Distinctive PDGF Biology of Autocrine Action Versus Paracrine Effects in Tumor Cell Growth/Proliferation Versus Metastatic Spread

Lawrence M. Agius[1, 2 *]

[1] 27 “Ballarat” Guzeppe Caruana Street, TAL-VIRTU, Rabat, RBT09 Malta, Europe.

[2] Formerly of Department of Pathology, Mater Dei Hospital, TAL-QROQQ, University of Malta Medical School, Msida, Malta, Europe.

Correspondence: Lawrence M. Agius, Telephone: 356-21451752, Email: lawrence.agius@um.edu.mt.

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ABSTRACT

Highly distinctive diversity patterns of operational dysfunction allow for the contrasting biology of autocrine attributes versus the promotional effects of paracrine action of the PDGF ligand/receptor complex. Indeed, the metastatic capabilities of malignant cells contrast with a primary localization of the parent tumor lesion within scopes of a predominant stromal series of activation as exerted by the PDGF/receptor complex. Homologous pairing of the PDGF ligand polypeptides contrasts with the heterologous pairing of the A-B polypeptides of the PDGF ligand in an extensive cross-talk of pathway effects and of receptor-receptor interactivity within the tumor cell membrane. Overall predominance of stromal biologic effects may paradoxically render the parent malignant cells with potent capabilities in metastatic deposition and further spread.

Keywords: Platelet-derived Growth Factor; Primary tumor; Metastasis; Autocrine; Paracrine

1 INTRODUCTION

Aberrant Platelet derived growth factor receptor signaling is a primary mechanism in the progression of gliomas, including anchorage-independent growth, adhesion, invasion and sphere-formation

and impaired cytoskeleton reorganization [1]. The paracrine and autocrine functionalities and dysfunctionalities of platelet-derived growth factor (PDGF) receptor-alpha and receptor-beta constitute a predominantly mesenchymal axis with stromal cells such as fibroblasts, pericytes and smooth muscle cells. PDGF-C enhances human melanoma invasiveness through activation of neuropilin-1, a co-receptor for VEGF receptors and contribute to a metastatic phenotype [2]. PDGF-BB is widely used as a biomarker in various pathologic states including malignant tumors [3]. The dimerization of the PDGF receptors is central to an ongoing variability response dependent on the uncovering of the tyrosine kinase domains by the activation loop situated in the C-terminal domain of these receptors.

In terms of overall functionality a link is created between autocrine malignant epithelial cells and glial cells in a manner that is further compounded by fusion receptor genes and the mutational and amplification dysfunctionalities of the receptor-ligand genes.

A recombinant lentiviral PDGF-driven mouse model allows for the facile in vivo testing of gene function in pro neural glioblastoma [4]. Insulin-like growth factor-binding protein-3 induce proliferation of hepatocellular carcinoma cells via IGF-1 that influences bFGF and PDGF autocrine/paracrine loops [5].

It is further to the ongoing dysfunctionalities that cancer-associated fibroblasts contribute to the progressive support and enhancement of tumor cell growth and proliferation on the one hand and also for migratory and metastatic phenomena that in turn define the tumor biology of such lesions as the pro-neural forms of glioblastoma. Hematopoietic stem cell-derived adipocytes promote neoplastic growth and cancer cell migration [6].

2 AUTOCRINE/PARACRINE DIFFERENTIATION

Autocrine processes of stimulation and activation of epithelial and glial cells account for self-sufficiency in terms also of tumor angiogenesis. Increased PDGF receptor beta expression on trephine biopsies correlates with advanced multiple myeloma stage [7]. The endothelial cell plays a crucial role in PDGF biology in the activation and pericyte response of supplying vasculature in a manner that is reflected in such phenomena as chemotaxis and increased tumor blood supply. Autocrine dual specificity phosphatase 28 signaling mediates pancreatic malignancy via regulated PDGF-A [8].

