Seminars in Cancer Biology 35 (2015) S25–S54

Contents lists available at ScienceDirect

Seminars in Cancer Biology

journal homepage: www.elsevier.com/locate/semcancer

Review

Sustained proliferation in cancer: Mechanisms and novel therapeutic targets

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ARTICLE INFO

Article history:
Available online 17 April 2015

Keywords:
Proliferation
Natural products

ABSTRACT

Proliferation is an important part of cancer development and progression. This is manifest by altered expression and/or activity of cell cycle related proteins. Constitutive activation of many signal transduction pathways also stimulates cell growth. Early steps in tumor development are associated with a fibrogenic response and the development of a hypoxic environment which favors the survival and proliferation of cancer stem cells. Part of the survival strategy of cancer stem cells may manifested by alterations in cell metabolism. Once tumors appear, growth and metastasis may be supported by overproduction

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http://dx.doi.org/10.1016/j.semcancer.2015.02.006

Therapeutic targets
Cancer stem cells
Cancer hallmarks

of appropriate hormones (in hormonally dependent cancers), by promoting angiogenesis, by undergoing epithelial to mesenchymal transition, by triggering autophagy, and by taking cues from surrounding stromal cells. A number of natural compounds (e.g., curcumin, resveratrol, indole-3-carbinol, brassinin, sulforaphane, epigallocatechin-3-gallate, genistein, ellagitannins, lycopene and quercetin) have been found to inhibit one or more pathways that contribute to proliferation (e.g., hypoxia inducible factor 1, nuclear factor kappa B, phosphoinositide 3 kinase/Akt, insulin-like growth factor receptor 1, Wnt, cell cycle associated proteins, as well as androgen and estrogen receptor signaling). These data, in combination with bioinformatics analyses, will be very important for identifying signaling pathways and molecular targets that may provide early diagnostic markers and/or critical targets for the development of new drugs or drug combinations that block tumor formation and progression.

1. The centrality of cell proliferation as a target in carcinogenesis

The cancer cell embodies characteristics that permit survival beyond its normal life span and to proliferate abnormally. Cancer therapy, involving cytotoxic drugs, kills cells that have a high basal level of proliferation and regeneration. While this type of therapy targets tumor cells, it affects rapidly proliferating, nontumor cells in the skin, hair, and epithelium of the gastrointestinal tract, accounting for the high level of toxicity associated with such treatments. Growth of normal tissue is tightly regulated while this regulation is lost in tumor cells. Lack of normal growth control is not only operative in early tumorigenesis but also during tumor metastasis. Thus, there is much to be learned from studies that address how and when abnormal growth begins, and then to use this knowledge to identify novel therapeutic targets and approaches that would more specifically treat cancer cells without damaging the normal host cells.

Carcinogenesis is a multistep process in which changes in tissue architecture and the formation of preneoplastic nodules precede the appearance of cancer. These alterations are associated with changes in cell phenotype that include epithelial to mesenchymal transition (EMT) and cell migration, resulting in local regions of hypoxia that promote the survival and growth of tissue stem cells [1–5], as well as angiogenesis [6–9] (Table 1). Autophagy also promotes the survival of preneoplastic and tumor cells under stressful conditions. While the growth and survival of normal cells are under partial control from growth factors and hormones, alterations in signaling pathways, resulting from mutations and/or epigenetic changes, renders cells resistant and independent of these pathways. Such changes promote survival and growth both by constitutively stimulating pathways that favor proliferation [10], and by inhibiting and/or overriding apoptotic pathways. Initially, altered signaling pathways, as well as changes in the metabolomics profile, epigenetically modify the patterns of gene expression in the cell, and as such are therapeutically reversible (Table 1). In contrast, tumor progression proceeds by "driver" mutations that are more difficult to target pharmacologically. Thus, elucidation of the underlying epigenetic mechanisms responsible for these alterations will provide meaningful targets for the development of novel therapeutics prior to or at the earliest stages of malignant transformation.

To facilitate a better understanding of the early changes seen in carcinogenesis, this review presents discussion of the major pathways, disruption of which promote unregulated proliferation of cancer cells. This review focuses on changes in tissue architecture (EMT and migration), formation of preneoplastic nodules, development of hypoxia, survival and growth of cancer stem cells, autophagy and growth factor independent proliferation (Table 1). Each section attempts to identify the "best" molecular targets (e.g., receptors, signaling molecules, etc.) that might be exploited therapeutically. The "best" targets were chosen based upon their altered expression/function that promoted proliferation in many different human cancers. Additional questions include: Does loss of a target prevent tumor initiation or block tumor maintenance? What is the effect of global loss of a target in other tissues? Will there be off target effects due to additional functions and/or because of a high degree of homology with other proteins? Many of these targets are pleotropic, regulating different pathways and as such their targeting might abrogate additional required hallmarks. At the end of this review, there is a discussion of natural products that are likely to be effective against these molecular targets and pathways, which may be useful in delaying the onset of cancer and/or reversing cancer cell proliferation, with reduced associated toxicity. Many natural products have much lower toxicity than compounds or derivatives obtained from chemical libraries, suggesting that their further development could provide distinct advantages.

Table 1
Factors in cell survival and proliferation the contribute to carcinogenesis.

Factor	Contribution to carcinogenesis
EMT	Promotes stem cell growth, metastasis
Hypoxia	HIFs promote proliferation of CSCs and angiogenesis; alters metabolism; constitutive activation of signaling pathways
Autophagy	Promotes cell survival in response dysregulated signaling-mediated proliferation, enhanced glycolysis, and hypoxia
CSCs	Dysregulation in "stemness," quiescence, self-renewal, the ability to produce differentiated progeny, resistance to apoptosis, and chemoresistance, resulting in altered cell fate and unregulated cell growth
Cell cycle proteins	Dysregulated expression of cell cycle proteins (Rb, CDKs, cdk inhibitors) promote uncontrolled cell proliferation
Signal transduction pathways	Constitutive activation of multiple signaling pathways promote uncontrolled proliferation (e.g., Wnt, Notch, IGF, PI3K/Akt, NF-κB, Hh)
Altered cell metabolism	Promotes altered survival and growth in the adverse conditions (e.g., hypoxia) in early stages of carcinogenesis (e.g., altered glycolysis and methionine metabolism)
Hormone signaling	Promote the growth of hormone responsive cancers through constitutive activation of estrogen and androgen signaling pathways
Tumor microenvironment	Stromal-tumor cell crosstalk promotes growth and metastasis of cancer stem cells

2. How does EMT contribute to tumor proliferation?

When EMT occurs in adult tissues in response to injury or during tumorigenesis, epithelial cells change morphological appearance, from an ordered structure with apical and basal polarity to a less ordered, migratory fibroblastic shape. The Snail family of transcription factors (Snail1/Snail and Snail2/Slug) is closely associated with