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MINIREVIEWS

Spatiotemporal switching signals for cancer stem cell activation in pediatric origins of adulthood cancer: Towards a watch-and-wait lifetime strategy for cancer treatment

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Abstract

Pediatric origin of cancer stem cell hypothesis holds great promise and potential in adult cancer treatment, however; the road to innovation is full of obstacles as there are plenty of questions left unanswered. First, the key question is to characterize the nature of such stem cells (concept). Second, the quantitative imaging of pediatric stem cells should be implemented (technology). Conceptually, pediatric stem cell origins of adult cancer are based on the notion that plasticity in early life developmental programming evolves local environments to cancer. Technologically, such imaging in children is lacking as all imaging is designed for adult patients. We postulate that the need for quantitative imaging to measure space-time changes of plasticity in early life developmental programming in children may trigger research and development of the imaging technology. Such quantitative imaging of pediatric origin of adulthood cancer will help develop a spatiotemporal monitoring system to determine cancer initiation and progression. Clinical validation of such speculative hypothesis-that cancer originates in a pediatric environment-will help implement a wait-and-watch strategy for cancer treatment.

Key words: Pediatric origins of adult cancer; Imaging of single cells

Core tip: How does "spatiotemporal tracking of cancer stem cells" should be achieved in an organism for

pediatric origins of adult cancer? Improving the resolution of current imaging technologies down to the single cell level is essential. However, how single cells could be tracked label-free throughout the lifetime of a human body will be challenging. Such technologies, if developed, can potentially provide an evidence base for cancer prevention and treatment.

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INTRODUCTION

In the United States, cancer affected more than 1.4 million individuals in 2007, with a treatment cost over $206 billion, about 33% of the aggregate medical services of $686 billion (the National Cancer Institute)[1]. Much progress has been made in defining the genetic mutations, known as the hallmarks of cancer[2] and in revealing the biological principles of metastasis[3], but this has not been effectively translated into significant benefits to patients. "Cancer genomic research has come to a crossroads with the realization that intratumoral spatial and temporal heterogeneity is a confounding factor"[4]. The discovery of this intratumoral spatiotemporal heterogeneity drives our understanding of epigenetics, which in turn defines the role of the environment[5], including chemical factors, cellular[6], and physical factors like tissue elasticity[7]. Managing tumor microenvironment may offer a holistic regimen for cancer patients with better ratio of benefit over risks[8]. These imply current cancer treatment do not address the root of cancer initiation and progression. New strategies are desperately needed.

MUTATION-TARGETED THERAPY FAILS IN CLINIC

As many mutated gene targeting drugs fail clinically, including mutation-targeted kinase inhibitors (bosutinib, ibrutinib, and cabozantinib) for glioblastoma (GBM)[9], multi-anti-HER2 targeted drugs(trastuzumab, lapatinib and/or T-DM1) for breast cancer[10], HSP70[11] and drugs through the regulation of mutant *p53* and *TAp63* in *p53*-mutated pancreatic cancer cells[12], we realize that not only the genetic mutations, but also the epigenetic changes (the role of the environment), shape cancer initiation and progression, in some cases, which may likely initiate in fetus development. Data from fetal exposome indicates that "utero exposures link to childhood cancer risk, and advances in epigenomics help understanding the effects of biological phenomena, environmental stressors, environmental and lifestyle factors on eliciting changes in the epigenome, leading to cancer initiation and progression"[13]. These data showing mutated gene targeting drugs alone fail in clinic demands a new concept for cancer initiation and progression, thereby improving treatment paradigm. Combining targeted and nontargeted therapy potentially leads to a paradigm shift from current targeted treatment of cancer.

PEDIATRIC AND ADOLESCENT PATIENTS RESPOND TO CANCER TREATMENT DIFFERENTLY FROM ADULT PATIENTS

Pediatric and adolescent patients have been speculated to respond to cancer treatment differently from those adult patients; however, lack of clinical trials on this population of patients led to inconclusive data sets thus far. For example, clinical trials "designed to determine the maximum tolerated dose of chemotherapies" (https://clinicaltrials.gov/ct2/show/NCT00993044?cond=pediatric+origins+of+cancer&rank=1, accessed August 31, 2017) by Children's Hospital Los Angeles conducted in 2009 "a phase Ⅰ study of vincristine, escalating doses of irinotecan, temozolomide and bevacizumab (Vit-b) in pediatric and adolescent patients with recurrent or refractory solid tumors of non-hematopoietic origin" (ClinicalTrials.gov Identifier: NCT00993044) without conclusion as it recruited on 12 patients. The primary objective of this study is "to evaluate the efficacy of moxetumomab pasudotox in pediatric participants with relapsed or refractory B-cell acute lymphoblastic leukemia (ALL) or B-cell lymphoblastic lymphoma" (The study was terminated prior to a planned interim analysis based on "lack of required efficacy in the first 32 participants enrolled", sponsor: MedImmune LLC) (ClinicalTrials.gov Identifier: NCT02227108, first received: August 21, 2014). Pediatricians demand for children-specific clinical trials to gain better efficacies.

