

Dynamics of Blood Supply Modulate Clonal.neoplastic Cell Progression

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Abstract: Subpopulations of tumor cells make up a neoplastic lesion that is primarily characterized by a blood supply that clonally and subclonally determines evolution of proliferation and infiltration of the cells. Proximity to blood vessels and subsequent proliferation of the neoplastic cells that infiltrate stroma or neuropil would undergo progressive increase in tumor grade and develop tumor necrosis and abnormal mitotic figures. Such clonally evolving subpopulations of neoplastic cells would give rise to differentiation and dedifferentiation mechanisms in the evolution of various cell subsets that determine blood supply dynamics of influence in their own right. Neoplasms constitute disturbances in blood supply that clonally progress as attributes of a cell of origin. Such a cell would variably differentiate, proliferate and spread according to an otherwise artificial concept of tumor grade and of stage of the lesion. Blood vessels would participate in the clonal proliferation of tumor cells beyond simple considerations of differentiation or dedifferentiation of the lesion but in terms of subpopulations of the neoplastic cells proximal or less proximal to the vessels.

Key words: Blood supply, neoplastic cell, clonal proliferation

INTRODUCTION

A Tendency For Suppression Of Malignant Progression In Pediatric Gliomas: Pediatric high-grade gliomas are essentially de novo, whereas many adult high-grade astrocytomas are secondary through progression of a pre-existing lower-grade lesion. Specific etiologic and pathologic attributes of the pediatric lesions would account for such a distinction.

It is important to note the much lower relative proportion of high-grade astrocytomas amongst all astrocytomas occurring in children when contrasted with those occurring in adults. An astrocytoma tends to be progressively of higher grade with increasing age of the patient, a phenomenon suggestive perhaps of a fundamental neoplastic attribute that contributes to a lower incidence of high-grade lesions in children.

A distinctive feature of pediatric high-grade glioma that contrasts with adult-type lesions is the preferential inactivation of the p53 tumor suppressor pathway and lack of Epidermal Growth Factor Receptor (EGFR) amplification in the pediatric de novo lesions.

Such a situation might be suggestive of distinctive pathogenic mechanisms for high-grade astrocytomas in the two age groups based essentially on an immature and still developing cellular genotype/phenotype of the cell of origin in the pediatric age group. Also, tumor angiogenesis varies according to tumor grade^[1].

It would appear that p53 mutation and other modes of inactivation of the p53 tumor suppressor pathway are

critical in the development of a high-grade astrocytoma in children. Such a feature would appear linked to a tendency for these lesions to arise as essentially de novo tumors in contrast to adult cases.

One basic difference may lie with the fact that secondary transformation of low-grade astrocytomas in children is far less likely to develop than in adults. Amplification of the EGFR would necessarily induce secondary progression of the glioma to a high grade, a phenomenon that would occur mainly in adults.

Is duplication of the EGFR a phenomenon linked to attributes of the adult-type of astrocytic cell undergoing neoplastic transformation? Is this essentially prevented in children due to preferential inactivation of the p53 tumor suppressor pathway characterizing pediatric cases?

In addition, less than 25% of pediatric high-grade astrocytomas show genetic alterations affecting the Rb tumor suppressor pathway. This contrasts with an over 80% frequency in high-grade adult gliomas.

A situation might arise in adults whereby a high-grade astrocytoma tends to be secondary, and associated with both preferential inactivation of the Rb suppressor pathway and amplification of the EGFR.

The p53 suppressor pathway inactivation would not allow much in the way of amplification of EGFR. This latter phenomenon would apparently be linked to both the tendency for the adult high-grade astrocytoma to progress from a pre-existing lower-grade lesion and also for the cell of origin of the astrocytoma in adults to be developmentally mature rather than immature.

The rather immature genotype/phenotype of the cell of origin for astrocytomas in children is a phenomenon linked to still active developmental pathways involving the brain in childhood and preventing EGFR amplification. The pediatric lesions would lack the cellular machinery for EGFR amplification that induce progression to a high-grade lesion, in contrast to the situation in adults.

Two distinct mechanistic pathways of neoplastic initiation and progression and of developmental/maturation processes within astrocytic cells in children would account for a phenomenon that prevents progression to a higher-grade lesion. Also EGFR amplification would occur due at least partly to preferential inactivation of the p53 suppressor pathway. Such a process would appear linked to the fact that very high-grade astrocytomas do develop in children as essentially *de novo* lesions. This is in contrast to a significant proportion of high-grade astrocytomas occurring in adults.

Superimposed on such a complex genetic background there would concurrently develop developmental and maturation processes occurring in an immature cellular environment preventing progression to a higher-grade lesion. Angiogenesis, in particular, appears to be potentially modulated in terms of biology of the neoplasm^[2]. Microvessel density is a quantitative estimate of such angiogenesis^[3]. A still actively developing cell of origin would be less liable to undergo progressive malignant transformation to a higher-grade lesion.

