

Epigenetic altering drugs as immunotherapies.

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Accepted on 1 January, 2018

Editorial

Despite of our increasing understanding of the molecular, genetic and phenotypic progression of cancers, treatments that can effectively combat most malignant cancers remain suboptimal [1]. A major challenge with current therapies is that they focus on existing genetic abnormalities but usually become ineffectual due to cancers becoming resistant or not expressing the specific mutation. Advances in high-throughput DNA sequencing of various cancers before and after treatment and after recurrence, has provided researchers with comprehensive collections of driver and passenger mutations that can be utilised to develop novel therapies. However, these sequencing techniques can be costly and usually results in the output of large and complex datasets that require specialised knowledge of different computational analysis [2].

In 1957, Burnet and Thomas postulated for the first time that the immune system in a person may have the capacity to identify and destroy irregular cells and possibly inhibit the growth of tumours [3]. The adaptive immune system, which primarily includes T cells, recognizes the expression of antigens on cancer cells, which the T cells consider to be foreign bodies, thus resulting in the activation of cancer eradicating mechanisms. However, this system is not always absolute or as effective, since activated T cells may attack the body's own cells if the same antigens are present, or if cancer cells possess low levels of cancer antigens or mutations, insufficient antigen specific T cells will be generated. Furthermore, cancer cells, such as stem cells may develop the ability to form resistance against the immune system further deeming this form of natural defence mechanism incompetent. Nonetheless, a great deal of pre-clinical research and clinical studies have gone into evaluating the anti-cancer effect of immunotherapies. Majority of cancer immunotherapies are centred at enhancing pre-existing immune responses such as immune checkpoint therapies which is the most widely prescribed immunotherapy, adoptive T cell transfer therapy, cytokines, oncolytic viruses and some types of vaccines [4]. The success in recent clinical trials involving immune checkpoint inhibitors have shown some promising therapeutic responses on cancer patients, however, despite the observed clinical benefit, a major issue was the median survival rate among all treated patients. It was reported that only a subset of patients had a therapeutic response, whereas nearly 50% of the treated patients achieved no clinical benefit. Hence, there still remains a great gap in immunological therapies that are not only effective at improving patient response but have the ability to stop cancer progression and resistance.

Recent developments on the role of epigenetics in altering immunological responses of the immune system has garnered a

lot of interest in the field of anti-cancer therapies. This has led to the study of various different epigenetic drugs that could help improve or restore immunogenicity, which could possibly augment a patient's reaction to conventional immunotherapeutics. Epigenetic regulation is characterised as all heritable changes, in particularly gene expression and chromatin structure, which occurs in the genome that is not allied to mutations in the DNA and does not cause any underlying changes to the nucleotide sequence [5]. In normal differentiated cells, regulated epigenetic mechanisms are utilised to activate or silence expression of key genes that are involved in cell development, growth and cell death. However, dysregulation of epigenetic pathways leads to abnormal upregulation of oncogenes or repression of tumour suppressor genes leading to the initiation and progression of cancer [6]. Two key mechanisms in epigenetic modifications include DNA methylation and histone modification. Current epigenetic therapies are focused on targeting various enzymes involved in these mechanism, in particularly, DNA methyltransferase inhibitors (DNMTi) and histone deacetylase inhibitors (HDACi). Countless studies have demonstrated the benefit of using these drugs on both immune and cancer cells, where targeting such enzymes have shown to be able to restore silenced tumour suppressor genes or block the expression of cancer genes [7]. Hence, recent studies have focused on the idea of using epigenetic drugs together with immunotherapies, such as immune checkpoint inhibitors, as a form of alternative therapy against various different cancers. Currently there are over 35 Phase I/II clinical trials that are exploring the therapeutic benefit of this combined regimen.

A clinical trial with patients having non-small cell lung cancer (NSCLC) explored the combination effect of entinostat (an HDACi) and nivolumab, an anti-PD-1 immune checkpoint inhibitor. It was reported that the combination of epigenetic therapy with immunotherapy showed an unanticipated positive response to the treatment, sparking a significant interest in these combination therapies. Other recent advances in combinatory therapies include studies conducted with HDACi and PD-1 inhibitors against melanoma and lung cancer, inhibitors of H3K27me3 and anti-CTLA-4 against melanoma and DNMTi, 5aza2'deoxyctidine and PD-L1 against ovarian cancer, colorectal or breast cancer. These pre-clinical studies demonstrated the superior anti-tumour activity of the combination therapy over the single agents and the reduced toxicity of therapy in mice. Furthermore, development of novel epigenetic agents are focusing on other enzymes such as histone demethylase inhibitors, histone methyltransferase inhibitors and bromodomain inhibitors as alternative epigenetic therapies. These novel epigenetic agents have shown to

stimulate immune cell activation and inhibit the growth of tumour progression in various different cancers [7].

These advances in epigenetic therapies have shifted the way immunotherapies are used in the fight against cancer. Understanding the complex interactions between tumours and immune cells play a major role in overcoming the pathological challenges faced in drug resistance, which will eventually aid in modulating improved drugs that can activate immune responses even after cancer resistance. Thus, epigenetic therapies together with immunotherapies may hold great potential in becoming alternative anti-cancer treatments against aggressive and malignant cancers.

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