HYPOTHESIS OF PEDIATRIC ORIGINS OF ADULT CANCER

As environment-derived epigenetic changes affect stem cell initiating development, most likely it occurs in early embryonic and fetus development. Dr. David Barker first observed that "low birth weight (LBW) is associated with chronic diseases"[14], such as coronary artery disease (CAD)[15], Type Ⅱ diabetes mellitus (T2DM), cancer (breast), osteoporosis and various psychiatric conditions, which led him to conceptualize "fetal origins of adult disease" (FOAD)[16], a.k.a., "pediatric origin of adulthood diseases" (POAD), or "developmental and environmental origins of adult disease" (DEOAD). POAD is based on the notion that, plasticity in early life developmental programming evolves local environments

to increase survival and reproduction[17]. The period for developmental plasticity extends from preconception to early childhood, which involves epigenetic modifications in response to environmental changes, and exerts the effects during life history phase transitions[18]. However, little is known about life history phase transitions responding to specific environmental cues.

One way of deciphering life history phase transitions for POAD would be to map out all the cells and their descendants throughout a lifetime using quantitative imaging technologies. The term stem cell originated in the context of embryological development by German biologist Ernst Haeckel in 1868 to describe the ancestor unicellular organism from which he presumed all multicellular organisms evolved[19]. Such "a prototypical cancer stem cell is a distinct cell in the embryo, responsible for giving rise to cancer found later in adulthood." In 1953-Leroy Stevens discovered "teratomas that contained mixtures of differentiated and undifferentiated cells, including hair, bone, intestinal and blood tissue." This implies the embryonic origin of tumor. Capable of tracing origin of cancer to cancer stem cells (cancer initiating cells), researchers can develop an innovative approach to treat the root of cancer. POAD in cancer takes on a new concept as cancers are being redefined as "common chronic and aging disorders" instead of "invading aliens," implying human beings may need to co-exist with cancer[20]. Indeed, cancer genomics reveals that genetic mutations exist in a wide range of human tumors as shown with different techniques[21], including detection of CX43 mutations in leukemia with microfluidic device[22]; thus, we need to reassess current mutation-target therapy, in particular current pharmaceutical strategies, focusing on multiple mutation targets, largely limited to small molecule blockade of gain-of-function mutations in accessible subcellular localizations, which to date, have not yet proven to be very effective. There is still "much to be learned about optimizing tumor responses, managing side effects, and minimizing the significant stochastic risk of drug resistance that is still too high"[23]. Mounting literature on tissue microenvironments and cell differentiation, which likely signal cancer initiation and progression, argues against a role for acquired cancer gene mutations as a critical event in tumorigenesis, such as "genetic mutations associated with metastatic clear cell renal cell carcinoma"[24,25]. This has caused "a waning of excitement regarding the direction of molecular oncology because of the large number of candidate cancer genes combined with detection of genetic heterogeneity within tumor subclones"[26]. The influence of host tissue microenvironment and cell differentiation and the role of acquired somatic mutations in tumorigenesis are not mutually exclusive, but being intertwined, thereby demanding integrated management of cancer to avoid activating dormant tumor subclones so as to maintain tumor dormancy[20]. Spatiotemporal monitoring of fetal subclonal programming engenders potential applications in diagnosis, preventive and curative measures for adult diseases. Such strategies include the development of novel preventive measures that are predicated on diet (tissue remodeling, metabolism changes)[27], life style (diet)[28], behavior (exercise)[29], stress, and medical care. Quantitative imaging of spatiotemporal biomarker expression would help define certain therapeutic windows-time-to-treatment-for pediatric origins of adulthood cancer, allowing clinicians perhaps to adopt a watch-and-wait strategy for prevention-based strategy for some predicted cancers.

EVIDENCE TO SUPPORT THE HYPOTHESIS

Stem cell origin of cancer emerges as a leading force in cancer diagnostics and treatment; however, little is known about the pediatric origin of adult cancer (POAC). Here, we will focus on POAC.

