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On the Dichotomous Aspect of Cancer Stem Cell

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Opinion

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Abbrevations: DACSC: Dichotomous Aspect of Cancer Stem Cells; CR: Complete Remission; PR: Partial Remission; IIT: Idiotope Image Transmission; NSC: Normal Stem Cell; EMT: Epithelial-Mesenchymal-Transition; MET: Mesenchymal-Epithelial-Transition; CDR: Complementary Determining Regions.

Hundred of oncogenes and suppressor oncogenes (soncogenes) have been identified. However cancer is still a formidable conundrum for cancer cell biologists and oncologists. During the last 30 years I have been developing a human monoclonal antibody CLN-IgG (INN: Pritumumab) as a new pharmaceutical agent against brain tumors. Its efficacy includes complete remission (CR) and partial remission (PR) at over 28%. The follow up showed a 9-fold improvement over standard therapy with little side effects [1]. I am still wondering how these remarkable responses to brain tumors was evoked in the course of CLN-IgG Pritumumab-tumor antigen specific immunotherapy. The tumor associated antigen (TA226) recognized by CLN-IgG was vimentin and the epitope was expressed in a sequence of 79 amino acids (aa) in vimentin coil 2B [2]. The sequence of vimentin-epitope79 was the same between malignant and normal cells. However CLN-IgG recognized the altered-vimentin instead of the normal version. In addition I found that anti-paratactic idiotypic antibodies (Idio-Abs) to CLN-IgG recognized the antigen p34K (TA34) that was co-purified from U251MG glioblastoma cells by use of CLN-IgG-coupled Sepharose affinity chromatography. This experimental result gave me the idea that protein-protein interaction (PPIN) between vimentin and TA34 proteins might be a cue for tumor regression and that repetitive administration of the human monoclonal antibody Pritumumab could augment the idiotope image transmission (IIT) of the antibody in idiotypic antibody networks [3].

I have advocated for the dichotomous aspect of cancer stem cells (DACSC) [4]. Cancer stem cells are born from normal stem cell (NSC) in an inappropriate niche surrounding the normal stem cells T-niche in Figure 1. Cancer stem cells are etiologic cells possessing malignant traits e.g. metastasis, invasion and apoptosis resistance. These tumor traits are converted by aberrant altered-vimentin which is the crucial marker of the epithelial-mesenchymal-transition (EMT) of the CSC. During metastasis the reverse transition called the mesenchymal-epithelial-transition (MET) is necessary in order for the circulating tumor cells to colonize the metastasized niche. Reprogramming EMT to MET would be an accomplishment that could lead to cancer recuperation. I have tried to delineate the intervention between Pritumumab and psychological effects on the regulation of tumor growth based on DACSC via the PPIN of TA34 and vimentin.

There are two inextricable phases in one state---dichotomous aspect of cancer stem cell (DACSC) development. Cancer stem cells (CSC) are initiated to grow from normal stem cells (NSC). CSC and NSC are reciprocally participating in EMT/MET when CSCs provoke malignant traits such as metastasis, invasion and anti-apoptosis. Under severe stress, NSC tends to be altered and carcinogenesis during their renewal, which is greatly, influenced by the spatiotemporal architecture of stem cells and their niche cells. Conversely CSC may revert to NSC by losing their carcinogenicity and become susceptible to regular apoptosis from normalized niche, which is implemented by an appropriate condition created by immune surveillance and the autonomous mechanisms for tissue repair which is affected by mental condition in relaxation-transcendency. NSC ordinarily renews for evolutionary adaptation. Simultaneously the state of CSC can adapt to tumor niche created by chronic inflammation and defiance of regular apoptosis. Defective cells that fail the survival game are eliminated by neuro-immune surveillance system, which also initiates the mobilization of stem cells to repair the tissue-gaps

regardless of carcinogenesis. The two aspects, the biphasic shift of NSC and CSC, turn over quickly (flip-flopping) according to the timing of the reprogramming of epigenetical chromatin assembly/disassembly. Two co-existing phases may frequently be competing at the threshold of carcinogenesis.

