

Review

The nature of context-conditioning in carcinogenesis and transforming growth factor-beta biology

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ABSTRACT

Abstract formulas of events that strictly demand definitions of consequence in carcinogenesis-related events contrast the induction of such tumor formation within potent dimensions of the mirror-imaging profiles of an event as malignant change. In such terms, an either/or formulation of incipient epithelial-mesenchymal transition (EMT) formulas of performance and of stimulation/suppression are exerted by a potent transforming growth factor beta (TGF- β) sequence determination. Inclusive dimensions are themselves incremental events in terms either of stimulation or of suppression within systems that are strictly defined as exerted performance formulas. Distributional parameters of either/or are hence a recapitulation of injury dynamics as further profiled by suppressed cell growth and proliferation on the one hand, and by the systemically professed incremental series of stimulated modulation of the micro-environment. Metastasis and invasiveness of tumor cells allow for the emergence of permissive influences that exert the mirror-imaging as projected by context-driven events and as substantial re-formulation of attributes of either/or and of transformation.

KEY WORDS: Epithelial-mesenchymal transition (EMT); Carcinogenesis; Transforming Growth Factor beta.

ABBREVIATIONS: EMT: Epithelial-Mesenchymal Transition; TGF- β : Transforming Growth Factor beta; ERK1/2: Extracellular Signal-Regulated Protein Kinases 1 and 2; PAR2: Proteinase-Activated receptor 2.

INTRODUCTION

Context-dependent induction of transforming factor-beta is an enigmatic series of phenomena that contributes in essential ways to the contrasting end-results of particular actions within the intra-cellular and especially intra-nuclear modulation of such processes as cell growth and proliferation.

A particular concern relates to the stimulation of the epithelial-mesenchymal transition (EMT) of tumors that is integral to the metastasizing potentials of malignant cells as induced by transforming growth factor beta (TGF- β). It is relevant to consider the suppression and arrest of the G1-phase of the cell cycle as inherent dimension towards the profound effects exerted in proliferative and invasive phenomena. miR-142 is a tumor suppressor gene in hepatocellular carcinoma and is often hypermethylated to enhance TGF-beta-induced carcinogenesis.¹ Metastases are especially relevant to the understanding of the EMT phenomenon itself. TGF-beta plays an essential role in cancer progression and regulates malignant cell proliferation and remodelling of the tumor micro-environment.² In such terms, incremental suppression of the native immune response is cardinal aspect in the promotion of the TGF-beta induction of both tumor-suppressing

and tumor-enhancing functions and dysfunctions of this growth factor. TGF-beta suppresses proliferation at early stages of carcinogenesis but promotes metastasis at late stages and implicates extracellular signal-regulated protein kinases 1 and 2 (ERK1/2) in this paradox switch.³

Translationally controlled tumor protein is required for epithelial-mesenchymal transformation in cells and is regulated by TGF-beta1 in carcinogenesis.⁴

CONTEXT FORMULATION

Of particular interest is context-evolving modulation of the dimensional spread of specific tumor types ranging from intestinal to such lesions as hepato-cellular, biliary and other forms of carcinogenesis. TGF-beta opposes the actions of oestrogen receptor-alpha and induces EMT programs that enhance dissemination, stemness and chemoreistance in breast cancer.⁵ In this regard, the evolutionary course of a core process of induction appears to promote immune-suppression in an analogous fashion, as well-illustrated by the contrasting roles of TGF-beta in autocrine and paracrine biology and of negative-feedback control of TGF-beta secretion and action. In 15% of cases of colon cancer, deficiency in mismatch repair leads to null mutations in TGF-beta type II receptor that, when combined with *Helicobacter hepaticus*, causes tumorigenesis and synergism between genotype and microbial environment.⁶

EPITHELIAL-MESENCHYMAL TRANSITION

Thus, it is relevant to induce EMT induction by TGF-beta as exemplary evidence towards the contributing roles of such a growth factor to homology domains of Mad-1 and Mad-2 in promoter activation of genes. The distributional evolution of such processes as DNA binding and of docking dynamics of the kinase-relevant processes depends largely on such processes as phosphorylation-relevant phenomena as well-projected by TGF-beta actions.

Low xanthine dehydrogenase mRNA levels correlate with higher tumor stages and poorer prognosis in patients with hepatocellular carcinoma; inhibition of xanthine dehydrogenase promotes migration and invasion but not proliferation of hepatocellular cancer cells.⁷

The EMT is a conserved re-formulation of events that is end-result dimension to the activation of the cellular micro-environment in terms of the ongoing proliferative activation of cancer-associated fibroblasts. Indeed, through the formulated modulation of the invaded micro-environmental stroma, there evolves an invasiveness that appears related but is essentially independent of the proliferation of the transformed malignant cells. TGF-beta1 enhances the adhesion, migration and invasion of urothelial cancer cells by up-regulating MMP-2, MMP-9 and calpain-2 expression.⁸ In such terms, conclusive end-result and dimensions of micro-environmental modeling are incremental dimension to the EMT phenomenon itself. The performance

impacts of induced processes include the essential event of induction of stem cells and hence of developmental processes of onset and contribution to the modulating systems of incremental and less incremental effects of the potent TGF-beta series of sequential processes. These involve especially Smads and adaptor proteins such as beta-2 Spectrin.

DEVELOPMENT DYNAMICS

Developmental induction thus emerges as core attributes to the subsequent tightly-formulated process of EMT within contexts of suppressive processes that are exerted on cell growth and proliferation on the one hand and the dimensionally induced categories of a coupled stimulation and inhibitory series of molecular interactivities.