Stem cell origin of cancer consists of two conceptual schools of mechanism of tumorigenesis: "reserve-born-with-preexisted stem cells" and "bone fide locally-produced stem cells"-both involve with stem cell developmental biology. The "reserve-born-with-pre-existed" concept involves "a cancer stem cell originating in the early development, which seeds in waiting for the right soil (spatial) and the temporal (switching signal) that contribute towards cancer." The "bone fide locally-produced stem cell" are derived from undergoing genetic modifications leading to dedifferentiation, a process triggered by spatiotemporal signaling molecules such as persistent inflammation. Neither of these two conceptually defined stem cells can be identified *in vivo* with current technologies (we cannot detect a single cell *in vivo*); thus, the identity of these stem cells remains controversial. Lineage tracing shows that "Lgr5-expressing chief cells recruited to function as stem cells to affect epithelial renewal following injury by activating Wnt signaling, thus acting for maintaining the homeostatic stem cell pool, while Lgr5+ chief cells act as a major cell-of-origin of gastric cancer in a non-variegated Lgr5-2A-CreERT2 mouse model"[30]. Clearly, the hypothesis of "cancer is to embryology as mutation is to genetics" postulates cancer as embryological phenomenon as reactivated in an entirely inappropriate context[31], thereby indicating a new approach to cancer-searching for such "inappropriate context" in stem cell development.

It has been puzzled to observe that some tissue types give rise to human cancers more often than other tissue types. It is interesting to find that "the lifetime risk of cancers of diverse types is strongly correlated (0.81) with the total number of divisions of the normal self-renewing cells (stem cells) maintaining that tissue's homeostasis"[32]. The tissue's homeostasis is regulated by environmental factors or inherited predispositions. Such "correlation between the incidence of cancers and the number of stem-cell divisions in the corresponding

normal tissues"[33] shed new light on how cancer initiates and progression.

The tissue-specific cancer risk (environmental factors) can regulate the lifetime number of tissue-specific stem-cell divisions[34], suggesting that "intrinsic risk factors contribute only modestly (less than 10%-30% of lifetime risk) to cancer development, based on that the rates of endogenous mutation accumulation by intrinsic processes are not sufficient to account for the observed cancer risks." "Concomitant activation of the Wnt pathway and suppression of Mapk signaling by two small molecule inhibitors (2i) in the presence of leukaemia inhibitory factor (LIF) (hereafter termed 2i/L) induces a naive state in mouse embryonic stem (ES) cells, indicating the epigenetic and genomic integrity is required for developmental potential of embryonic stem cells"[35]. All above data shows that cancer risk is heavily influenced by extrinsic factors. These signal transduction management is supported by the female ES cells that display 2i/L-ES-cell-like transcriptional signatures while preserving gamete-derived DNA methylation and autonomous developmental potential[36].

Increased lines of evidence show "inappropriate context" (*i.e.*, environment) in stem cell development may contribute to cancer development through their interactions with abnormal environmental elements such as inflammation. We pointed out that the crosstalk for tumorigenesis may have a critical stage characterized as a "therapeutic window", which can be identified by association of molecular, biochemical and biological events in the converge developmental stages of different types of stem cells [*e.g.*, normal stem cells (NSC), CSC and embryonic stem cells][37]. Such convergence of NSC and CSC demands spatiotemporal confinement of boundary for breaching to malignancy in response to stress (tissue injury/wound healing). Stress-responsive transcription factor levels rise to reach excess, thereby causing stem cell lineage commanders to cancer[38]. It is challenging to distinguish NSC and CSC as both share common features.