The incremental populations of PDGF receptor number attest to a dysfunction that links parent cell populations of the tumor lesion with the participation of mesenchymal stromal elements such as fibroblasts and pericytes within a further context of smooth muscle cells.

Dermatofibrosarcoma protruberans is driven by a translocated PDGF gene, and gastrointestinal stroll tumors and leukaemia are driven by point mutations and fusion proteins of the PDGF receptors that are constitutively activated [9].

It is indeed in such milieu that PDGF ligands and receptors operate in an overall system mechanism that enhances in particular both the growth/proliferation activities of tumor cells. PDGF-induced activation of protein phosphatase 1 in the regulation of Collapsing Response Mediator Protein 2, a microtubule bundling protein [10].

Such phenomena are significant in the context of cancer-associated fibroblasts and other cellular elements of the stroma. Aggressive meningiomas can be induced by simultaneous activation of neurofibromatosis type 2 gene and the PDGF/PDGF-Receptor system [11]. Fusion gene formulation with the 1A1 collagen gene is further proportional increment in the support of the autocrine/paracrine dysfunctionalities of the malignant cells.

3 ANGIOGENESIS

Considerations regarding the linkage phenomena are indicative of a contributing and synergistic dysfunction of vascular endothelial growth factor in a system mechanics that allows for mesenchymal paracrine involvement in tumor cell growth/proliferation and particularly of metastatic attributes of the primary tumor lesion.

Target molecule-based inhibition of the cancer-stomal cell interactivity may be promising as effective antitumor management [12]. PLX3397, an inhibitor of colony stimulating factor-1 receptor, blocks glioma progression, suppresses neoplastic cell proliferation and reduces tumor grade in a preclinical glioblastoma model and render the tumor more susceptible to receptor tyrosine kinase suppression [13]. H3.3K27M mutation, a histone H3 variant, and PDGF signaling act in concert to accelerate diffuse intrinsic pontine glioma in a genetic mouse model and indicates p16 tumor suppressor as target, and implicates the G1-S cell-cycle as a promising therapeutic avenue [14].

The prognostic determinants of a given neoplastic lesion such as a glioma is therefore dependent on inherent dysfunction that bridges stromal cell

components within the further contributing diversity of a whole range of mesenchymal cells within the malignant lesion. Over-expression of PDGF has been shown to produce experimental gliomas in rodent models [15].

4 TYROSINE KINASE DOMAIN

Tyrosine kinase activation and auto-phosphorylation of tyrosine residues indicate the molecular dynamics of incremental numbers of PDGF receptor isoforms. Angiogenesis-related proteins in serum of women with breast cancer may facilitate the growth and metastatic spread of breast cancer partly through tubule formation [16].

The further promotional activation of tyrosine kinase domains allow for the institution of docking domains with a whole constellation of intracellular substrates that contribute in turn to an intensive cross-talk between many intracellular pathways of activation in their own right.

5 KNOCKOUT LESION MODELS

Knockout animal models of PDGF ligands and PDGF receptors indicate a vascularity phenomenon that is in part dependent on pericyte depletion. Such phenomenon is a central axial dimension that allows for further progression of the neoplastic lesion within an added context of improved blood supply of the tumors. Improved blood supply to neoplasms is a cardinal referential point of operative dysfunction that is supported by the VEGF pathways. Silencing of peroxiredoxin5 and PDGF-B suppresses the proliferation of gastric cancer cells in vitro [17]. It is further to such phenomena that clinical studies have validated PDGF ligand/receptor pathways as relevant targets in tumor targeting.

6 RECEPTOR/LIGAND TURNOVER

Dimensional reconstruction of tumor biology mechanics also implicate turnover of internalized PDGF receptors that are either sorted in ubiquitin degradation or are returned to the cell plasma membrane. Such mechanics is a divergence phenomenon that further and critically implicates a receptor biology both in terms of possible increment or in terms of replacement supplementation of pathway constituents and pathway cross-talk.

