癌症免疫細胞治療的現在與未來

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【摘要】

在台灣，2017 年有四萬人死於癌症，且這數字每年不斷在攀升中。根據全球統計，癌症是過去 30 幾年來死亡率的主因，世界衛生組織（WHO）更估計，在未來的 20 年中，罹癌的人數將會增加 57%。儘管經過醫師及科學家不斷的努力，至今我們發現，沒有任何一種單一癌症治療方式是有效的。

傳統的癌症治療包含：手術、化療、放射性治療及標靶治療，但這些治療結果往往不盡人意且癌症後期的預後情況也不佳。近代醫學最振奮人心的突破，即是發現免疫系統在生物體內對抗癌症的功能，免疫療法也因此成為癌症患者的一道曙光。造成癌症患者預後情況不佳的主因，是因為癌細胞抑制了免疫系統的抗腫瘤反應，所以我們的目標就是找出可以增強患者免疫系統的方法，去消滅不正常的細胞。

以往的免疫治療在臨床上沒有顯著的成果，主要因為我們對免疫系統的機制還沒有充分的了解，然而在這近十年，科學家有了重大的突破，免疫治療因此在許多癌症治療上有了顯著的成果。免疫治療大致上可分為兩大類，一是免疫藥物治療，一是免疫細胞治療。免疫藥物治療包括使用單株抗體去增強患者的免疫系統，進而去辨識及消滅癌細胞；而免疫細胞治療則包括癌症疫苗和免疫細胞的體外過繼培養／調整，利用身體的免疫細胞幫助對抗癌細胞。

在正常的情況下，我們的身體每天都會產生癌細胞，但我們的免疫系統本身就有能力藉由抗原呈現細胞，將腫瘤抗原呈現給 T 細胞，使 T 細胞利

用各種方式去辨識和消滅癌細胞。然而癌細胞會隨著時間突變偽裝成正常細胞，躲過免疫系統的辨識。為了解決此問題，現在科學家能夠從人體分離出所謂的“已教育的 T 細胞”，然後在實驗室裡擴增培養，再注射回體內對抗癌細胞。除此之外，我們也可以從患者的血液裡採集抗原呈現細胞（例如樹突細胞），利用抗原去教育抗原呈現細胞，之後再回輸身體，最後藉由抗原呈現細胞去教育 T 細胞，讓 T 細胞能夠辨識癌細胞，有效攻擊癌細胞。儘管看似有效，但我們還是面臨到許多挑戰，因為只有少數的患者受惠於此治療方式，原因在於癌細胞會利用不同的機制逃過我們的防禦。

經過多年的研究，T 細胞已被臨床證實是免疫治療的焦點。事實上，有許多藥物也被發展用來增強我們的 T 細胞特性，而現在我們也可以利用許多不同的方式在體外增強 T 細胞毒殺的能力。因此，未來的免疫治療重點在於增進 T 細胞的辨識及消滅能力。例如一個典型的例子是：利用從患者身體癌組織取得的新型抗原，去培養 T 細胞。除此之外，合併治療將會是未來癌症的主要治療方式，因為我們可以透過化學藥物或放射性治療去抑制不正常細胞的逃避機制，讓我們回輸至患者體內的細胞能更精準的辨識癌細胞。

免疫細胞治療的另一項挑戰即是生產成本，以現今的技術，免疫細胞治療需要許多人力資源，以確保細胞在培養的過程中是安全不受汙染且保持著最佳療效的。因此我們必須發明新的生產方式以降低成本，讓一般民眾能受惠於此治療方式。

在癌症治療上，這是我們期待已久且振奮人心的時刻，但我們仍面臨著許多挑戰。如何提升治療效果、降低生產成本及合併治療的策略都是未來免疫治療的重點，免疫治療毫無疑問的是癌症病人最大的希望，我們希望能邀請更多的醫師及科學家在免疫治療的技術發展上協助我們。

Current & Future of Cellular Immunotherapy

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【摘要】

In Taiwan, cancer is responsible for over 40,000 deaths in 2017 and the number is increasing annually. On a global scale, cancer has been the leading cause of death for more than 3 decades and WHO estimates that the prevalence of cancer will increase by 57% over the next 20 years. Despite tremendous effort invested by physicians and scientists, we have yet to discover any treatment that is effective when used individually as of yet.

Conventional cancer treatments include: surgery, chemotherapy, radiotherapy, targeted therapy, of which all of them deliver disappointing results and prognosis of advanced stage cancer remains poor. The discovery of our immune system and its roles in fighting cancer in vivo is one of the most exciting discoveries in modern medicine and indeed immunotherapy has been a ray of hope for many cancer patients. One major reason for the poor prognosis of patients suffering from cancer is immune evasion by cancer cells that dampen the anti-tumor immune response. It is therefore our goal and vision to find ways to exploit and enhance the properties of the host's immune system to eliminate malignant cells.

Previous clinical results of immunotherapy has been disappointing as we have yet to understand the mechanism of our immune system fully. However, scientists have made extraordinary breakthroughs over the last decades and immunotherapy has finally become a clinical validated treatment for many cancers. Immunotherapy can be categorized broadly into: drug based and cellular based.

Drug based immunotherapies include the use of monoclonal antibodies to enhance the host's immune system to recognize and eliminate cancer cells, while cellular based immunotherapies include cancer vaccines and adoptive transfer of ex vivo cultured and/or modified immune cells to assist our body to fight cancer cells.

In a natural setting, we have cancerous cells growing in our body everyday, but our immune system is able to eliminate these cancerous cells by the uptake of cancer antigens by antigen- presenting cells (APCs) and presenting these antigen information to our T cells which will in turn recognize and eliminate cancerous cells by various means. But as time passes, cancerous cells will mutate and mimic the states of natural cells to evade our immune recognition system. In order to reverse the tide, scientists are now able to isolate the so-called "trained T cells" from our body and enhance them in a laboratory before infusing them back into our body to fight the fight again. In addition, we could also collect professional APCs (e.g., Dendritic Cells) from the patient's blood and educate them with known antigens before injecting them back into our body to process the reorganization information to T cells. As promising as it may seem, we are still faced with many challenges as only a small group of patients can benefit from such treatments as cancerous cells have employed many different mechanism to escape our defense.

After years of research, T cell has been proven clinically to be the center of focus for all immunotherapies. Indeed, various drugs are developed to enhance the properties of T cells and we now have different means to enhance the killing properties of T cells in ex vivo settings. The future of immunotherapy therefore lies in our ability to strengthen the recognition and elimination properties of T cells. One classic example is the culture of T cells using neo-antigens derived from patient's cancer tissue. In addition, a multi-modality approach will be the mainstay of cancer treatment in the future as we are able to exploit mechanisms of existing chemotherapeutic drugs or radiotherapy to dampen the evading mechanism of malignant cells so that cells that we infuse into the patients are able to recognize

the target accurately.

Another major challenge of cellular immunotherapy is the cost of production. Using current technologies, cellular immunotherapy is very labor demanding as we need to make sure that the cells are safe from contamination while maintaining high efficacy during the culture process. Therefore, it is necessary for us to invent new production methods to decrease the cost of production so that the treatment will be accessible to the general public.

These are exciting times for cancer immunotherapy but there are still many challenges that lie ahead. Increasing efficacy, reducing cost, and combination strategies are the focus of future immunotherapy. Immunotherapy is definitely the most promising cancer therapy and we wish to invite more physicians and scientists to assist us in the development of the technology.