POAC DEMANDS FOR DEVELOPMENT OF INNOVATIVE DETECTION TECHNOLOGIES

Safety is the most important for POAC detection technologies, as pediatric development plays a critical role in adult life, including cognitive capacity, physical and physiological functions. In practice, the neglect of pediatric origin of adult diseases desperately calls for innovative concepts and technologies to be developed. The Chinese proverb state that from the health of three-year-old body, you can predict the health care needed for an 80-year-old - from seven-year-old to see a lifetime health situation-which makes sense based on the pediatric (fetal, childhood) origin of adulthood diseases. As the cost of human genome sequencing reaches $1000[39] or even $100, physicians can know human genome so well that genomics will play a vital role in the future – thereby mapping out each step molecular profiles in a lifetime. Quantitative imaging is needed to define "therapeutic windows"[40] with predictive values for single cells based on life style measurement and biomarker profiles, with suitable criteria robust enough to determine therapeutic intervention. A biological global positioning system (bGPS)[41] could be considered for tracking spatiotemporal cancer stem cell behaviors throughout the body. Quantitative imaging is expected to improve to the point where it is sufficiently sensitive to detect subclonal growth and progression on the single-cell level[20]. Quantitative imaging may include genetic-tagged labeling and non-genetic-tagged labeling, presumably for a lifetime and at the single cell level[41]. Ideal imaging would be label-free, not invasive or minimally invasive. Such technologies might include "Raman spectroscopy for spontaneous and coherent Raman scattering microscopic imaging in the context of single cells, laser tweezers, tissue sections, biopsies and condensing Raman spectrum for a single-cell phenotype analysis"[42,43], as currently used for defining nasopharyngeal carcinoma[44]. Raman profiling for the single-cell analysis requires establish Raman spectra of individual cells by using filtering methodologies for pre-processing of Raman spectra signature, allowing to distinguish and feature as Raman-based biomarkers for single-cells with capture of spatial and temporal changes.

Big data based on supercomputing, such as the team led by University of Washington's David Baker in collaboration with researchers at the United States Department of Energy Joint Genome Institute (DOE JGI), can lead to an integrated comprehensive approach to cancer. Part of this integration is a lifetime imaging system that can define the convergence of normal stem cell and cancer stem cell developmental stages to determine appropriate therapies and assess their effects[37], for example, in monitoring maintenance immunotherapy[45]. Spatiotemporal monitoring of single cells will be high demand in the future because cancer originates from a single cell. The hypothesis of origin of a functional single cell has gained attention through time, including the Nobel Prize committee. For example, the 2014 Nobel Prize in Physiology or Medicine was awarded to John O'Keefe, May-Britt Moser and Edvard Ⅰ. Moser for their discovery that neurons in the brain are firing in response to the positioning of the body in a known space, which is referred to as the biological positioning system. This finding implies on a single-cell origin of a biological function or a single cell origin of an organ. Currently, "cancer stem cell" and the cell of origin for a tumor are not necessarily the same, as these terms have not been used carefully throughout the literature. Publications frequently flip back and forth between normal stem cells and cancer stem cells, and it is often unclear whether they refer to a normal or transformed stem cell when referring to "stem cell". It is still in debate whether cancer exists as cancer stem cells

or cancer is through de-differentiation of an adult cell, as in colon cancer[46]. Tracking down the cancer-initiating cell (CIC) subset of human colon cancers helped identify "nicotinamide phosphoribosil transferase (NAMPT) as a novel therapeutic target in colon cancer progression and relapse"[47,48], suggesting a possible solution to the puzzle. All these imply "the single-cell origin of cancer in colon cancer, which is supported for clonal origins of synchronous multifocal tumors in the hepatobiliary and pancreatic system"[49] and in the same subclone of cells of colorectal cancer[50]. Another report shows the patterns of glioma cell of origin, as somatic Nf1 loss in CD133+ neural progenitor/stem cells during late embryogenesis results in optic gliomas at three months of age, demonstrating that the cell of origin dictates the time to tumorigenesis[7], which can expose a break time or a "therapeutic window" of cancer progression[40].

Thus, the long-term advantage of imaging the single-cell and monitoring the origin of cancer for staging cancer initiation and progression as well as utility of promising advances in immunotherapy remains to be seen in clinical trials on patients with malignancy. This FOAD concept, historically, was started with poor nutrition, and the "fetus adapts to survive but the ramifications of the FOAD extend beyond low birth weight (LBW) to responses to stressors later in life, resulting in various diseases[51]". In 2017, a population-based cohort study of families in Suihua, China, shows that "prenatal exposure to famine led to the development of hyperglycemia and type 2 diabetes in adulthood across consecutive generations[52]". The cohort study consisted of 1034 families - 2068 parents [parental generation (F1)] and 1183 offspring [offspring generation (F2)] – both F1 and F2 were affected by the Chinese Famine of 1959-1961. The found that, "Prenatal exposure to famine was associated with elevated risks of hyperglycemia (multivariable-adjusted OR: 1.93; 95%CI: 1.51, 2.48) and T2D (OR: 1.75; 95%CI: 1.20, 2.54) in adulthood in F1. Furthermore, compared with the offspring of nonexposed parents, the F2 with exposed parents- especially both exposed parents-had increased hyperglycemia risk (OR: 2.02; 95%CI: 1.12, 3.66) in adulthood." However, neither did they predict nor they could track the disease progression, so they could not come up with prevention and treatment ahead of incidences of disease. They did one-time point blood testing, not sufficient to trace the disease. By improving understanding of FOAD or/and POAD, therefore, healthcare experts can prescribe preventive measures and treatment for those at higher risk, by using precise quantitative spatiotemporal imaging. Such imaging will guide how one could manipulate stem cell developmental programs for therapeutic use through time and space of single-cell in stem cell development.

