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Is Tumorigenesis an Abiogenesis?

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Opinion

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Abstract

CLN-IgG (Pritumuab) was subjected to clinical trials aiming at regression of brain tumors. The mechanism underlying the dramatic recuperation of cancer patient was considered by means of augmentation of idiotypic antibody-mediated internal image transmission of the vimentin epitope-*vipidam*. Silencing of prionogenicity of vimentin by chaperonic antibody CLN-IgG was a pertinent modality to elongate cancer patient's senescence with little side effect.

Keywords: Vimentin Epitope; Cancer Stem Cell; Chaperonic Antibody; EMT/MET; Prion; Liquid- Droplets; Amylome; Coacervate; Idiotypic Antibody; Immune Clock; Anti-cancer antibody Pritumumab

Abbreviations: DACSC: Dichotomous Aspect of Cancer Stem Cell; CR: Complete Remission; PR: Partial Remission, IIT: Idiotope Image Transmission; CSC: Cancer Stem Cell; NSC: Normal Stem Cell; EMT: Epithelial Mesenchymal Transition; MET: Mesenchymal Epithelial Transition; TME: Tumor Micro-Environment; CDR: Complementarity Determining Regions; *vipidam*: Vimentin Prionogenic Idiotope Determining Amino Acids Motif; PrP: Prion; PrLP: Prion-like Protein; PrPP: Protein with Prion Propensity; TAA: Tumor-Associated Antigen; VEE: Vimentin- Exposing Ectosomes; CJD: Creutzfeldt-Jakob Disease; GSS: Gerstmann-Sträuscler-Scheinker; SBs: Stress Bodies; SAS: Senescence-Associated Stemness; OIS: Oncogene -Induced Senescence; PPIN: Protein-Protein Interactions; LD: Liqid-Droplets; LLPS: Liqid-Liqid Phase Separation.

What kind of Cellular Responses happened when Autochthonous Tumor Regressed?

CLN-IgG (INN: Pritumumab) the autologous anti-vimentin human monoclonal antibody was found in 1982 [1], which was produced from the human x human hybridoma CLNH11 (ATCC: HB8307) secreting γ-heavy chain and κ-light chain of human type glyco-immunoglobulin [2]. It had been applied in clinical trials for brain tumor in Japan early 1990 through Phase I, early Phase II and late Phase II, which resulted in 28.5% efficacy (over CR + PR) with little side effects [3]. The augmentation of anti- anti-idiotypic antibody (Ab3) of CLN-IgG (Ab1) was found in the serum of the glioma patients who responded well under the usage of intravenous repetitive administration of Pritumumab with 1 mg twice in a week [4].

The tumor-associated antigen (TAA) recognized by CLN-IgG was vimentin (an intermediate filamentous protein) and its epitope rid on 79-amino acids in Coil2B [5]. The core epitope was called *vipidam* (vimentin prionogenic idiotope determining amino acids motif) consisting with linear 16-18 aa and it was expressed on the special protrusions (buddings) of the plasma membrane (vimentin- exposing ectosomes, VEE) at the G2/M cell cycle of U251MG glioblastoma cells [6]. The epitope motif was studied to determine the tertiary surface structure of the TAA (a trope of TAA) by use of affinity-chromatography coupled with 5 kinds of anti-

paratactic idiotypic Abs toward the paratope of CLN-IgG that was composed of 6 CDRs at the antigen recognition site of CLN-IgG [7]. On the other hand, comparative analysis of the sequelogs of the CDR1 of idiotypic Abs (Idio-Abs) sufficed to show prionogenicity of the *vipidam.* A variety of prionogenic proteins (including α-Synuclein) possessed the segment of *vipidam* termed as EZΦNX (E: glutamate or aspartate, Z: any aa preferably leucine/alanine, Φ: bulky hydrophobic aa, N: glutamine or glycine or serine, X: any aa preferably tyrosine or glutamine or asparagine) [8]. The augmentation of *vipidam* which recognizes Ab3 was observed in the brain tumor patients who responded to vaccination of Pritumumab and resonated with idiotypic antibody internal image transmission in idiotope immune network gave rise to a chaotic fractal pattern which I compared to Lorenz's chaotic attractor [9]. Taking the dramatic response of augmentation of Ab3 in the brain tumor patients into consideration, the silencing of prionogenicity by *vipidam* through repetitive administration of chaperonic Pritumuab (*chap*CLN-IgG) could evoke the resiliency of the aberrant vimentin networks in malignant cells and recuperate patients from malignancy by reprogramming cancer stem cells (CSCs) into normal stem cells (NSCs)-conducted regenerative organogenesis.

