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Paradoxical Dimensions of Autonomous Oncogenicity and Maintenance Conditioning Due to Anaplastic Lymphoma Kinase

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ABSTRACT

Dimensions of ALK-fusion proteins such as NPM-ALK and a series of consequential steps in tumor reproduction allow for an apparent contradictory or opposing series of events in autonomous growth of tumor cells and of events in conditioning and re-conditioning of the neoplastic process as cells acquire constitutive tyrosine kinase over-activity. The serial representations of events of acquisition of oncogenic attributes on the one hand and of systems of immunogenicity and of spread allow for suppression of such cardinal processes as self-programmed apoptosis and necrosis. As such events propagate within systems of excessive cell cycling and spread, it is significant to view the ALK and ALK-fusion proteins to constitute a conditioning/reconditioning event in the oncogenicity series of cycling events, as tumor cells are induced in paradoxical terms to grow autonomously but only within maintaining conditioning of extra-cellular and intra-cellular milieu.

Keywords: ALK-fusion proteins, Neuroblastoma, Oncogenesis, Oncogenicity, Tumorigenic

INTRODUCTION

The intriguing multiple roles of Anaplastic Lymphoma Kinase (ALK) are implicated in the activities of fusion proteins with constitutively active kinase functionalities. One of the most challenging investigations in cancer research is identification of oncogenic drivers within a given tumor as in lung cancer that is directly targetable by a clinically available therapeutic drug [1]. The borne-out dimensions of nucleophosmin-ALK fusion protein (NPM-ALK) extensively implicates a range of tyrosine kinase activities that invariably show a susceptibility in inducing such phenomena as cell cycle over-activity, differentiation, migration in terms that bear wholly on dysfunctional physiology of the NPM-ALK fusion protein. Recognition of the pathological spectrum of anaplastic large cell lymphoma is crucial to understand its pathogenesis and its boundaries with other entities; this neoplasm shows strong CD30 expression and variable loss of T-cell markers [2]. ALK gene activation is seen also in lung cancer, inflammatory myofibroblastic tumors and neuroblastoma with accompanying fusion to other oncogenes such as NPM, EML4, TIM or gene amplification, mutation or protein over expression [3]. Identification of ALK-mediated molecular pathways related to glioblastoma carcinogene-sis/pathology and putative therapy resistance is of high priority [4].

LOCALIZATION

The subcellular localization within the cytoplasm of NPM-ALK is indicative of the constitutively active tyrosine kinase domain of the ALK and further conforms to the dimensions of dysregulatory functionalities that indeed dominate the pathophysiology of diffuse large cell anaplastic lymphoma cells and a significant number of other malignancies such as neuroblastoma, glioblastoma and others. The further confirmatory indicators for oncogenic attributes implicate ALK fusion proteins in a manner that transcends the scope functionality of tyrosine kinases in general and further confirm the central roles for oncogenesis by NPM-ALK fusion proteins in particular. Genetic epistasis (gene-gene interactions) plays a central role in ALK-driven advanced stage lung cancer; an unmet need to deepen the current under-standing of genomic attributes of ALK rearrangements exists to also overcome ALK inhibitor resistance [5]. Dysregulation of microRNA expression and

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methylation affect several signaling pathways in ALK carcinogenesis and control tumor growth both in cell lines and mouse models [6]. Multiple/compound resistance mechanisms to ALK inhibitors can occur; comprehensive genomic profiling remains the gold standard to assess resistance mechanisms and to direct subsequent rational clinical care in lung cancer [7]. The carcinogenesis of non-small cell lung carcinoma is associated with activating and resistant mutations in the tyrosine kinase domain of specific oncogenes [8].

