ISSN: 2755-0141

Japan Journal of Clinical & Medical Research

SCIENTIFIC Research and Community

Short Communication

Open Access

Proteins and Cancer Therapy-A Complicated Duet

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Received: July 30, 2021; **Accepted:** August 06, 2021; **Published:** August 13, 2021

Cancer is a leading cause of death worldwide, with some forms of exhibiting low survival rates due to poor prognosis and absence of early diagnosis. To effectively treat cancer, various interactions governing cellular subdivision and growth must be investigated. Carcinogenic tissue growth and metastasis are directed by genetic modifications due to genetic and epigenetic changes, which include the activation of certain oncogenes directly affecting their mutation [1,2].

Receptors affecting the cancer growth factor are investigated for their structure, binding sites and various domains which are responsible for cell signaling pathways. The epidermal growth factor receptors (EGFR) have been widely researched for their activation of the tyrosine kinase activity which starts a signaling pathway inducing cell proliferation via several mechanisms including protein synthesis, enhancement of genetic expression required for EGFR and glycolysis [3]. Other growth factors like nerve growth factor (NGF), α transforming growth factor and platelet derived growth factor are also responsible for cell division and growth. A detailed understanding of the interactions between the receptor and the growth factor helps in targeting specific receptors to induce apoptosis of cancer cells.

Several studies on the interaction of growth factor receptors and adhesion-based molecules (known as cell adhesion molecules or CAM) and integrins have been carried out to try and understand the cellular signaling pathways [4,5]. In order to extrapolate this knowledge towards the development of targeted drug delivery, the structural assessment of the cavities, 'druggability' of a protein and the binding capacities between the molecule and receptor are essential factors [6]. More precisely, the interactions of a protein in the particular microenvironment to generate cellular signaling pathways defines its ability to be used as a suitable targeting agent. In this context several drug delivery techniques harnessing the microenvironment changes like pH, hypoxia or temperature have been devised [7-16]. This is assessed by investigating protein interactions with gene data, differentiating the interactions between healthy and malignant cells and the proteins as well as the structure-functional assessment of the drug molecule with the protein [6,17,18].

Among the multitude of proteins that have been identified as potential targets for the development of pharmaceutical drugs, the extracellular matrix is a host to a variety of such important targets, since it provides both structural support and controls various functions. The interaction of these proteins with various growth factor receptors, cytokines and hormones regulate a host of cellular functioning pathways [19-37]. The CCN family of proteins is a vital target in understanding the progression of cancer as they regulate cell adhesion, proliferation, differentiation, apoptosis, and gene expression [38]. The CCN proteins play vital roles in cell signaling, migration and proliferation, wound healing, tumorigenesis and angiogenesis [39]. They are functionally made up of an N-terminal secretory peptide and 4 other domains: : (i) an insulin-like growth factor binding protein-like module (IGFBP); (ii) a von Willebrand factor type C repeat module (VWC); (iii) a thrombospondin type-1 repeat module (TSP-1); and (iv) a cysteine-knot-containing module (CT) [40].

Due to their role in the regulation of signaling between the ECM and cell surface as well as influencing cell growth, vasculature and metastasis, the CCN family is considered as an important target for therapeutic applications [39]. Multiple forms of cancer including pancreatic and breast cancer has seen the upregulation of certain CCN proteins and they are used as important biomarkers for the detection and diagnosis of these diseases. CCN1 is an important marker for esophageal cancer, while CCN4 upregulation has been reported in prostrate cancer. Due to their role in angiogenesis and inflammation, these proteins can also be used as therapeutics. CCN1 has been reported to affect inflammation and decrease immune infiltration [41,42]. CCN1 targeted by siRNA was also proven to reduce orthotopic glioma. While CCN2 has been used as a marker for fibrotic diseases [43].

Although they present attractive druggable features, a complicated rile within the cancer microenvironment makes it difficult to select a particular target in a heterogenous cancer model. The mode of interactions of the proteins with the ECM and modulation of cell and matrix interactions is ambiguous. However, a deeper insight into the cellular mechanism and the CCN family of proteins would pave the way for targeted and personalized therapies in cancer with a well-defined mode of action.

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