What is meant by the "Prionogenicity of *Vipidam*"?

Prions have been primarily characterized as etiological proteins showing heat resistant, detergent insolubility, self-replication, self-perpetuation, and with the capacity for horizontal transmission found in Creutzfeldt-Jakob Disease (CJD) and Gerstmann-Sträuscler-Scheinker disease (GSS) [10].

When the definition of prionogenicity was broadened to include PrP, PrLP, and PrPP, they showed a tendency to form amyloid structures that are the aggresomes which possess physicochemical property of membrane-less liquid-droplets (Coacervates). Each cancer cells possesses each kind of liquid-droplet during tumorigenesis to malignancy. The taxonomy of these liquid-droplets has not been determined so far, thus I tentatively call them "Stress Bodies (SBs)". The reports about SBs including Prions, PML- Bodies, Stress-Granules, ESWR-FLI1, Nuage, and HuR-RNP complexes are listed in Table 1. Almost all proteins that constitute SBs possess the intrinsic disordered region (IDR) [11,12] that contributes to form an "Amylome" [13]. IDR is a non-structural domain but a cassette of oligopeptide segments that contribute amyloidosis [14]. I found the homologous segment of the IDR amino acid sequence (the sequelog) in *vipidam* that was evolutionary transmitted into the sequelog of α-Synuclein [15] and 14-3- 3[16], and many other prionogenic proteins [8].

Why Cancer Cells need to form SBs during Tumorigenesis to Malignancy?

Numerous prionogenic proteins have been found with the propensity to form amyloid (Amyloid- prions) that is conformationally characterized with the steric zipper of β-sheet [17].

Ribonucleoprotein (RNPA1/B1) and RNA binding protein (RBP HuR) are especially prionogenic having the physicochemical properties of liquid-droplets and liquid-liquid separation [18,19]. It was reported that the membrane-less stress-granules are necessary for stabilization of mRNAs at the translation site [20]. Furthermore prionogenicity of RBPs is well linked to cellular phase shift with regard to EMT/MET programming [21]. Under severe environmental stress (e.g. oxidative stress, UV radiation, starvation, heat, osmolarity), normal stem cells (NSC) have to adapt to these quickly changing environmental conditions for survival by all means. Sustenance of stem cells is the source of regenerative evolution [22]. Rudimentary operations in cancer stem cells (CSC) are not exempt from stress responses but instead CSCs recruit anomalous stress responses during tumorigenesis via aberrant cytochemical reprogrammings. Aberrant vimentin expression (under Snail/Slug, Zeb, Twist transcription operators) is deeply associated with tumor-EMT/MET in connection with malignancy [23-26].

Why Tumor Cells need Amyloid-prions from Amylome?

Malignant cancer cells were generated from cancer stem cells. In the case of glioma, cancer stem cells (CSCs) were born from neural stem cells [27] that generated brain tumor initiating cells [28]. CSCs communicated with the tumor-niche (T-niche) cells that surrounds CSCs in stroma (extracellular matrix) including immune effector cells for the purpose of the maintenance of their stemness. NSC and CSC with each niche-cell are reciprocally converted to each other exchanging a variety of chemokines, cytokines, interleukins, and RNA/DNA for adapting to T-niche (micro-malterrain) under immune surveillance. I postulated this aspect as the dichotomy of CSC (DACSC) [29,30]. Tumor microenvironment (TME) is

considered important for the persistence of CSCs [31]. Moreover cellular senescence and tumorigenesis are interwoven. This concept is called SAS (senescence-associated stemness) and/or OIS (oncogene -induced senescence) [32,33]. Prions deposits (liquid droplets) found in age-related neurodegenerative diseases are thought to be amyloid-prions that could protect stem cells from acute injury [34]. Since it is pertinent to protect neural circuitry from stressful injures, amyloid- prions must be a priority in neural stem cell development. The function of amyloid has been extensively studied in regard to whether they are cytotoxic or cytoprotective to neurons [35,36]. It seems that tumorigenesis is a program to accelerate ageing (senescence).

