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Cancer vaccination and targeting nanog for enhanced CTL-mediated immune response

Abstract

Evasion of the immune-mediated cytotoxicity is an all too common hallmark of cancer. A recent study revealed that cancer vaccination - through the establishment of tumor reactive CD8+ CTLs- drives the evolution of tumor cells toward an immune-resistant and stem-like phenotype and they identified the transcription factor Nanog as a pivotal player in this process. Tellingly, the suppression of Nanog expression via using Nanog siRNA renders tumour cells more sensitive to immune response and leads to reduction of tumour growth. Taken together, the results of these studies support the notion that inhibiting Nanog may have therapeutic implications with respect to immune-based cancer therapy.

Keywords: cancer, vaccination, immune response, tumor reactive CD8+ CTLs

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Introduction

Suppression of immunological reactivity is one of the major mechanisms by which tumor cells are thought to escape host immune system as well as cancer immunotherapeutic approaches. CD8+ CTLs can be found in peripheral blood, lymph nodes and tumors in some tumor-bearing patients. CTLs have exquisite specificity and potency to destroy neoplastic cells throughout the body without causing significant damage to normal tissue. Accordingly, the use of tumor-reactive CD8+ CTLs by vaccination represents a potentially effective route for controlling cancer. However, current vaccination regimens showed poor clinical outcomes in terms of tumor progression and long-term survival.

A recent report by Noh et al.[1] revealed that vaccination selects for immune-resistant tumor cells. They demonstrated that vaccination induce tumor cells to express Nanog, a homeobox transcription factor crucial for self-renewal of embryonic stem cells.[2] They showed that Nanog mediates immune-resistant and stem-like phenotype of tumor cells selected by vaccination (Figure 1). Furthermore, they found that Nanog was highly expressed in human cervical cancer cell lines like CUMC6 and Hela.They then go on to provide a potential avenue for therapy by showing that inhibition of Nanog with siRNA renders the tumor vulnerable to immune response and results in reduction in tumor growth.

The results by Noh et al.[1] demonstrated that vaccination selects for tumor cells with stem-like properties. They built on their previous development of system-coined as vaccination induced cancer evolution (VICE)- that selects for tumor immune escape variants (P3 cells) after vaccination in cervical cancer cell model. Compared to P0 (parental cells), they found that P3 cells divided more rapidly and have greater proliferative capacity. P3 cells also had elevated expression levels of stemness markers as CD133, CD44 and ALDH. Tellingly, P3 cells were found to be more than 100-fold more tumorigenic than P0 cells.

As vaccination confers stem-like phenotype to tumor cells, one would expect that vaccination induce the expression of one or more of stemness factors. Indeed, Noh et al.[1] found that only Nanog is upregulated in P3 cells with respect to P0 cells. Using retroviral transduction of TC-1 P0 cells with either DNA-encoding Nanog or empty vector, they indicated that Nanog expression confers the enhancement of the tumor stem-like phenotype of cancer cells upon vaccination.

In agreement with the cancer imunoediting theory, vaccination selects for immune-resistant tumor cells. Nanog expressing cells were found to be impervious to CTL-mediated killing but have similar growth rate like no insert (control) cells suggesting that this phenotype could be a consequence of intrinsic protection from CTL-mediated killing regulated by Nanog expression. Nonetheless, the molecular mechanism by which Nanog functions and the relevance of Nanog expression in human cancer cells wasn't explored.It has been shown that Nanog expression regulates cell cycle of embryonic stem cells via Akt signalling pathway and hence it is of notable interest to examine whether Nanog function in tumor cells is mediated by Aktpathway.[3]

Finally, the finding that Nanog inhibition led to tumor retardation could provide an effective strategy to control human cancer, particularly in the context of immune-based therapy (Figure 1).

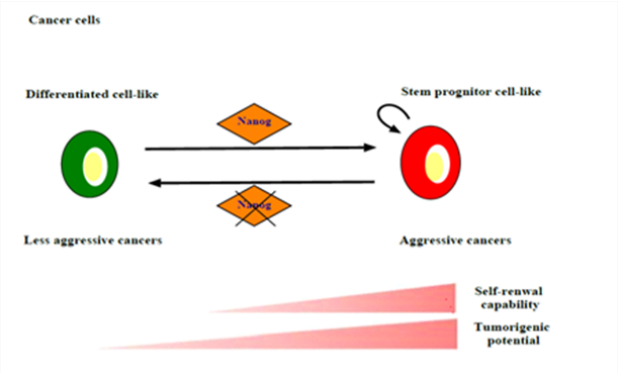

Figure 1 Nanog expression in cancer cells drives the evolution of tumor cells toward an immune-resistant and stem-like phenotype. Concomitantly, Nanog inhibition led to tumor growth retardation.

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Conflicts of interest

The authors declare there is no conflict of interests.

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