High Proliferative Rate And Infiltrative Behavior of Tumor Cells Due To Genotypic and Phenotypic Loss of The Differentiated State: It appears true that neoplasms that are of low proliferative activity are also indolent in terms of infiltrative behavior. Angiogenesis is a prerequisite for growth of solid tumors beyond a diameter of about 2mm^[4]. Conversely, highly proliferative lesions are often or generally characterized as highly infiltrative. A link appears to underlie both proliferative rate and infiltrative behavior in a manner that would characterize cell proliferation as an integral component of tumor cell infiltration. Early vascularization is induced by differentiation of mobilized bone marrow cells^[5].

Perhaps actively proliferating cells are prone to infiltrate adjacent tissues. The angiogenic response of the infiltrated brain would determine, in large part, morbidity of the invading glioma^[6]. Subsequent to neoplastic cell proliferation, a series of mechanistic pathways would promote the infiltration of adjacent neuropil or stroma within concurrently evolving proliferative pathways. Mast cells, in particular, that are present perivascularly, are implicated in angiogenesis of tumors and in vascular remodeling^[7].

In what ways might a rapidly dividing tumor cell progress and become highly infiltrative? Tumor cells would incorporate a high proliferative rate with decreasing differentiation of the lesion. A poorly differentiated or a high-grade neoplasm is one essentially characterized by a strong tendency for spread and for a high proliferative index. PRL3, a protein tyrosine phosphatase, appears especially implicated in tumor metastasis and tumor angiogenesis^[8].

What characterizes a concept of specific levels of differentiation of neoplasms? There is a tendency for various parameters of "differentiation" to evolve together and to progress sequentially as increasing grade of the neoplasm.

A basic concept of variable differentiation of a neoplasm would directly imply a strict correlation between proliferative rate and degree of infiltration by tumor cells that essentially arises as a biologic attribute of the individual tumor cell making up integral subpopulations of such tumor cells^[9].

Cellular biologic processes would implicate infiltrative behavior of a tumor cell that involves relative proliferation and infiltration as tumor-related activities. The Eph family of receptor tyrosine kinases and their ligands, ephrins, are central to modulation of tumor neovascularization^[10].

Infiltrative behavior would involve loss of the fully differentiated cell phenotype in malignant transformation. Loss of a differentiated phenotype would implicate the acquisition of all essential attributes of neoplastic transformation and progression leading to loss of stability of cells and of the neoplasm, both genotypically and phenotypically.

The Gemistocytic Astrocytic Component In Gliomas As A Dedifferentiation/differentiation Phenomenon In Many Neoplasms:

The phenomenon of gemistocytic astrocytes appears to incorporate multiple possible modes of involvement of the astrocyte. The appearance of abundant cytoplasmic staining for glial fibrillary acidic protein (GFAP) on immunohistochemistry would indicate effective synthesis followed by a process of accumulation of such GFAP+ filaments. An analogy between the gemistocytic astrocyte and the active fibroblast is one possible interpretation related to accumulation of fibers in tumor cell subpopulations. Strong trophic influence would, at some stage, account for the laying down of abundant glial fibers extracellularly. There would evolve coupling between effective accumulation of glial fibers intracellularly and the subsequent deposition of glial fibers extracellularly as seen in persistent states of reactive gliosis.

Purely gemistocytic astrocytomas are rather uncommon, but a component of gemistocytic astrocytic cells is often noted in many cases of otherwise typical

astrocytomas, especially with increasing grade of the lesion.

Attempts at interpreting the presence of a predominant gemistocytic astrocytic component in terms of prognosis would be perhaps suggestive of a correlation with very active tumor cell phenomena that are central to neoplastic progression.

The minigemistocytes found in a number of oligodendrocytomas would contribute to developmental cell biology affecting the cell of origin of the neoplasm. Is it possible to consider the gemistocytic astrocyte a stage in the partial transformation of an oligodendrocyte to a lesser stage of astrocytic differentiation? Such a process might evolve as complex events in a differentiation/dedifferentiation series of pathways in tumorigenesis.

Disparate Groups of Biologic Subpopulations of A Tumor Make Up The Integral Lesion: The differentiation process would refer to a whole host of biologic attributes of tumors that implicate distinct subpopulations of neoplastic cells relative to proximity to blood vessels.

Various tumor types such as bladder carcinoma show a range of hypoxia, proliferation and vascular density influencing particularly outcome of different therapeutic modalities^[11].

Such a distinct overall phenomenon would prove significant with regard especially to astrocytic neoplasms. Pilocytic astrocytomas are a distinct subtype of astrocytic tumor that biologically incorporates a vascular component as a main morphologic component of the lesion. The endothelial cells of tumor vessels are considered normal diploid cells that do not acquire mutations. On the other hand, in B cell lymphomas, the microvascular endothelial cells are, in part, tumor-related^[12].