EMT/MET is a key program for the propagation of CSCs. EMT/MET is crucial state for CSC's invasion, migration, and metastasis. Furthermore during tumorigenesis CSC-T-niche cells provoke immune suppressive factors (e.g. PD-L1/2 and CTLA4) [37] toward immune effector cells in immune surveillance. Vimentin is not only a positive marker of EMT but also of cellular senescence [38], and vimentin is a potent pro-inflammatry (inflammage) protein [39]. I found the more expression of *vipidam*, the more exhausted myoblastic cell shape was from the fibroblastoids of U251MG glioblastoma cells [6]. The senescent U251MG expressed the altered *vipidam* on special protrusion called with vimentin-exposing ectosomes (VEE), which may be involved in cell coalescence with senescent cells to diversify tumor heterogeneity [40]. In addition I found the inter-cellular horizontal transmission of v*ipidam* between neighboring glioma cells through thin thread-like protrusions [8].

Thus several application of senolytics have been attempted aiming to decelerate cellular senescence (ageing), which in turn postpones tumorigenesis [41,42]. It is noteworthy that small biochemical senolytics [43] and prion silencers [44] somewhat overlap in some aspects of antioxidants such as Quercetin, Resveratrol, Ganbogic acid, Catechin, Curcumin and Withaferin in regard to anti- amyloidosis and anti-carcinogenesis.

Why *vipidam* expresses Prionogenicity?

"Life is stress, stress is life". Life has been evolving for at least 4.1-billion years [45]. Cells have overcome severe stresses (e.g. Coldness, Heat, UV radiation, Osmosis pressure, Oxidative stress, Gravity) by all means up to now. The cell must have adaptation mechanisms to respond quickly to changing environments. AI Oparin advocated for "Coacervates" at the origin of life in primordial soup [46]. Coacervates possess physicochemical properties such as fusion/fission, assimilation/dissimilation of environmental substances, self-propagation/degradation, and viscoelastic morphological change as seen in the field of rheology or topological biology. Recently the compartmentalization of coacervates was experimentally found [47]. The viscoelastic properties of coacervates observed in amyloid support their prionogenicity as characterized by the prion's properties such as self-perpetuation, self-templating, self-replication, and horizontal transmission etc.

Vimentin is significant not only in EMT/MET but also to stress sensing [48]. Especially when cells were under mechanical shear stress, vimentin was expressed. One of genetic transcription factors involving in mechano-signal-transduction is NF-κB [49]. Asbestos exposure revealed lung cancer can be accompanied by EMT with up regulation of vimentin [50]. I presented a hypothesized coacervatic property of *vipidam* under mechanical stress [8]. The 16-aa sequelog in vimentin molecule, 346EMEENFAVEAANYQDT361(EZΦNX), may correspond to intrinsic/extrinsic stressors of TME. EZΦNX/*vipidam* may behave like a seed segment to introduce vimentin prionogenesis in which tumor cells tend to form SBs. I found the sequelog of EZΦNX/*vipidam* in a variety of prions and amyloid proteins [8]. In glioma patients, targeting cell surface vimentin (VEE) with Pritumuab evoked dramatic augmentation showing a fractal aperiodic oscillation of anti-anti-idiotypic antibody activity (Ab3) with circaseptan chaotic rhythm [9]. In 2019 it was reported that chaotic response of NF-κB expression was beneficial for antibody production from B-cell [51]. Furthermore vimentin and its autologous anti-vimentin antibody were measured in autoimmune diseases such as Rheumatoid arthritis, which is positive for amyloid proteins [52]. Amyloid proteins themselves possess self-clearance property capable of reverse cytotoxicity to a neuro-protective state [53]. Moreover the antibodies against pathogenic amyloid proteins in the neurodegenerative diseases indicated the clearance of amyloidosis [54-56]. In tumorigenesis, the posture of *vipidam* (a stress-trope) was carried over one after another through the vimentin network by means of its prionogenicity [8]. These findings indicated that immune surveillance has the ability to produce chaperonic antibodies which reverse the misfolded, denatured, and distorted proteins into normal configurations [57]. In the end the impairment of immune surveillance to amyloidosis leads to accelerated cellular senescence

(ageing) [58]. The chaperonic CLN-IgG (*chap*CLN-IgG) induced resiliency in prionogenic vimentin during the course of Pritumumab antigen-specific therapy accompanied by antibody-mediated vaccination via evoking idiotope image transmission (IIT) in idiotypic antibody networks [9].

What is the function of Prionogenic Vimentin?

