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Emerging Approach to Cancer Immunoprevention

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Abstract

Recent identification of stemness pathways in embryonal stem cells (ES) as well putative cancer stem cells (CSCs) provides novel opportunity toward immunologic approaches targeting of pathways associated with stemness.

Also, human full-term placenta has been reported to contain a population of broadly multipotent stem cells. A single transcription factor Oct4 is sufficient to convert nonembryonic-derived trophoblast stem cells cells into pluripotent stem cells i.e. placenta embryonic-like stem cells). As the above types of cell undergo deprogramming to a proliferative stem cell state as result of complex signals in the microenvironment, including oxygen availability the transient expression of hypoxia-regulated Oct4 protein is sufficient to induce stem cell dedifferentiation.

Current studies have demonstrated that most healthy humans (> 80%) have naturally occurring memory T-cell responses to specific epitopes derived from OCT-4 protein (without any signs of autoimmune disease), indicating that most individuals lack immune tolerance to this critical pluripotency antigen. Most of the OCT-4 specific T cells consist of CD4+T cells.

Our preliminary clinical and laboratory immunological studies have shown that women with different genital cancer and obstetrical and gynaecological patients with clinical conditions that show pathophysiological settings in which hypoxia occurs, particularly when rapid cell growth exceeds blood supply return to the proliferative stem cell state, promote syncytiotrophoblast hyperplasia and endometrial hyperplasia and that hyperplastic placental cells, hyperplastic endometrial cells, but also cancer cells are all immunogenic and are cross-reactive against a pharmaceutical Placental Suspension (phPS) prepared upon Filatov's method that qualifes it as an immuno-modulator for a prophylactic cancer vaccine.

These suggest that the immunogenicity of hyperprolferative phenotype of placental stem cells is a direct result of upregulation of Oct-4 expression and overexpression of Oct4-associated prot ein (MW 38, 6 kDa).

Thus, our previous prophylactic vaccination method proposal with human allogeneic phPS/BCG Vaccine by harnessing the patient's natural immune surveillance for the stem cell marker Oct-4, potentially could lead to elimination of premalignant lesions before their progression to cancer. By pre-conditioning the vaccine site with a potent recall such as BCG Vaccine to induce inflammation, dendritic cells (DCs) mature and migrate to draining lymph nodes and induce immune responses.

Introduction

Recent identification of stemness pathways in embryonal stem cells (ES) as well putative cancer stem cells (CSCs) provides novel opportunity toward immunologic approaches targeting of pathways associated with stemness [1].

Monk M., and Holding C [2] described a re-expression of

embryonic genes of human preimplantation embryonic cells, including Oct-4, in cancer cells. Both types of cell undergo deprogramming to a proliferative stem cell state and become potentially immortal and invasive. OCT4, are highly expressed in human tumours but not expressed in normal somatic tissues, indicating that OCT4 is a potential tumor stem cell biomarker and an ideal target in cancer immunoprevention.

Also, human full-term placenta has been reported to contain a population of broadly multipotent stem cells that also shows expression of embryonic stem (ES) cells markers such as c-KIT, OCT4, SOX2, SSEA3, SSEA4, TRA-1-60 and TRA-1-81 [3].

Wu T., Wang H, et al., (2011)) [4]. have reported that overexpression of a single transcription factor, Oct4, in trophoblast stem (TS) cells is sufficient to reprogram TS cells into a pluripotent state (PS). The division, differentiation, and function of stem cells and multipotent progenitors are influenced by complex signals in the microenvironment, including oxygen availability. Covello et al. (2006) [5] have identified *Oct-4* as a novel HIF-2α target and demonstrate that expanded expression of hypoxia-induced HIF-2α is sufficient for up-regulation of *Oct-4, Tgf-α,* and *Vegf* in different biological contexts, including embryonic development and tumor growth.

The successful reprogramming of somatic cells to induced pluripotent stem (iPS) cells indicates that differentiated cells retain the capacity to revert to immature cells. Kumar M. Liu S. et al. (2012) [6] have showed that transient expression of hypoxia-regulated Oct4 protein is sufficient to induce dedifferentiation of melanoma cells and suggest that CSC phenotypes can be acquired through dedifferentiation.