The pattern of distribution of the vessels in pilocytic astrocytomas would appear to differ from that of the higher-grade astrocytomas and glioblastomas relative to other biologic attributes of the lesion.

Functionality of the blood supply as well as the blood vessel architectural pattern of development of the neoplasm help characterize biology of distinct subpopulations of the tumor cells.

Degree of delivery of oxygen and probably of nutrients would have an impact on the degree of biologic aggressiveness and also on the tendency for distinct subpopulations of tumors to progress as variable components in malignant transformation.

It is conceivable that the indolent nature of pilocytic astrocytomas as essentially noninfiltrative lesions is related to an inherent biology of its blood-supply pattern. Both the pilocytic astrocytoma and the oligodendroglioma show less dense vascularity and no focal festoons of vessels as typical of glioblastomas^[13]. The fact that

pilocytic astrocytomas show such a poor tendency to progress to higher grade would set them apart from astrocytomas of Grades II to IV.

A high-grade neoplasm appears to intrinsically incorporate a tendency for biologic progression to even higher grade. Such a phenomenon would correlate with the degree of aggressiveness of the tumor that, from its time of inception, would progress to a higher grade of lesion. A Grade III astrocytoma would appear more prone to transform to a Grade IV lesion than a Grade II lesion to transform to Grade III.

Pilocytic astrocytomas are slow to transform to higher grade in terms arising from their inherent Grade I attributes.

A fundamental phenomenon would however operate across a whole range of different grades of astrocytoma involving higher grade with progression of the lesion. This may be due to various factors that incorporate blood supply affecting distinct subpopulations of tumor cells.

In hepatocellular carcinoma, microvessel density and telomerase activity cooperatively influence tumor growth and spread^[14].

Biologic progression of a neoplasm in terms of grade might actually depend on a phenomenon of strict subpopulations of tumor cells. Heparin-binding epidermal growth factor-like growth factor strongly induces angiogenesis and tumor growth^[15].

Degree of proximity of subgroups of tumor cells to blood vessels might very well dictate both the degree of biologic aggressiveness of the tumor cells concerned and also its tendency for subsequent progression to higher grade. Also, complex formation between antibodies to tumor vascular endothelial cells and anti-tumor drugs may freely access target tumor cells irrespective of vascular permeability^[16].

Tumor cells immediately surrounding blood vessels might account for increased biologic aggressiveness for various reasons. A greater delivery of oxygen and nutrients would concurrently develop with a process of angiogenesis and increasing tumor grade as induced by anti-angiogenesis therapy that targets endothelial cells and/or the extracellular matrix in malignant gliomas^[17].

Distinct subpopulations of tumor cells would dictate dynamics of evolution of the neoplasm in terms both of proliferation of cells and of infiltration of adjacent tissues as related to proximity to vessels supplying the lesion and involved region.

Indeed, variations in the biology of the blood supply of tumors would regionally determine attributes of a lesion that evolves mainly in terms of spread of subpopulations of the neoplastic cells. Density of angiogenesis indicates degree of risk for metastasis in tumors such as breast

carcinoma, and as influenced by vascular endothelial growth factors (VEGFs)^[18].

In this manner, tumor cell subsets would tend to undergo necrosis as they proliferate and outstrip their blood supply. Such a phenomenon of necrosis of different tumor cell subsets might be related to intrinsic attributes of proliferation and infiltration away from the immediate proximity of the blood vessel of supply. VEGF levels correlate with prognosis in lesions such as non-small-cell lung cancer^[19].

A highly dynamic series of mechanistic pathways would evolve as distinct subpopulations of tumor cells that make up one single neoplastic lesion. Targeting survivin in cancer therapy induces both a proapoptotic effect and also interruption of tumor angiogenesis^[20].

Clonality Of Glioblastoma Tumor Cells As A Basis For Biologic Attributes Of The Lesion: Clonality of glioblastomas appears an attribute of the tumor cells that might affect or modulate various histologic components of the lesion including endothelial cells. Necrosis of the neoplastic cells and the peripheral pseudopalisading of the cells around these foci would evolve in terms also of high mitotic rate and nuclear pleomorphism in determining essential clonality in genesis and progression of the glioblastoma.

Zones of necrosis would constitute impaired viability of clones of tumor cells that arise in terms of a proliferation derived from single cells of origin. Genetic defects would consequently progress as a function of such clonal proliferation predisposing to further genetic abnormalities.

The endothelial cell proliferation is probably a component of such clonal proliferation that effectively involves tumor cells as subpopulations. Nuclear mitotic figures tend to progressively become abnormal as a function of clonality and of subsequent necrosis. The gemistocytic cell component of glioblastomas would contrast with clonality determining mitotic activity in various regions of the neoplasm.

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