Vimentin forms a nebulous network but integrates to the plasma membrane, subcellular organelles, and the nuclear membrane connected to chromatin in the nucleus. It flexibly responds to mechanical stresses by changing cell stiffness or brittleness and by interacting with other cytoskeletal proteins and membrane scaffold proteins. Many proteins localized on subcelluar fractions contain amylome which possesses the ability of coacervate forming liquid droplets (e.g. Aβ, TDP-43, Tau, HuR, α-Syn, hnRNPs/RBPs, Zip-11, TIA-1, CPEB4, IRBIT, DDX23, SAP, Pin2). SBs are aggresomes consisting basically of coacervatic proteins having IDRs. Coacervation by polyelectolytes (e.g. Prions, RNAs, DNAs, poly-ADP ribose, polyamines) show drastic phase change for the biochemical compounds with valency burst in protein-protein interactions (PPIN). The liquid droplets possess the fluidity, conductivity, plasticity and electivity of viscoelastic material. Rheology of coacervates indicates their state and condition are intensively influenced by their milieu condition (Temp, Ion concentration, pH, electromagnetic field and piezoelectricity). The competency of coacervates generated by their dissimilation/assimilation abilities give the cells the ability to adapt and survive in quickly changing environments via liquid flow dynamics rather than by discrete motions.

For example:

a) Activation of super enhancer in chromatin forms coacervate at the transcription site of mRNA, then crucial transcription regulators express a pertinent PPIN corresponding to the stimuli from the milieu [59].

b) mRNA splicing processing is influenced by coacervatic stress granules at the ribosome or epi-ribosome of the translation site [60].

Cancer stem cells communicating with T-niche recruit the prionogenic vimentin during EMT/MET. The liquid and solid states of coacervates are basically reversible as in MET (dissimilative vimentin) to EMT (assimilative vimentin). This leads me to imagine that CSCs are able to maneuver the T-niche including immune surveillance by manipulating the timing for their invasion and metastasis by expeditiously retracing the long evolutionary processes of life for CSC to seek out the pertinent PPIN for their survival in stressful environment via amylome-coacervatogenesis. In this connection, I advocated "Tumorigenesis recapitulates abiogenesis".

Tentative Conclusion and Perspectives of Antigen-Specific Tumor-Immunotherapy

CR Darwin mentioned in the letters to his friend Hooker "All the conditions for the first production of a living organism are now present, which could ever have been present" [61]. If his intuition was right, about 30,000 polypeptides expressed in a cell still maintain the capacity to adapt to new environments by means of a certain mechanism which amylome-coacervation possess.

Coacervatogenesis is an ancient adaptation process of life which it has been carrying on up to now. A dramatic chaotic fractal augmentation observed in the brain tumor patients treated with Pritumumab (*chap*CLN-IgG) therapy gave me an idea about an Immune Clock [62]. Cellular senescence accelerates tumorigenesis. To rejuvenate immune response, in turn, delay senescence-associated tumorigenesis.

Immune surveillance bridges in between ageing and cancer. The Immune Clock would measure the timing of growth or regression in tumorigenesis. This means that silencing prionogenicity of vimentin targeting EZΦNX/*vipidam* by repetitive administration of Pritumumab was a pertinent modality aimed at tumor regression with little side effects.

Prionogenicity	Type of Stressor	Subcellular Stressee	Stress Body
Amyloid	Geriatric	Cardiovasculature	AL/AH amyloid [63,64]
Amyloid	Geriatric	Muscle/ALS	Myo-granule/TDP-43 [65,66]
Amyloid	Geriatric	Nervous system	Amyloidosis// Aβ [35]
PrLP	Virus/Immunity	ER/Mitochondria	MAVS [67]
PrLP	Neurodegeneration	Nervous system	Lewy-Body/α-Synuclein [68]
PrLP	Neurodegeneration	Epi-Ribosome	Stress-granule [69]
Prion	Neurodegeneration	Endosome	CJD [70], GSS [71]

Coacervate	Sperm-oogenesis	Chromosome	Nuage [72]
Coacervate	As-Oxide	Ribosome	Stress-Granule/P-Body [69]
Coacervate	APL Leukemia	Chromatin	PML-NB [73]
Coacervate	Ewing's sarcoma	Chromatin	EWS-FLI1 complx [74]
Coacervate	Neuropathy	Ribonucleoprotein Complx	RBP-HuR [75,76]
Coacervate	Asbestos/Coal-tar	Cytoskeleton	Vipidam#/IFP [50]
Coacervate	Hepatoma	Nuclear membrane	Mallory-Denk Body [77]

Table 1: *Prionogenicity (PrP; prion protein, PrLP; prion-like protein, PrPP; proteins showing prion propensity) is standing for any coacervation-aggresomes that possess the physicochemical features of liqid-droplets (LD), liqid-liqid phase separation (LLPS), Amyloidosis (Amyloid), and Coacervatogenesis of Amylome (Coacervation).

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Conflict of Interest

Author has no competing interest concerning this article.

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