tumor suppressor can be effectively treated by giving the exactly same tumor suppressors through the macromolecular therapy. This innovative application is out of scope of any small molecular drugs. For another example, LAL-D is an innate genetic fatal disease; the median life of LAL-D patients is only 3.7 month. LAL is referring to the lysosomal acid lipase; D means deficiency. The lethal effect is caused by the deficiency of an essential human enzyme, the lysosomal acid lipase, because its corresponding gene is not functional. The patients can be treated by administrating a macromolecular drug that functions as the lysosomal acid lipase. Though the drug is still very expensive, its therapeutic effect is obvious. It is approved by FDA (Food and Drug Administration). As the best Canadian scientists, the senior author Dr. Sun and coworkers had made significant contributions to the drug development. When the first baby patient celebrated its five year birthday, Dr. Sun received heart-touching acknowledge to thank the tremendous effects that make this possible.

Hereby, we proposed the applications in cancer patients suffering from the deficiency of Dlc2 gene. This gene's product is Dlc2, which functions as a tumor suppressor. Since there are no conflictions of interests on the original Dlc2 research, it is safe to discuss more details. The Dlc2 deficiency causes cancer. The genes for Deleted in Liver Cancer (Dlc) are frequently silenced in many cancer cases. Dlc deletion is associated with ~ 50% of breast, liver and lung tumors and in over 70% of colon cancers. There are several types of Dlc genes. Among them, Dlc1 and Dlc2 genes are tumor suppressor genes, which express the Dlc1 and Dlc2 tumor suppressors, which is a large group of molecules that are capable of controlling cell division. Dlc2 is downregulated in breast, liver, glioblastoma and lung tumors. Our recent research found that the ceramide can interact Dlc2 and, subsequently, alter the Rho activity. The ceramide can directly interact with Dlc2 through its START domain and enhance the Dlc2's anticancer action (Figure 1).

To date, there is no commercial conflicts for its therapy, so it is safe to discuss in open-access publications. To precisely treat Dlc2 deficiency, Dlc2 recombinant protein can be developed as a macromolecular drug. The disadvantage will be same as aforementioned for most macromolecular drugs. Through rigorous studies, we found the ceramide can enhance the effects of Dlc2 [1]. In addition to chemically synthesized, ceramide can be easily acquired from food; thus, the ceramide could be used as an enhancer to enhance the macromolecular drug (recombinant Dlc2 protein) according to the Sun Strategy. During treatment, a pleasant environment created by playing music (music therapy) will facilitate the positive therapeutic effect. According to the Sun Strategy, both ceramide and music can be used as enhancers: one plus one plus one is over three!

In order to achieve the optimized effect, the enhancer(s) has to be carefully selected. The sources of ceramide can be taken from food; ideally, it can be designed as a small molecular drug by structure-based drug design to maximally enhance the therapeutic effects. Our research found ceramides interact with Dlc2 through binding to its START domain; in this sentence, we use plural forms for the word of "ceramides" because 1) ceramides have variant forms with different lengths of carbon chains; 2) we found there are

case of Dlc2 deficiency, a personalized therapy could be developed via integrating music meditation, food therapy (ceramide-rich food) and a medicine. Hereby, the medicine refers to a medicine containing the active pharmaceutical ingredient (API) of Dlc2 protein (macromolecular drug). Moreover, the structure of ceramide can be better designed to have more positive interactions with Dlc2 protein. More precisely, an advanced medicine can be made by APIs containing both the macromolecular drug, Dlc2 protein, and the small molecule that is well designed to facilitate the action of Dlc2 protein. This promising therapy is expected to be highly specific with minimal negative effects.

