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Early cancer screening and prophylactic immunotherapy – A stem cell approach

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Abstract:

Prevention is better than cure. This is more so applicable to inheritable Cancers, where a likely event could be predicted with close statistical probabilities. This study is an attempt that uses advanced prophylactic treatment options to look into the reduction in the frequency or statistical probability of development of cancer in the high risk group of female individuals with family history of BRCA1/2 mutations. Briefly, critical genetic insults and epigenetic alterations of somatic cell (or stem / progenitor cell) create primordial Tumor-initiating cell (TIC) with stem-cell like properties that in due course accumulate progressive genetic lesions that confers a growth and/or survival advantage over its normal counterparts, eventually developing into a full blown cancer. A cancer-initiating cell must survive long enough to accumulate three to seven genetic mutations necessary to generate cancer. Most terminally differentiated cells, even if they encounter mutations, are neither long-lived nor possess the ability to produce tumors with the limited number of divisions remaining in their differentiation program. In contrast, acquisition of longevity and extensive proliferative capacity of a somatic cell or a stem cell precursor make it an ideal candidate for cancer-initiating cell. Tumor initiating stem-like cells (TICs) are a small subset of precursor lesions which are capable of self-renewal and resistant to various chemotherapeutic drugs and radiation. This subpopulation behaves like stem cells by undergoing either asymmetric or symmetric cell division thereby maintaining its population. Generation of TICs is an extremely rare event, though is greatly propelled by any inheritable or germinal mutation, such as BRCA 1/2 mutations, that provides a mutagenic background for superimposition of further insults. Naturally, over 25-45% of breast cancer (BC) patients below 35 years of age have hereditary origin involving BRCA1/2 mutation. Similarly, 80% of the families with the history of Ovarian Cancer (OC) have BRCA1 mutation and 15% of them with BRCA2 mutation. BRCA1 mutation carriers have an 18% risk (15% for BRCA2 mutation carriers) for developing BC up to the age of 39 years, and the risk increases to 59% (BRCA2 - 34%) at ages 40–49 years. Such an overt association calls for prophylactic measures to prevent the likely development of cancer. In this study, we aim at using Autologous Immunotherapy involving Dendritic Cells (DCs), Natural Killer (NK) Cells and Lymphokine Activated Killer (NAK) cells primed with allogenous breast and ovarian cancer antigens as prophylactic measures to activate host immune system in the normal but BRCA1/2 mutation careers against the likely development of neoplastic lesions, whose development frequency is statistically predicted. Our objective here is to demonstrate the efficacy of the immunotherapeutic regimen in reducing the statistical probability of development of the breast and ovarian cancer in the test individuals.

Stem cells from different sources exhibit different capacities of proliferation, migration, and differentiation, which determine their application in anti-tumor therapy.

Embryonic stem cells (ESCs) isolated from the undifferentiated inner mass cells of embryo possess the ability to give rise to all types of cells except those in the placenta. However, the applications of ESCs for clinical trials are restricted due to ethical considerations. In 2006, the invention of Yamanaka factors to induce pluripotent stem cells (iPSCs) from somatic cells in culture marked a breakthrough in cell biology. These iPSCs share the same characteristics with ESCs while removing ethical concerns from embryo destruction.

It is well-established that molecular signaling pathways, including Notch, Hedgehog, Wnt/β-catenin, PI3K/PTEN, JAK/STAT, and NF-κB, regulate normal stem cell proliferation. The persistent change in those signaling pathways will bring about the formation of CSCs and subsequent cancer cells. CSCs have a high capability of self-renewal and differentiation to aid tumor growth, recurrence and metastasis .ASCs can give rise to many specialized cell types of the tissue and organ. In this group, hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), and neural stem cells (NSCs) are often utilized in cancer treatment. HSCs, located in bone marrow, can form all mature blood cells in the body. Till now, the infusion of HSCs derived from cord blood is the only procedure of stem cells that were approved by the FDA to treat multiple myeloma, leukemia, and some kinds of blood system disorders.Tumor microenvironment where extracellular matrix (ECM) and secreted paracrine factors are deposited defines tumor growth and invasion by attracting the directional migration of various types of cells, such as endothelial cells, infiltrating immune cells, and MSCs. Tumors are considered chronic wound tissue with sustained hypoxia, inflammation, and oxidative stress events but never heal . Therefore, the migration of MSCs toward tumor microenvironment is supposed to be similar to their migration to injured or ischemic sites. In fact, both tumor cells and tumor-associated immune cells can involve this process through the secretion of various chemoattractant factors .

Treatment of aggressive cancers that involves invasive tumor removal and high-dose therapy often leads to damage in normal tissues and hematopoietic system. Clear evidence has shown the infusion of MSCs helps maintaining the undifferentiated state and proliferation of HSCs, thereby enhancing the overall outcome of the treatment. Meanwhile, small molecule drugs could be encapsulated into exosomes by two approaches. First, it was found that after priming with exogenous materials, stem cells can uptake, package those agents into exosomes, and then release them to culture medium by exocytosis process. Pascucci et al. reported that exosomes extracted from paclitaxel-priming MSCs dramatically inhibited the proliferation of human pancreatic adenocarcinoma cell line. In addition, these exosomes were found to suppress tumor growth of leukemia and myeloma cell lines . Other drugs, including doxorubicin, gemcitabine, and cisplatin, have been used to prime MSCs . In fact, the content of drugs in exosomes largely depends on their priming concentration.Allogeneic HSC transplantation becomes an effective procedure to treat hematologic and lymphoid cancers. However, it can induce long-term side effects in a large number of patients, including chronic GVHD, tissue/organ dysfunction, abnormal immune response-related infections, recurrence and secondary cancers, and final patient quality of life.

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