The proposed context relevant series of promotional and suppressive functions of TGF-beta are integral summation of the formulated dimensions of the EMT phenomenon. The TGF-beta and ERK/glycogen synthase kinase 3 beta pathways are critically implicated in radiation-induced EMT.⁹ In such terms, ongoing dynamics of induced contrast in end-results of TGF-beta actions is beyond the simple tumor-suppressor roles of this growth factor. TGF-beta signature in liver cancer with mutations in almost 40% of samples of hepatocellular cancer carry prognostic significance; inflammation and fibrosis result from up regulation of the TGF-beta pathways whereas loss of TGF-beta suppressor tumor activity with down regulation.¹⁰ Indeed, promotional increments are negative mirror images of a paradoxical contextual relevance of TGF-beta in terms of suppression of carcinogenesis that is further computed as EMT processes of invasion and metastasis.

CARCINOGENESIS

Untoward effects as enhancing carcinogenesis hence are an inducing process of ongoing developmentally related dimensions for further escape from processes of core suppression of the malignant transformation process. It is clearly in terms of contextually contrasting stimulation as exerted by the micro-environmental events that determine an essential conditioning and re-conditioning of the epithelial and mesenchymal cells towards ongoing increments of stimulation and suppression. Constitutive dynamics of TGF-beta assume the re-appraisal development of cell proliferation and invasiveness as further defined by models of contact and loss of cellular adhesion.

COMPARATIVE DYSFUNCTION

Understanding the cooperative dysfunctions of contrasting suppression and enhancement of exerted potency in DNA-binding come to define the inherent characterization of gene-activation machineries. TGF-beta and interleukin-10 levels are significantly higher in patients with gastric cancer, particularly with regard to Epstein Barr virus induced lesions with anti-EA antibodies indicating EBV reactivation.¹¹ In terms inclusive to evidential reformulation towards EMT emergence there also evolves the

persistence of a stimulating series of events that persist as permissive de-control and as conditioned end-result re-formulation.

PERFORMANCE ATTRIBUTES

Performance of a stimulus-response is performed through the characterization of constitutive permissiveness within contexts of inducing events, as indeed highly indexed formulation of the binding to a series of molecular adaptor proteins such as beta-2-Spectrin. The realization of events that recruit the performance of dually contrasting stimulatory attributes allows for the propagation of cellular characterization as well-illustrated by cellular proliferation and growth-arrest in G1-phase interruption of targeted cells. TGF-beta/SMAD pathway, particularly SMAD2, may play a critical role for down regulation of tight junction protein CLDN6 through DNA methyltransferase 2 mediated DNA methylation.¹²

SUPPRESSION/STIMULATION

Traditional anti-oncogenic approaches of suppressive actions of chemotherapeutic agents on processes of DNA synthesis and DNA repair include the dimensions of a modulated micro-environment that parallels the onset dynamics of suppression of cell growth and proliferation within essential contexts of an either/or series of exerted attributes, as well-illustrated by potentially formulated performance dynamics. Heat Shock Protein 27 is critical to lung cancer progression and TGF-beta-induced cisplatin resistance in human lung cancer cells, and may allow effective clinical strategy in lung cancer patients that are resistant to chemotherapy.¹³

MIRROR-IMAGING

Inclusive mirror-imaging emerges as an inherent reflection of processes of development that are consequent dimension of the carcinogenic phenomenon of either/or within systems of context and suppression in particular. It is relevant to the recognition of contrasting reactivities that DNA-binding is itself a performance dynamics of sequential contribution to early and late phenomena in carcinogenesis. Strict dimensionality is an inherent end-result to the further sequential evolution of pathways of phosphorylation-related pathways of consequential impact in carcinogenesis per se.

Promotion and suppression hence underlie the essential dynamics of a modulated micro-environment that paradoxically parallels the dynamics of gene-binding and activation. Promoter regions of genes are performance-defined in such realization within the systems of a potentially-exerted formula of either/or and within the contour-determining phenomena of enhanced cell proliferation and invasiveness of such stroma.

INDUCTION

Induced action and reaction define the semblance performance of an injury that persistently stimulates in biologic terms the on-

set of carcinogenesis in terms strictly of the EMT and of metastatic spread. Hence, a tangible re-formulation of such metastatic spread is inherent performance of relative dimensions of the EMT process itself. Proteinase-activated receptor 2 (PAR2) and TGF-beta1 synergy may involve TGF-beta1 induction of enzymes that cause autocrine cleavage/activation of PAR2, possibly through a biased signaling function; PAR2 is necessary for TGF-beta1 induced cell motility.¹⁴ Mesenchymal stem cells can interact with multiple types of tumor cells and manifest as tumor-associated fibroblasts and thus induce migration of cancers and enhance carcinogenesis; they directionally migrate toward tumor cells and cause tumor cell apoptosis.¹⁵

TGIF2LX (transforming growth factor beta-induced factor 2 like, X-linked) is a homeodomain protein that is implicated in the negative regulation of cell signaling pathways; it may act as a tumor suppressor in colon adenocarcinoma cells.¹⁶

CONCLUDING REMARKS

Realization and actuation of processes of increased cell proliferation and growth are seen within reflected attributes of a paradoxical suppression of such cell proliferation and metastatic/growth dimensions of contextually relevant action of pathways of a primarily sequential nature in TGF-beta promotion and suppression. Protein deacetylase SIRT7 is significantly down regulated in breast cancer lung metastases and modulates TGF-beta signaling and enhances EMT.¹⁷ It is indeed within substantial re-formulation of pathways of contrasting identity that TGF-beta inducing influence is re-capitulated action of contextually conditioned system machinery. It is relevant to consider the series of sequence-induction as a primarily outlined developmental dimension furthering the progression of a carcinogenesis-event within systems of end-result performance and determination.^{18,19}

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