Review

Targeting protein–protein interactions as an anticancer strategy

Andrei A. Ivanov[1,3], Fadlo R. Khuri[2,3], and Haian Fu[1,2,3]

[1] Department of Pharmacology, Emory University, Atlanta, GA 30322, USA
[2] Department of Hematology and Medical Oncology, Emory University, Atlanta, GA 30322, USA
[3] Emory Chemical Biology Discovery Center, Emory University, Atlanta, GA 30322, USA

The emergence and convergence of cancer genomics, targeted therapies, and network oncology have significantly expanded the landscape of protein–protein interaction (PPI) networks in cancer for therapeutic discovery. Extensive biological and clinical investigations have led to the identification of protein interaction hubs and nodes that are critical for the acquisition and maintenance of characteristics of cancer essential for cell transformation. Such cancer-enabling PPIs have become promising therapeutic targets. With technological advances in PPI modulator discovery and validation of PPI-targeting agents in clinical settings, targeting of PPI interfaces as an anticancer strategy has become a reality. Future research directed at genomics-based PPI target discovery, PPI interface characterization, PPI-focused chemical library design, and patient-genomic subpopulation-driven clinical studies is expected to accelerate the development of the next generation of PPI-based anticancer agents for personalized precision medicine. Here we briefly review prominent PPIs that mediate cancer-acquired properties, highlight recognized challenges and promising clinical results in targeting PPIs, and outline emerging opportunities.

Rising interest in targeting PPIs

PPI interfaces represent a highly promising, although challenging, class of potential targets for therapeutic development [1]. In cancer, PPIs form signaling nodes and hubs that transmit pathophysiological cues along molecular networks to achieve an integrated biological output, thereby promoting tumorigenesis, tumor progression, invasion, and/or metastasis. Thus, pathway perturbation, through disruption of PPIs critical for cancer, offers a novel and effective strategy for curtailing the transmission of oncogenic signals. As our understanding of cancer biology has significantly increased in recent years, interest in targeting of PPIs as anticancer strategies has increased as well (Figure 1).

PPI interfaces constitute basic units in oncogenic signaling networks

A variety of environmental, genetic, and epigenetic factors induce the reprogramming of cancer-initiating cells and the acquisition of physical and molecular features that promote tumorigenesis and provide resistance to therapeutics. These characteristics, including sustained proliferative signaling and evasion of growth suppressors, permit the development and progression of cancer and have been recognized as distinctive hallmarks of cancer (Figure 2) [2]. These hallmarks provide a molecular framework for our understanding of cancer, linking molecular signaling events to pathological outcomes. The oncogenic potential of cells is determined by a combination of genetic and epigenetic alterations through the operation of well-orchestrated signaling networks. Importantly, PPIs represent the basic units within such vital networks.

On oncogenic stimulation, PPIs play essential roles in linking networks that relay oncogenic signals, allow the acquisition of hallmark features of cancer, and serve diverse roles in driving and maintaining the growth of cancer cells (Figure 2). From the engagement of receptors with dysregulated growth factors to dimerization of receptor tyrosine kinases triggered by gene amplification or mutations, PPIs initiate a cascade of reactions to promote uncontrolled cell proliferation [3]. Activated Ras, due to perturbations such as epidermal growth factor receptor (EGFR) activation, neurofibromin 1 (NF1) deletion, or intrinsic mutation, assumes a conformation that allows it to bind to multiple regulatory proteins and results in enforced proliferation and survival. Survival signaling, activated by proteins such as insulin-like growth factor 1 (IGF1) and phosphoinositide-3-kinase (PI3K) or disabled by the negative regulator PTEN, enables tumors to resist cell death through a number of different mechanisms. For example, the Akt–FOXO3a–14-3-3 complex mediates a transcription-dependent mechanism, whereas the Akt–Bad–14-3-3 interaction mediates a transcription-independent antiapoptotic mechanism [3]. In addition to providing resistance to cell death, Akt also regulates the mTOR complex to control cap-dependent translation, through the eIF4E–eIF4G PPI, of a large number of growth-promoting genes, including c-Myc. In turn, amplified c-Myc favors binding to Max over Mad and thereby drives transcription of growth-promoting genes such as cyclin D that modulate cell cycle progression [4].

For cancer progression, cells must acquire mechanisms to evade growth suppression. Several PPI complexes, including MDM2–p53 and CDK4–pRB, play key roles in neutralizing such tumor suppressive functions [2]. These tumor suppressor mechanisms are often hijacked by viral

Corresponding author: Fu, H. (hfu@emory.edu).
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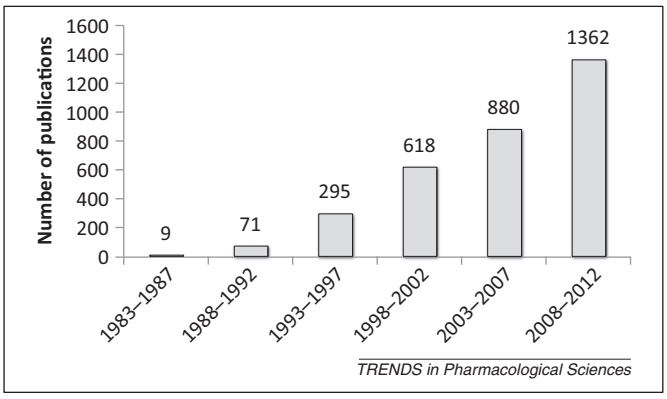

Figure 1. Rising number of publications in the field of cancer-related protein–protein interactions. The PubMed database was searched using the following keywords: protein–protein interaction, tumor, cancer, and inflammation.