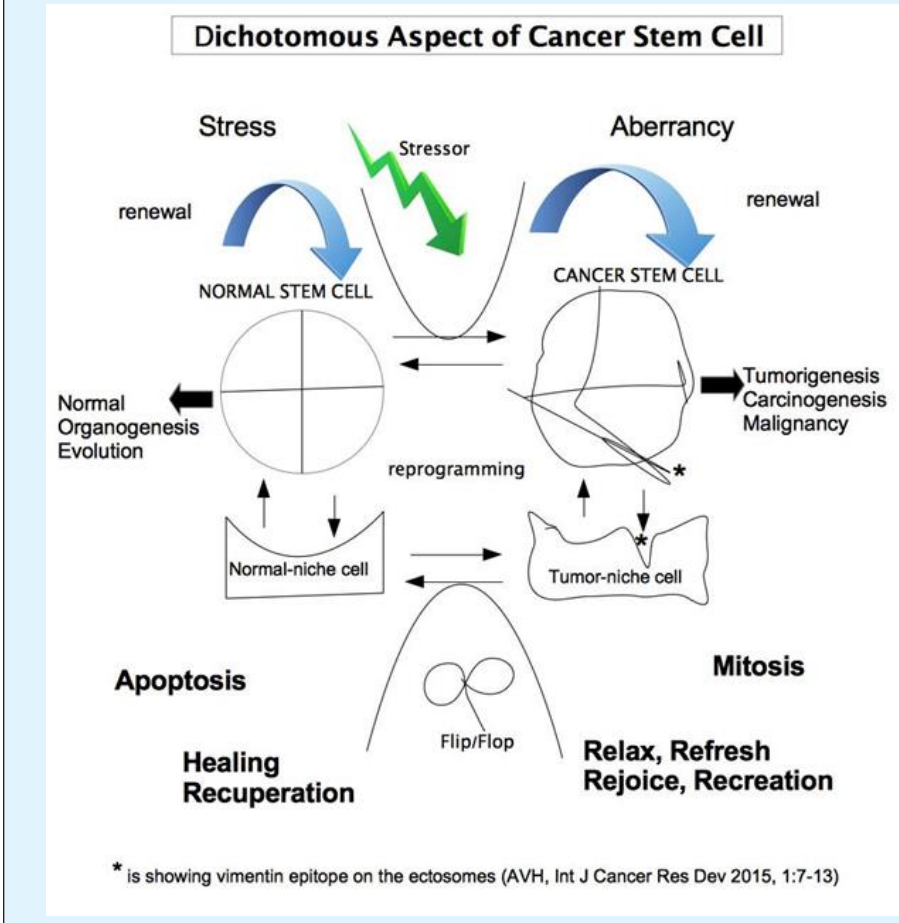

Figure 1: Dichotomous Aspect of Cancer Stem Cell (DACSC).

14-3-3γ is oncogenic, 14-3-3σ is soncogenic, and 14-3-3ε is involved in the EMT/MET transitions [5-7]. Vimentin and 14-3-3 are stress inducible proteins. It emerged that both are concomitantly expressed in prion-associated neurodegenerative diseases e.g. Alzheimer (AZ), Parkinson (PD) and Creutzfeldt-Jakob-disease (CJD). I found that TA34 possesses an aa sequence homologous (sequelog) to the sequences found in 14-3-3s and CLN-IgG VL. These sequelogs were found in the complementary determining regions (CDRs) which are the idiotope moieties for the paratope motif of CLN-IgG. The 14-3-3s also share the sequelog with a prion α-synuclein [8]. Prion expression and amyloidogenesis are found not only in neurodegenerative diseases but also in chronic inflammation and tumorigenesis. If we can regulate the inappropriate prion expression in neoplasia, we may resile the malignant cell traits to normal organogenesis through renaturation of the altered-vimentin associated with aberrant EMT. I found the altered-vimentin was expressed on the ectosomes of malignant cells [9]. Prion functions in the maintenance of cancer stem cells [10] and activates EMT [11]. Therefore prion silencing may be a new avenue not only for treating neurodegenerative diseases but also cancer.

It's not difficult to imagine that reactivation of soncogenes and their related genes could evoke tumor regression. How does mental care relate to the reprogramming of CSC to NSC? I will present prognostic reports regarding stress management that leads to cancer

recuperation via DACSC. Mood stabilizers expand neural stem cells through activation of Notch [12] and the soncogene RUNTX3 reversion of EMT to MET [13] coupled with miR-30a that was a suppressor microRNA of vimentin expression [14]. RUNTX3 expression was influenced by nursing strategy and nutritional care in gastric cancer [15]. The neurotransmitter receptor, β2-adrenoreceptor, is a regulator of prion α-synuclein [16]. These findings indicate how important stress management is on the renewal of cancer stem cells.

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