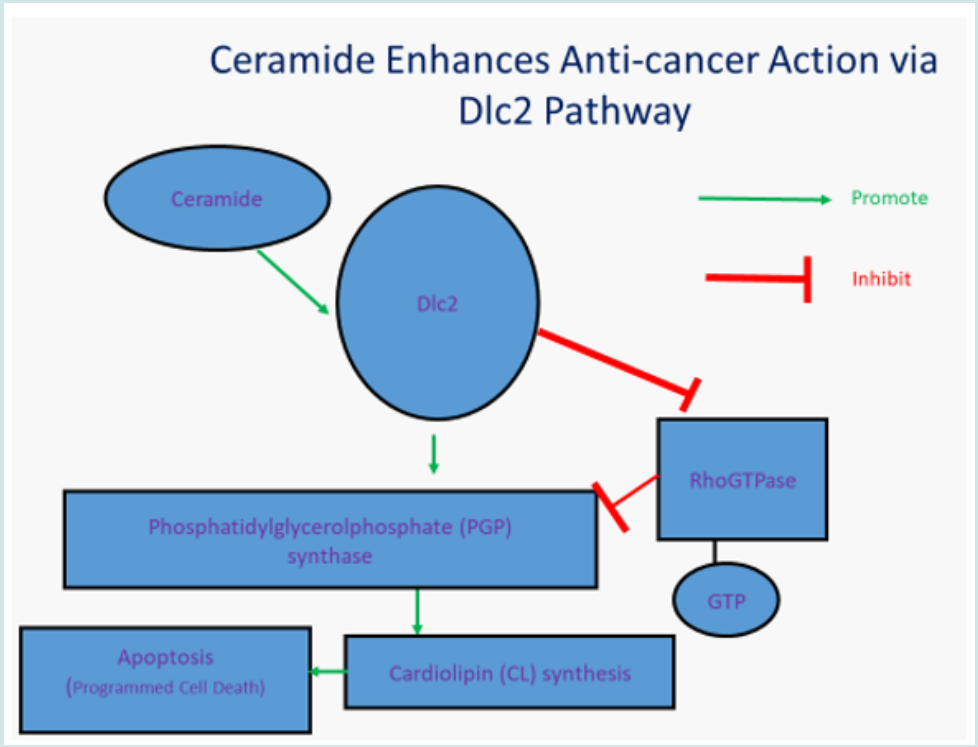

Figure 1: The pathways for how the ceramide can enhance the Dlc2's anticancer action.

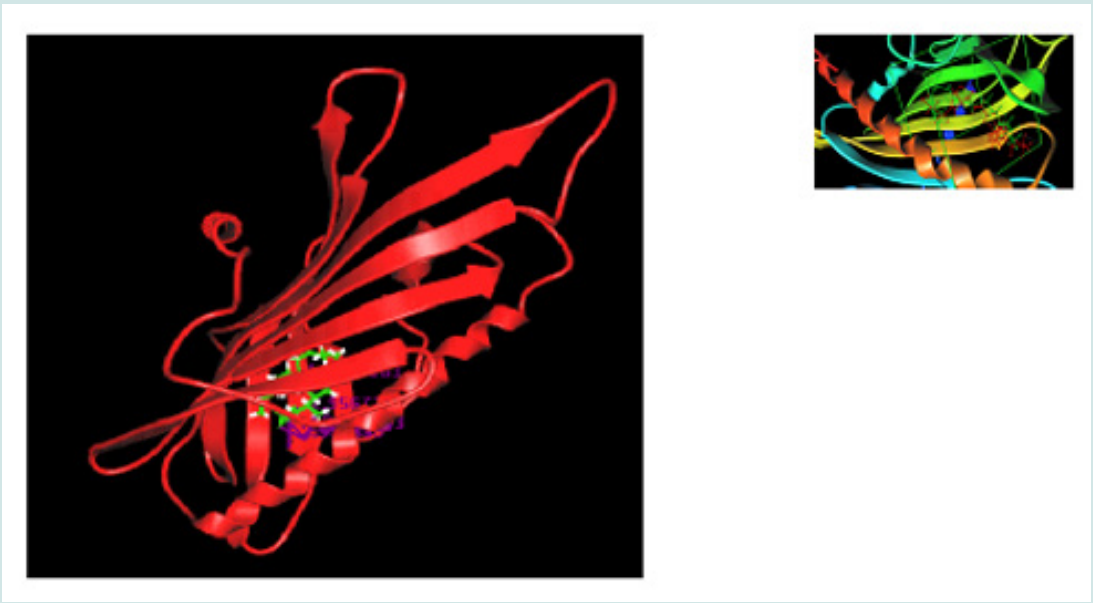

Figure 2: 3D model on the interaction of the ceramide with the START domain. Courtesy of Sun et al. 2024 (Drug Des Int Prop Int J [1]).

Discussion and Conclusion

The above-proposed application of Sun Strategy on the drug development for the Dlc2 deficiency is just one of many examples. In average, it usually takes one billion dollars for a drug from basic research to marking approval. The cost for developing a cancer drug is far more than that. To avoid competition, the authors are very cautions to select a scenario to discuss. Since there are no conflictions of interests, it is safe to discuss more details for Dlc2 research. Actually, the similar applications can be applied to almost all macromolecular drug developments to treat certain critical gene deficiencies.

Under current science frame, there are several ways to cope with a gene deficiency. One of the most straightforward way is to administer a protein (macromolecular drug) that has the same function as the gene product. The use of an enhancer, e.g. a secondary small molecule, active food therapy, complementary music therapy or their combinations, will improve the action of the therapeutic protein drug and keep the administrated dose of a protein drug to the minimal level. This strategy could dramatically reduce the side effects while easing the difficulties encountered during the macromolecular drug deliveries.

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