RECREATION

The distributional recreation of dimensions for constitutive kinase activity of ALK fusion proteins attests for amplification and point mutability in a manner that is not limited only to such observed events. There arises a dimensional and perpetuating inter-phase series of events that undergo progressive evolutionary contexts for ALK functionality and dysfunctionality. Rare oncogenic aberrations, such as the ALK fusion and KRAS mutation, may drive pancreatic carcinogenesis independent of the KRAS mutation [9]. It is significant to observe a series of additional attributes further to dimensions of cooperative intervention that implicate the progressive contextual dysfunctions in a series of neoplasms such as evidenced by production of increased cellular populations within the hippocampus that have been observed in ALK-knockout mice. Inhibition of NPM-ALK induces long-lasting complete remissions in a large sub-group of heavily pretreated adult patients and the vast majority of children with high-stage ALK-positive anaplastic large cell lymphoma [10].

A positive feedback loop involving the Wnt-beta-catenin/MYC/Sox2 axis defines a highly tumorigenic cell subset in ALK+ anaplastic large cell lymphoma [11].

NERVOUS SYSTEM

The roles of ALK in neural development in particular attest to dimensional non-resolubility of the nature of the oncogenic effects with the advent of constitutive tyrosine kinase situated intracellularly. It is within the scope of dimensional perpetuation of such effects that mouse, Drosophila, *C. elegans* models implicate the cellular roles of ALK that in turn show restricted normal tissue distribution but wide-spread tumor distribution in oncogenesis.

The widespread scope of neural development is significantly emphasized as an attribute of the ALK fusion proteins and further stressed within both hematopoietic and non-hematopoietic neoplasms. Such attributes appear unique to ALK and further confirm the specificity of oncogenic roles of this tyrosine kinase as a member of the insulin family of receptors in general. Flotillin-1, a plasma membrane protein involved in endocytosis, regulates tumorigenic signaling in neuroblastoma cells by modulating ALK membrane association [12]. A complex pattern of genetic rearrangements consistent with chromoplexy of TPM3-ALK has been reported in a patient with inflammatory myofibroblastic tumour [13]. A patient was reported to show three years sustained complete remission achieved in a primary refractory ALK-positive anaplaetic T large cell lymphoma treated with crizotinib [14].

In such manner, the incremental deficits of expression of ALK in the nervous system in developing models attest to the dimensional reproducibility of mode of involvement also in oncogenesis by ALK and ALK fusion proteins. Upon ligand binding to the extracellular domain, the receptor undergoes dimerisation and subsequent autophosphorylation of the intracellular kinase domain [15].

TYROSINE KINASE DOMAIN

The study of imitinib and other small molecule inhibitors has been possible especially with the use of xenograft models of ALK-induced tumors and indeed attests for the central role of ALK fusion proteins within oncogenic experimental steps for verification and confirmation of tumorigenic roles in progression. Responses to crizotinib in patients were reported with ALK-positive lung adenocarcinoma that tested immunohistochemistry (IHC)-positive and fluorescence in situ hybridisation (FISH)-negative [16]. There is re-expression of this developmentally regulated protein in a broad subset of pediatric cancers, providing therapeutic targeting opportunities for diseases with shared molecular etiology [17]. Dual inhibition approaches targeting both ALK and the escape pathways bypassing ALK are currently un-der investigation [18].

The dimensions of ALK-fusion proteins are such a widespread phenomenon that the nervous system components such as especially sympathetic neurons play an important role in accompanying conditioning in at least some cases of oncogenicity. It is in such terms that overall dimensions for oncogenesis allow a permissive re-distribution of oncogenic effects that parallel the scope reproducibility of oncogenesis within such controlling settings as neuroblastoma susceptibility. Activated Alk triggers prolonged neurogenesis and Ret up-regulation as a therapeutic target in ALK-mutated neuroblastoma [19].

Reproducibility is maintained as a significant reappraisal of the dimensions for further oncogenic activity as suggested by prior and on-going perpetuation of cycles of oncogenicity. The subsequent emergence of such reproductive activity is suggested within the contextual conditioning and re-conditioning of events as perpetuated by ALK-fusion proteins with specifically constitutive tyrosine kinase over-activity. Silibinin suppresses NPM-ALK, potently induces apoptosis and enhances chemosensitivity in ALK-positive anaplastic large cell lymphoma [20]. Inherited conditions affecting genetic aberration, viral oncogenesis, reduced immune surveillance and long-lasting antigen

stimulation may build the way to lymphomagenesis in humans [21].