oncoproteins, such as human papillomavirus E7 protein, which binds to pRb, and E6 protein, which binds to p53, that allow the virus to induce tumors. Such PPIs offer tumor-specific targets. In addition to the examples given above, a large number of PPIs dictate signaling networks that allow the acquisition or maintenance of other hallmarks of cancer. For instance, the VEGF–VEGFR and HIF1α–CBP PPIs mediate signals that induce angiogenesis, the catalytic activity of TERT dimers enables replicative immortality, and a variety of reprogrammed enzyme–substrate interactions, such as the onco-fusion gene-regulated PDHK1–PDHA1 PPI, play integral roles in dysregulated cellular metabolism by controlling a metabolic switch between glycolysis and oxidative phosphorylation [5]. In addition, mutated p53 and Myc also play key roles in the regulation of cancer metabolism. The IKK–NEMO–ASK1 complex integrates the proinflammatory function with stress response signaling initiated by reactive oxygen species [6]. It has recently been shown that epigenomic reprogramming is a critical part of cancer development [7], and PPIs involved in epigenomic dysregulation, such as SMARCA4 interactions, have been described [8].

As a result of oncogenic network reprogramming, some PPIs contribute to distinct features of cancer, whereas other PPIs are vital for multiple characteristics of cancer. For example, the MDM2–p53 and Myc–Max PPIs play key roles in evading growth suppression and cell death, as well as in promoting genomic instability and cancer metabolism. Thus, it is expected that interception of certain

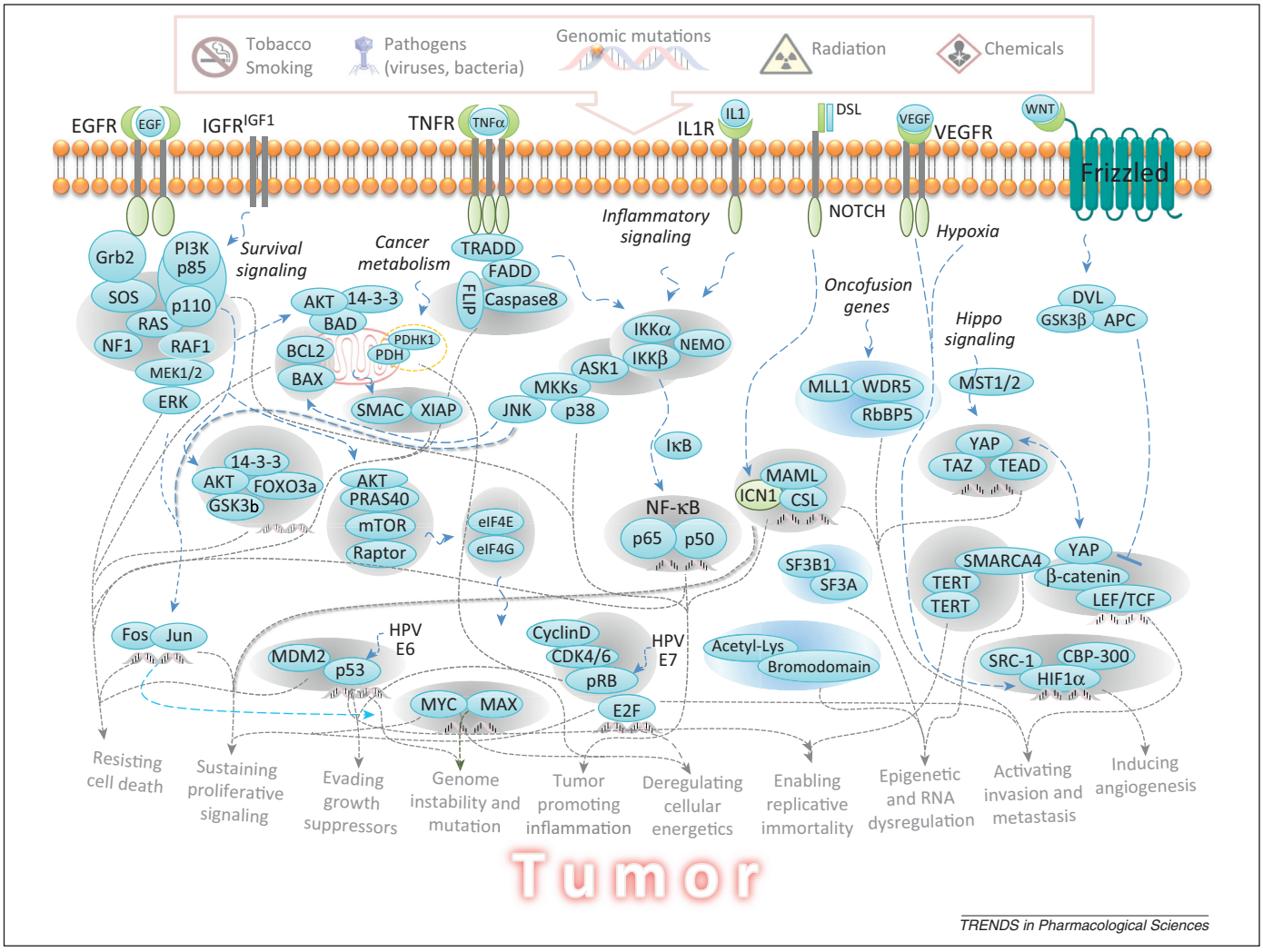

Figure 2. Representative PPIs in oncogenic signaling networks that drive the acquisition and development of hallmarks of cancer. Grey broken arrows connect PPIs to corresponding cancer hallmarks. Some PPIs contribute to multiple features of cancer. It should be noted that some PPIs may impact global processes of cell growth and their precise connections to cancer remain to be established.