Review of literature

As hypoxia stimulates cytotrophoblast cells (CTBs), but not other cells, to undergo mitosis [7], the above data suggest that human placenta embryonic stem cells equivalents, termed also placenta embryonic-like stem cells originate from a post partum placenta as result of transient episodes of hypoxia associated with labor intermittent uterine contractions that by exposure to low pH and physical squeezing, some adult placental stem cells undergo deprogramming to a proliferative stem cell state, all comprising immunogenic epitopes as result of Oct-4-associated protein overexpression. This novel stem cell behaviour suggests, besides immune-based targeting of stem-cell pathways in cancers, but also the involvment in the enhancement of the immuo-surveillance mechanism of the binomial mother-fetus, during labor.

Dhodapkar K.M. [8] has demonstrated that most healthy humans (> 80%) have naturally occurring memory T-cell responses to specific epitopes derived from OCT-4 (MW~40 kDa) protein (without any signs of autoimmune disease), indicating that most individuals lack immune tolerance to this critical pluripotency antigen. Most of the OCT-4 specific T cells consist of CD4+T cells. OCT4 is a transcription factor critical for the pluripotency of human embryonal stem (ES) and induced pluripotency stem (IPS) cells. OCT4 protein is commonly expressed in germ-cell tumors as well as putative cancer stem cells in several tumors.

Also. J Di et al. [9] have found naturally occurring multifunctional $CD4^+$ and $CD8^+$ T cells specific for the stem cell marker OCT4 among the peripheral blood mononuclear cells (PBMCs) of both healthy individuals and ovarian cancer patients and have demonstrated the existence of anti-CSC specific T cells in ovarian cancer patients.

Our preliminary clinical and laboratory immunological studies [10] have shown that women with different genital cancer and obstetrical and gynaecological patients with clinical conditions that show pathophysiological settings in which hypoxia occurs, particularly when rapid cell growth exceeds blood supply, promote syncytiotrophoblast hyperplasia and endometrial hyperplasia and that hyperplastic placental cells, hyperplastic endometrial cells, but also cancer cells are all immunogenic and are cross-reactive against a pharmaceutical Placental Suspension (phPS) prepared upon Filatov's method. The immunochemical characterization of the cross responsible antigen in the phPS crude placental preparation is an alpha-2-glycoprotein with a MW of 40 kDa.

Discussion

These data have suggested that in defined clinical conditions with pathophysiological settings in which hypoxia occurs, particularly when rapid cell growth exceeds blood supplay, placental stem cells and endometrial stem cells repress differentiation, unergo deprogramming and turn on overexpression of embryonic self-renewal genes followed by adaptive stem cell hyperproliferation and differentiation. Dedifferentiation could induce trophoblast lineage-committed cells to become multi-potent cells with the capacity to proliferate and redifferentiate. In this process, expression of HIF-2α is sufficient for up-regulation of stemness gene Oct-4 and overexpression of Oct-4-associated protein (MW~40 kDa) considered a master transcription factor for pluripotent cell self-renewal.

These suggest also that the immunogenic epitopes of hyperprolferative phenotype of placental stem cells is a direct result of upregulation of Oct-4 expression and overexpression of Oct4-associated protein (MW 38, 6 kDa).

Taking advantage of the similarity between the expression of embryonic gene products by placental embryonic-like stem cells and cancer cells and/or cancer-initiating stem cells, but also of the long window period for cancer development suggests that an alternative immune-based anti-cancer strategy might be prophylactic vaccination by enhancing immunosurveillan-

ce which could effectively eradicate or at least control the few precancerous cells undergoing neoplastic transformation during early premalignant stages in cancer development. Thus, our previous prophylactic vaccination method proposal [11] with human allogeneic phPS/BCG Vaccine can stimulate an immune response against both embryonic antigens and immune suppressive compounds found in the placenta, which can keep precancerous lesions under control by switching the immune response from a tumor-promoting profile to a tumor-destructive profile, through presence of specific T cells and cytokines thereof. As alternative proposals are: patented compositions comprising phrmaceutical allogeneic human placenta embryonic-like stem cells preparation used alone or in a mixture with other stem cell population, or Oct-4-associated protein and all co-admnistered with BCG Vaccine.

Conclusion

By pre-conditioning the vaccine site with a potent recall such as BCG Vaccine to induce inflammation, dendritic cells (DCs) mature and migrate to draining lymph nodes and induce immune responses.

Harnessing the patient's natural immune surveillance for the stem cell marker Oct-4, potentially could lead to elimination of premalignant lesions before their progression to cancer.

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