Another challenge is how many single cells (*i.e.*, the critical mass) should be analyzed for the clinical manifestation, in which treatment must be applied. How do we know a dormant subclone of cancer switches to a dominating subclone? How many single cells in such a dormant subclone or a dominating subclone can manifest in its clinical phenotype? A recent study shows that integrating 14226 single-cell RNA sequencing (scRNA-seq) profiles from 16 patient samples with bulk RNA-sequence profiles from 165 patient samples[53] into the body physiology[54,55], can reveal a comprehensive strategy of cancer prevention and treatment. Such comprehensive strategy is based on the tissue organization field theory (TOFT) on tumor initiation and development[56]. Studying the POAC process through single cell imaging may likely help map out TOFT-evolved changes within an organism during development. In fact, the tissue organization field is reorganized through time and environmental factors such as dietary and lifestyle, a concept that has been speculated and yet to be elucidated. For example, "evaluation of sociodemographic and health data collected from 2310922 (2.3 million) 16-19-year-old Jewish Israeli adolescents (mean age 17.3 ± 0.4, 59.5% male) shows that adolescent risk factors (*e.g.,* Body mass index) for developing acute myeloid leukemia (AML) corelate that higher BMI in adolescence with the higher AML incidence in adulthood in this multiethnic population"[57]. The possible mechanism for this impact may be through a "hotspot for pre-neoplastic metaplasia and malignancy" in a transitional zone (TOFT) between diverse types of cells[58]. Multiple models and lineage trace imaging of single cells may therefore lead to show how this transitional zone serves as a source of malignancy for the transitional progenitor. Thus, controlling such transition may prevent cancer. Transitional zones can be assessed with "ultrasound shear wave elastography (US-SWE) in the normal prostate, which can be used to correlate with multiparametric magnetic resonance imaging (mpMRI) tissue characteristics, specifically quantitatively defining the peripheral zone (PZ) and the transitional zone (TZ) for prostate cancer"[59]. In the transitional zone, interactions between different cell types are essential for multiple biological processes, demanding concomitant multiple-single cell tracing techniques to be developed. A new report shows that "the labelling of 'kiss-and-run' interactions between immune cells 'Labelling Immune Partnerships by SorTagging Intercellular Contacts' (LIPSTIC)", which captured the two-phase "interactions between dendritic cells and CD4+ T cells during T-cell priming *in vivo*"[60]. Phase #1, "an early, cognate stage, during which CD40–CD40L interactions occur specifically between T cells and antigen-loaded dendritic cells;" and phase #2, "non-cognate stage during which these interactions no longer require prior engagement of the T-cell receptor," as shown *in vivo* in mouse models. Such a direct measurement of dynamic cell–cell interactions is expected to use in clinical settings to observe pathological processes. For example, "integration of diffusion-weighted-magnetic resonance imaging with dynamic contrast-enhanced-magnetic resonance imaging for imaging biomarkers of response to treatment, can add predictive value of pathologic response to neoadjuvant therapy in breast cancer"[61]. Whether such imaging technologies can be adopt to

other cancer types remains to be elucidated.

CONCLUSION

We attempt to address the nature of cells responsible for POAC, however; given the limitation of literature, many questions remain to be addressed, such as how to identify and target stem cells for POAC in infants or in fetus to trace the development at the single cell level? For example, will it be based on the cell surface marker, cell density, or certain transcriptional or translational features such as genetic mutations? Should the latter a case be, how one can distinguish such a cell from others without destroying tissue? Without such knowledge, it will be impossible to follow the development of a single stem cell even when the technical hurdle to image and monitor cells at the single cell level is resolved. We can predict that comprehensive artificial intelligence of medicine will lead to how "spatiotemporal tracking of cancer stem cells" should be achieved in an organism for pediatric origin of cancer. Supercomputing atlas of collecting big databases of cancer characteristics will offer a spatiotemporal tracking of all single cells in an organism throughout the lifetime of a human, thereby demonstrating a pediatric onset of adult cancer. Such advanced technologies, if developed, can potentially provide an evidence base for prevention and watch-and-wait treatment of cancer.

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