PERFORMANCE DYNAMICS

Performance dynamics are borne out by the emergence of oncogenic lesions that perpetuate the dimensions of oncogenesis within systems for further malignant change. ALK is a MYCN target gene and regulates cell migration and invasion in neuroblastoma [22]. The use of methyl transferase inhibitors together with microRNA-specific drugs could be a useful addition to our current armamentum in the fight against ALK(+) Anaplastic large cell lymphoma [23]. It is significant to view the overall integrity of downstream events as repeatedly de-noted by the emergence of neoplasms that further conform to the at-tributes of increased cellular cycling, differentiation and spread as further attested by contextual conditioning of the extra-cellular environment. It is towards further such conformational setting that the oncogenic series of cycles increment the dimensional spread of the resulting neoplasms as evidenced for example by diffuse large cell anaplastic lymphoma. The importance of the STAT1/STAT3 functional inter-action is highlighted by the observation that short interfering RNA knockdown of STAT1 significantly decreased apoptosis induced by STAT3 inhibition; thus, STAT1 is a tumor suppressor in ALK+ Ana-plastic large cell lymphoma [24].

ONCOGENICITY

Increased understanding of intertumoral heterogeneity at the genomic level has led to significant advance in the treatment of solid neoplasms [25]. Comprehensive genomic analysis has uncovered surprisingly large numbers of genetic alterations in various types of cancers [26]. Oncogenicity thus emerges as a constitutional over-activity of tyrosine kinase domains within the contextual conditioning of amplification, point mutability and translocation of the ALK gene within systems of reproducible effect and consequence. Unlike many other oncogenes with high frequency of hotspot mutations, ALK point mutations tend to span along the entire gene [27]. In such manner, proportional over-activity is product-result of incremental over-activity within scopes for further increment as borne out by the creation of ALK-fusion proteins. Aggressive transformation of anaplastic large cell lymphoma has been observed with an increased number of ALK-translocated chromosomes [28]. Contextuality is hence a cardinal marker for conditioning dimensions in oncogenesis as further confirmed by the intricate down-stream pathways that significantly conform to increasing oncogenic potential. Activating mutations in the ALK gene remain the most frequent draggable mutations identified in neuroblastoma to date [29]. The maintenance of oncogenic stimulation of tumorigenesis is central to the development of tumors that arise consequent to malignant trans-formation, but that increase in size and subsequently spread as a direct result of such maintenance and self-amplifying mechanisms in tumorigenesis.

CONCLUDING REMARKS

Dimensions of reproduction of oncogenicity and of further growth and tumor spread attest for an incremental series of compounding influence whereby induction of tumorigenesis interacts with the conditioning contexts for spread and further growth of primary and secondary tumor lesions. The pleiotrophin-ALK axis is required for tumorigenicity of glioblastoma stem cells [30]. This perpetuating series of cyclical growth and spread is an oscillatory series of events that persist as further dimensions for incremental activity of the ALK-fusion proteins as borne out by the spread of prototype lesions as diffuse large cell anaplastic lymphoma. The discovery of ALK fusions has provided the basis for the characterisation of distinct subsets among anaplastic large cell lymphoma patients [31]. The further conformational re-distribution of oncogenicity effects is thus another independent parameter in tumorigenicity and appears to satisfy the stringent requirement for a lesion whose development depends largely on over-activity issues of spread and growth of constituent tumor cells. The preparatory contexts of evolutionary growth and spread of tumors is hence an evidential point in supporting further spread as end-result in vivo modeling of events in oncogenesis. Performance increments are therefore consequential reproduction of induction phenomena that exhibit the phenomenal attributes of autonomy within systems of paradoxical dependence on such gene entities as ALK and ALK-fusion proteins in particular.

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