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REVIEW ARTICLE

Exploring Dysregulated Signaling Pathways in Cancer

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Abstract: Cancer cell biology takes advantage of identifying diverse cellular signaling pathways that are disrupted in cancer. Signaling pathways are an important means of communication from the exterior of cell to intracellular mediators, as well as intracellular interactions that govern diverse cellular processes. Oncogenic mutations or abnormal expression of signaling components disrupt the regulatory networks that govern cell function, thus enabling tumor cells to undergo dysregulated mitogenesis, to resist apoptosis, and to promote invasion to neighboring tissues. Unraveling of dysregulated signaling pathways may advance the understanding of tumor pathophysiology and lead to the improvement of targeted tumor therapy. In this review article, different signaling pathways and how their dysregulation contributes to the development of tumors have been discussed.

Keywords: Angiogenesis, apoptosis, cell invasion, cell proliferation, drug targets, metastasis, signaling pathways, tumor microenvironment.

1. INTRODUCTION

Cancer is a disease affecting millions of people worldwide. Cancer cells have the ability to abnormally divide and grow as a result of alteration or mutation in specific genes. The common signaling pathways and processes underlying cancer are now easily understood due to the advanced DNA sequencing over the past few years [1]. The genes and pathways altered, varies across different individuals and different types of tumor. There must be a complete understanding of all these dysregulated cancer pathways in order to identify and broaden therapeutic options [2]. The cell signaling systems that control the fate of the cell are disrupted by oncogenic mutations which contribute towards the malignant behavior of the tumor cells. The development of a malignant tumor depends on the acquired traits of cancer cells, which are known as "Hallmarks of cancer". There are ten major hallmarks of cancer: sustained proliferative signals, replicating immortality, evading growth suppression, resisting cell death, activating invasion & metastasis, inducing angiogenesis, tumor-promoting inflammation, avoiding immune destruction, genomic instability & mutation, and deregulated cellular energetics [3].

Many studies have shown that solid tumors are highly complex eco-system infiltrated with many immune cells, endothelial cells, cancer-associated fibroblasts (CAFs), endocrine cells entangled in the extracellular matrix (ECM) proteins which together make the Tumor Microenvironment (TME). This TME, by secreting various growth factors, immune-suppressive factors recruit tumor-promoting macrophages, inflammatory cells, cancer-associated fibroblasts [4], help escape immune recognition [5], and provide a permissive environment for tumor progression, metastasis and development of resistance to therapy [6]. In addition, the accumulation of genetic and epigenetic alterations during the cancer progression results in the clonal selection of cells with more aggressive phenotypes. As the tumor size increases, its core loses access to the oxygen and nutrients that promote the formation of new blood vessels called angiogenesis as a compensatory mechanism to obtain more oxygen and nutrients, thus allowing cancer cells to enter the blood circulation to establish distant metastasis. Recent high throughput genomic data has identified a trove of mutations that result in the deregulation of many signal transduction pathways promoting cellular characteristics favoring carcinogenesis. In this review, the deregulated pathways imparting proliferative, survival, and invading advantages to various tumors have been comprehensively described [7].

2. SIGNALING PATHWAYS

Many signaling pathways are interconnected with each other and form complex networks. The activation of these cellular pathways by various external and internal cues and their integration lead to the execution of various cellular functions controlling cell growth, motility, cell architecture & polarity, differentiation, programmed cell death, protein synthesis, *etc*. [8] (Fig. **1**). While these signaling pathways are precisely controlled in normal cells, the deregulation of these pathways results in uncontrolled proliferation and development of cancers. The most common genetically/epigenetically altered signaling pathways in various cancers are discussed below [2].

2.1. ErbB/EGFR Signaling Pathway

The ErbB family, including ErbB-1/EGFR, HER2/neu/ErbB-2, HER3/ErbB-3 and HER4/ErbB-4 is a family of receptor tyrosine kinases that modulate numerous signal transducers and activate many intracellular pathways [9]. While mutations and alternative splicing play an important role in protein function, expression, and their stability, mutated and truncated EGFR (EGFRvIII) has been shown to play an important role in the development, progression, metastasis and therapeutic resistance of many cancers including

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