FEBS Letters xxx (2014) xxx–xxx

journal homepage: www.FEBSLetters.org

Review

Deregulation of cell signaling in cancer

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ARTICLE INFO

Article history:
Received 20 January 2014
Revised 3 February 2014
Accepted 5 February 2014
Available online xxxx

Edited by Shairaz Baksh, Giovanni Blandino and Wilhelm Just

Keywords:
Cancer cell biology
Cell signaling
Tumorigenesis
Targeted therapies

ABSTRACT

Oncogenic mutations disrupt the regulatory circuits that govern cell function, enabling tumor cells to undergo de-regulated mitogenesis, to resist to pro-apoptotic insults, and to invade through tissue boundaries. Cancer cell biology has played a crucial role in elucidating the signaling mechanisms by which oncogenic mutations sustain these malignant behaviors and thereby in identifying rational targets for cancer drugs. The efficacy of such targeted therapies illustrate the power of a reductionist approach to the study of cancer.

1. Introduction

Oncogenic mutations disrupt the signaling systems that govern cell fate, endowing tumor cells with several attributes that sustain their malignant behavior. About a decade ago, it has been argued that six enabling traits ("hallmarks") underlie the development of a malignant tumor: self-sufficiency in growth signals, insensitivity to anti-growth signals, limitless replicative potential, evasion of apoptosis, sustained angiogenesis, and tissue invasion [1]. Since then, it has become clear that metabolic fitness and genomic instability also contribute to tumor malignancy, suggesting the existence of two additional traits [2,3]. Furthermore, a large body of evidence has established that tumor cells must evade immune recognition [4] and recruit both angiogenic and non-angiogenic normal cells, such as macrophages, activated fibroblasts, and inflammatory cells, and mould a permissive microenvironment – the tumor microenvironment – in order to progress to full malignancy [5] (Fig. 1).

Modern cell biologists do not view cell biology as an approach or group of approaches, but rather as a discipline that integrates multiple approaches to study cell function. From this expanded vantage point, it is possible to appreciate the contribution of cell biology to our current understanding of tumorigenesis and, vice-versa, the contribution of studies on cancer to our current understanding of normal cell function. In this Review, I will focus on how cell biological investigations have shed light into the mechanisms by which oncogenic mutations endow tumor cells with three cardinal aberrations: de-regulated mitogenesis, resistance to apoptotic insults and other forms of cell attrition, and ability to invade through tissue boundaries. My choice is informed by three considerations: (1) These three major aberrations encapsulate all previously described tumor cell-intrinsic hallmarks and are the defining features of malignantly transformed cells ("driver functions"). In contrast, genomic instability and recruitment of a tumor microenvironment foster tumor progression by enabling and sustaining one or more of the tumor cell-intrinsic hallmarks ("Fostering functions") (Fig. 1); (2) Studies on cell signaling have revealed the mechanisms by which oncogenic mutations induce and maintain these cardinal aberrations; and (3) Blockage of oncogenic signaling results in tumor regression in mouse models and, increasingly so, in the clinic, validating the usefulness of a mechanistic approach to the cell biology of cancer.

Loss-of-function mutation and epigenetic silencing of tumor suppressor genes are prevalent driver alterations in cancer. My intent is to provide an overview of the signaling networks in which the proteins they encode operate and thereby introduce the individual Reviews that comprise this special issue of FEBS Letters.

2. Cancer as a disorder of cell signaling

During development and tissue repair, individual cells or population of cells undergo expansion in response to contextual cues that regulate their ability to enter into and progress through the cell cycle, to migrate, and to survive within provisional microenvironments [6]. Cell biological studies have revealed that these

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http://dx.doi.org/10.1016/j.febslet.2014.02.005
0014-5793/