Activated mammalian target of rapamycin, PDGF, VEGF, and c-kit signaling have been implicated in Kaposi sarcoma pathogenesis and suggest that beneficial effects may be obtained by using targeted inhibitors [18]. Paradoxical support of metastatic lesions such as lung lesions or bone deposits as in prostatic carcinoma allow for the promoted spread characteristic that attributes the primary tumor lesion with systemic cooperative synergism in given tumor patients. Lesions such as prostate carcinoma are hence attributes to dimensional spread as reflected particularly in a context of stromal mesenchymal cell populations and vascular endothelial cell subpopulations. Cancer-Associated fibroblasts are the crucial cellular determinants for metastatic spread [19].

Proposed activation of the tyrosine kinase domain is thus a potent referral point of axial activities that permits the centralization of phenomena of metastatic spread as the primary tumor lesion grows, proliferates and infiltrates the tumor stroma.

Proportional increment of receptor activation is a generic phenomenon within the system profile of ongoing carcinogenesis and as further indices of characterization of the tumor diversity in metastatic spread. PDGF-B and nestin have been proposed to be operative in neoangiogenesis in malignant ovarian tumors and are implicated as markers of newly formed micro-capillaries and perivascular cells in these neoplasms [20].

7 MODULATED EFFECTS OF RECEPTOR DIMERIZATION

Modulated effects of the PDGF ligand/receptor biology are a gene-diversification process that promotes response phenomena based on such genetic compilations as well-exemplified by fusion of genes and also as amplification of the PDGF receptor gene. Complications involving the dimerization of the PDGF polypeptide chains include the homologous pairing or AB heterologous pairing as incremental effects in PDGF ligand/receptor stimulus response involving tumor cells and stromal cells in autocrine and paracrine dysfunctionalities.

Aberrant PDGF signaling is primarily tumorigenic and it regulates the surrounding micro-environment; PDG is a major mitogen and chemoattractant for mesenchymal and glial cells [21]. The contrasting profiles of autocrine versus paracrine mechanisms involve a diverse cell series of subpopulation diversities that are potentially highly characterizable

within the systems of cooperative pathway dynamics.

Strict interactivity and pathway cross-talk delineate a unique series of axial dimensions that contrast the dynamics of autocrine stimulation with the paracrine processes for further contributed pathways of modulation.

In this sense, distinctive patterns of cell receptor activation are not only products of dimerization of the PDGF polypeptides but also an interactivity series of promotional events within the receptor populations present in the cell membrane. Such modulated dimensions involve interactions as further promoted by gene mutation, fusion genes and amplified genes within the genome. PDGF-driven tumor initiation and progression have been induced in tv-a transgenic rats and these recreate crucial features of human brain gliomas [22]. The positive regulatory role associated with PDGF-nitric oxide-signalling-driven activation of inhibitor of differentiation 4 may play a pivotal role in self-renewal and tumor-initiation of glioblastoma stem cells [23].

The autocrine production of PDGF ligand by malignant cells is hence contributing factor in the realization of systems of paracrine dysfunctionality that underlies the dynamics of metastatic spread of the primary lesion. Inclusive dimensions of cell and receptor activation further promote the distributional array of ligand/receptivity phenomena as axial contexts for spread of the malignant tumor cells.

8 CONCLUDING REMARKS

Promotional diversity of PDGF dimerization and the further receptor cross-talk as inherent products of incremental activation allows for the further propagation of the receptivity in terms of strict patterns of proliferative and growth of tumor cells. It is further to such cell activation patterns that there ensue attributes of vascularity and angiogenesis as systems of paradoxical predominance in the biology of tumors that is inherent to stromal cell elements. Indeed, stromal cells are resident participants in the biology of metastatic spread that renders spread of the malignant cells within a milieu of amplification and variability of biologic dysfunction of stromal cell elements.

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