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Re-defined mechanics of cell cycling as active binding interactions induced by 14-3-3 protein dysfunctionalities

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Abstract

There emerges a series of global cellular functionality/dysfunctionality with regard to the scaffold protein 14-3-3 in the realization of close affinities of a cell cycling series of events and the promoted progression of DNA injury. DNA repair systems are central issues in the evolutionary dimensional emergence of DNA injury in terms of global cellular mishaps as evidenced by over expression of genes in amplified gene expression. The realization of DNA injury is further promulgated as system pathway disruption and as protein molecular interactivities within the concurrent systems for promoted progression of a vulnerable cell cycle series of events in carcinogenesis.

Keywords: *Cellular Functionality; Scaffold protein 14-3-3*

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Introduction

The scaffolding functionality and dysfunctionality of 14-3-3 assumes considerable significance in molecular interactivity, molecular sequestration and transport and in targeting events as applicable to carcinogenesis. The alpha-helical dimerization structure of 14-3-3 is fundamental denotation in the recognition of two binding sites, one on each monomer of the 14-3-3 protein scaffold. The incremental binding of such events is central to the targeting processes as applicable to the G2-M checkpoint in mitotic progression in general and as specific significance in carcinogenesis. The phosphorylation and acetylation phases in activation of 14-3-3 protein are central dimension in the projected dysfunction of this protein in tumorigenesis and allow for the binding of some 200 different proteins.

Gene 33 is a proximal regulator of the DNA damage response that promotes DNA repair; it is regulated by its 14-3-3 binding domain [1]. Protein-protein interactions are pivotal in normal cellular functions and in carcinogenesis with the formation of functional clusters during signal transduction [2]. Oncogenic lesions are closely intertwined with metabolic alterations promoting cancer progression; cancer progression requires cellular metabolic reprogramming as both direct and indirect consequence of oncogenic lesions [3]. PDZ/14-3-3 switching may be a broad biologic paradigm with binding to PRMT5 when unphosphorylated and to 14-3-3 proteins when phosphorylated [4].

It is within the subsequent transporting facilities for binding that 14-3-3 scaffolding dysfunction allows for much of the cytoplasmic sequestration of such moieties as Cdc25 phosphatase and hence induces activation/deactivation cycles of influence in functional protein turnover. 14-3-3 sigma has been reported to be frequently methylated in breast cancer and may constitute a useful blood-based biomarker [5]. 14-3-3 sigma is dispensable for normal epidermal homeostasis but crucial for suppression of chemically-induced skin carcinogenesis; ER mutation of 14-3-3 sigma may include a gain-of-function variant [6].

Determined Response

Determination of the huge repertoire of protein moiety binding creates an extensive series of conflicting data in the attempt to generalize the effects of 14-3-3 isoforms in cell cycle control and in apoptosis in particular. It is further to dimensions for extensive manipulative signals that 14-3-3 proves to provide key node functionality in the context of tumor activation or inactivation. 14-3-3 is a critical reader of mammalian DNA (cytosine-5) methyltransferase 1 pSer143 that regulates DNA methylation and altered gene expression that contributes to cell invasion [7]. It is significant to consider the dimensions for further steps in carcinogenesis that the breast tissues around the region of a neoplasm assume further confirmation as applicable to the absence of specific isoform of 14-3-3 sigma.

14-3-3 proteins have been proposed as prognostic factors and as specific target in the treatment of cancers [8]. The tumor suppressor dysfunction of 14-3-3 is best typified as a release dysfunction that operates on molecular interactivities as borne out by the cytoplasmic sequestration away from nuclear events such as DNA binding. Down regulation of 14-3-3sigma correlates with multistage tumorigenesis and poor prognosis of oesophageal squamous cell carcinoma [9].

Post-Translation

14-3-3 phosphorylation of residues, particularly serine and threonine domains, is a very sensitive functionality feature that operates in the binding of various proteins within systems of a Ying-Yang fashion of operability. In such manner, there is a fluctuation in operability of the G2/M checkpoint leading to progression of the cell cycle. The protein 14-3-3 sigma plays a role in cell cycle arrest by sequestering cyclin-dependent kinase 1 cyclin B1 complexes, as well as cyclin-dependent kinases 2 and 4, hence its definition as a cyclin-dependent kinase inhibitor [10]. The molecular effects of 14-3-3 protein are particularly implicated in such progression of mitotic activity within such pathways of effect as phosphatase activity. Generalization of the dysfunctional effects of 14-3-3 is best viewed within the subsequent categorization of the mid-body division of the late stages of the cell cycle as induced genetic instability leading directly to tetraploid cells and carcinogenesis.