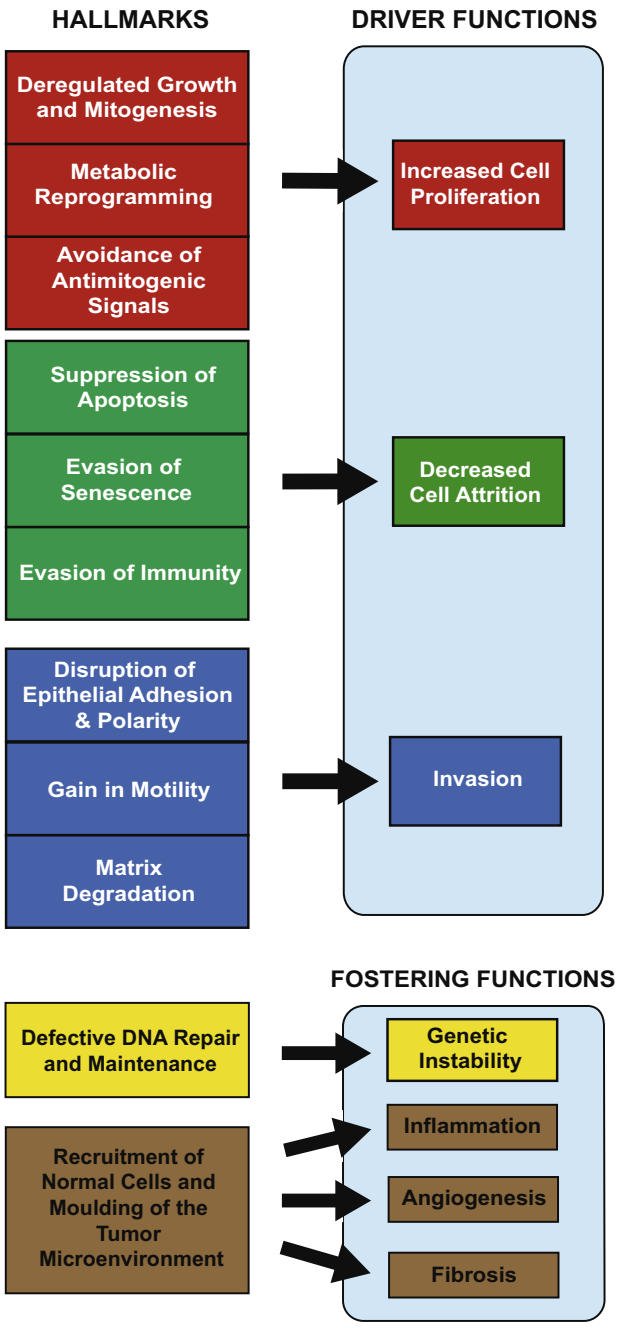

Fig. 1. Hallmarks and oncogenic functions. Deregulated signaling endows tumor cells with several attributes (hallmarks or traits), which in turn sustain oncogenic functions. Increased cell proliferation, decreased cell attrition, and invasion are necessary for oncogenesis and are thus categorized as driver functions; genetic instability and a permissive tumor microenvironment are provisionally classified as fostering functions.

processes are governed by multiple signaling systems, which operate – often in a tissue and cell-type specific manner – to govern the cell cycle, anti-apoptotic, and pro-migratory machineries [7,8]. In parallel, studies on retroviral oncogenes, on transforming genes isolated by transfection of cancer genomes into normal cells, and on genes identified as mutated in human cancer have indicated that most oncogenic mutations can be mapped onto nine distinct signaling systems [9]. Prevalent oncogenic mutations disrupt the normal operation of these pathways leading to deregulated mitogenesis, resistance to pro-apoptotic insults, and a gain in motility [1]. Although biochemical and genetic analyses have played an indispensable role in elucidating the molecular underpinnings, and thereby shaping our understandings, of the signaling systems altered in cancer, additional approaches, such as advanced imaging and computational modeling, have helped to place the linear pathways defined by biochemistry and genetics within spatially organized signaling networks regulated by cross-talk and positive and negative feedback loops [10,11]. Such an integrated approach to cell biology has been instrumental to the development of our current model of cancer development and to the design of therapies interfering with the operation of cancer-causing genes.

3. Powering the engine

3.1. Receptor tyrosine kinases

The ability of normal cells to survive and proliferate depends on engagement of growth factor receptors endowed with tyrosine kinase activity (receptor tyrosine kinases; RTKs) [12]. The biochemical reactions that underlie RTK signaling have been elucidated and placed in the context of core pathways through a combination of genetics and biochemistry. Ligand binding and the ensuing oligomerization of RTKs leads to phosphorylation of tyrosine residues within the receptor tails or on surrogate proteins (such as IRS, Gab, and FRS) creating docking sites for signaling adaptors containing phosphotyrosine-binding domains [8] (Fig. 2a). Shc and Grb2 are two of such adaptors and play an essential role in recruiting the guanine-nucleotide exchange factor SOS and thereby activating Ras. This process is facilitated by inactivation of the GTPase-activating proteins p120 and neurofibromin, which is encoded by the NF1 gene. GTP-bound Ras engages multiple target-effectors [13,14] (Fig. 2b). Whereas Raf commands activation of the MEK–ERK cascade, PI(3)K, which is initially recruited to the plasma membrane by tyrosine-phosphorylated receptors or surrogate adaptors, enables conversion of PIP2 to PIP3 on the inner leaflet of the membrane. PIP3 in turn attracts Akt, which upon activation by PDK phosphorylates and inactivates multiple effectors, including TSC2, GSK3-β, the CDK inhibitors p21 and p27, BAD, and FOXO transcription factors [15,16] (Fig. 3). Akt signaling is opposed by PTEN, which dephosphorylates PIP3, dampening recruitment to the membrane and thereby activation of Akt [17]. Through these and additional mechanisms, receptor tyrosine kinases promote cell survival, progression through the G1 phase of the cell division cycle, and cell migration (Figs. 2b and 3).

Oncogenic mutations causing deregulated activation of receptor tyrosine kinases or their downstream signaling components are prevalent in human cancer. *HER2* is amplified in approximately 30% of breast cancers and *HER1*, encoding the EGFR, in a slightly larger fraction of glioblastomas. Furthermore, activating mutations in *HER1* have been identified in the 10% or so of non-small cell lung cancer (NSCLC) patients that responds to EGFR kinase inhibitors, and similar and therefore potentially activating intragenic mutations in *HER2* have been found in about 4% of NSCLC patients [12,18]. Activating mutations of *KIT* and *PDGFRA* are commonly found in gastrointestinal sarcomas [19]. In addition, PDGF and its receptor are overproduced in a subset of glioblastomas, although the underlying mechanisms are unclear [12]. *KRAS* and *BRAF* mutations occur frequently in multiple tumor types and are prevalent in melanoma, pancreatic adenocarcinoma, colorectal carcinoma, and lung adenocarcinoma [20,21]. Activating mutations in *PIK3CA*, encoding a catalytic subunit of PI(3)K, occur frequently in breast, ovarian, and colorectal cancer, and loss of heterozygosity of *PTEN* is one of the most common genetic alterations observed in multiple tumor types [15,17]. More recently, activating mutations in the *JAK2* kinase have been found in myeloproliferative neoplasms, *KIT* mutations have