Protein/Ligand Scaffolding

The conceptual frameworks for operability of scaffolding proteins is essential feature in recyclable dimensions of cell proliferation in tumors in general and allows the manipulative control of cell division cycles and also the de-control of substantial regulatory mechanisms away from the DNA binding sites. The epithelium specific cell cycle regulator 14-3-3sigma is required for preventing entry into mitosis following ultraviolet B exposure [11]. 14-3-3 protein has been implicated in numerous pathways such as regulated gene expression, metabolism and apoptosis, and in growth factor receptor signaling and DNA damage responses besides cell cycling. It is further evidential incorporation of such events as dysfunctional conformations of the molecular structure that 14-3-3 protein has been likened to an “anvil” in terms of molecular conformation.14-3-3beta regulates astrocytic proliferation and proliferation of glioma cells through the glycogen synthase kinase 3beta/beta-catenin signaling pathway and so induces tumorigenesis and progression of human astrocytomas [12].

Consensus Motifs

The consensus motifs for binding are further projected as critical and complex issues in 14-3-3 protein interactivities. 14-3-3 protein is found in all eukaryotic cells and is very well preserved during evolution. It is further estimated that this central series of roles exerted by this binding protein includes a large number of potential ligand combinations within systems for molecular interactivity. Plakoglobin interacts with the transcription factor *p53* and regulates the expression of 14-3-3sigma [13]. Significant re-appraisal of DNA repair pathways includes 14-3-3 as system conformation in the face of cell cycle progression. In such manner, the departure events in re-constitution of DNA damage is tantamount consideration in the understanding of protein scaffolding in general and as further exemplified by systems of nuclear localization motif and nuclear export. The expression level of 14-3-3gamma is significantly increased in human nasopharyngeal carcinoma patient tissues and correlates with N classification, distant metastasis, and clinical stage [14]. The realization of eventual degradation of *p53* is also of central concern in the developmental history of a carcinogenic series of events that incorporate fundamental features of gene binding.

Central Node Functionality

14-3-3 protein functionality hence assumes the complex roles of a central node of regulatory dysfunctions as further induced by

the DNA machinery in particular. 14-3-3 proteins are ubiquitously expressed and key mediators of many cell signaling pathways in multiple cell types by mediation through binding to selective phosphoserine/threonine proteins [15]. Isoform-specific phenotypes of 14-3-3 appear dictated by a relatively few amino acids within variable regions [16]. The resultant ongoing dimensions for re-appraisal allow a series of transportation events that shuffle the bound ligands to and from nuclear DNA and also to and from mitochondria. Dimensional reconstitution is sufficiently developed for a central functionality of 14-3-3 that allows the ligand-induced actions to modulate systems of carcinogenesis especially following DNA damage lesions and as further propagated in effects on the G2/M checkpoint in cell division. Cdc25 phosphatase is important regulator of the cell cycle and its knockdown is related to reduced 14-3-3 protein expression [17].

Constitutional significance in ligand binding, particularly in view of dimensional re-localization of ligand inter-activities, allows for the developmental series of amplification/over expression modalities of various oncogenes in the emergence of carcinogenesis that may follow DNA lesion infliction.

Reduced 14-3-3epsilon expression in gastric cancer and investigation of 14-3-3 epsilon interaction partners may help elucidate carcinogenesis [18]. In such manner, the overall dimensions for the 14-3-3 protein has extensive potential impact on the operability of various pathways such as the classic MAPK and other pathway events involving Ras and Raf.

Concluding Remarks

Operative dimensions of 14-3-3 protein and other scaffold protein moieties include potential degradation systems as induced by Cdc25 phosphatases and furthered by the proteasome/ubiquitin machinery. The operability of protein activation is certified towards the assumption of real outline maneuverability as substantiated by systems of such protein activation as borne out by conformation dysfunction induced by 14-3-3 protein/ligand binding. The realization of DNA injury is of fundamental concern in the generalized upset in cell pathway progression and as further projected by systems of progression of the cell cycle beyond the G2/M checkpoint.

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