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Review

Genetic instability and the tumor microenvironment: towards the concept of microenvironment-induced mutagenesis

Ranjit S. Bindra[a,b], Peter M. Glazer[a,c,*]

[a] *Department of Therapeutic Radiology, Yale University School of Medicine, 333 Cedar St., New Haven, CT 06520-8040, USA*
[b] *Department of Experimental Pathology, Yale University School of Medicine, 333 Cedar St., New Haven, CT 06520-8040, USA*
[c] *Department of Genetics, Yale University School of Medicine, 333 Cedar St., New Haven, CT 06520-8040, USA*

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Abstract

It has been well established that tumor progression is correlated with genetic instability. Growing evidence suggests that the tumor microenvironment itself constitutes a significant source of such genetic instability. The adverse conditions of this microenvironment are associated with the induction of mutagenesis and numerous types of DNA damage, including DNA strand breaks and oxidative base damage. While such DNA lesions pose a significant threat to genome integrity, recent studies now suggest that genetic instability in the tumor microenvironment also may arise from the dysregulation of DNA repair pathways. In this review, we will summarize the case for the tumor microenvironment as a key culprit in the induction of genetic instability and the potential mechanisms by which this phenomenon occurs.

Keywords: Genetic instability; Microenvironment; Hypoxia; DNA repair

Contents

* Corresponding author. Tel.: +1 203 737 2788; fax: +1 203 737 2630.
E-mail address: peter.glazer@yale.edu (P.M. Glazer).

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1. Introduction

The tumor microenvironment is characterized by hypoxia, low pH and nutrient deprivation [1]. These changes have consistently been linked to underlying perfusion deficits in solid tumors, which result from rapid tumor growth and profoundly disorganized vasculature [2]. As expected, such perfusion defects are associated with significant levels of both chronic and acute hypoxia in solid tumors, including anoxia [3]. Indeed, early studies by Thomlinson and Gray in the 1950s established that tumors commonly contain regions beyond the limits of oxygen diffusion [4]. In these experiments, analysis of histological sections of human lung tumors revealed a fixed distance of approximately 160–200 μm between blood vessels and necrotic regions. Based on oxygen diffusion calculations, it was proposed that cells in areas immediately adjacent to these necrotic regions would be hypoxic while still supporting viable tumor cells. In addition to hypoxia, numerous studies have described increased formation and excretion of lactic acid, with subsequently decreased pH in solid tumors [5,6], and this phenomenon has been attributed to the shift from aerobic respiration to anaerobic glycolysis in hypoxic tumor cells. Decreased pH has also been shown to be caused by increased production of carbonic acid in the tumor microenvironment [7]. Collectively, these phenomena suggest that the tumor microenvironment is a unique setting for tumor progression, likely requiring genetic and adaptive changes in cancer cells for further survival and proliferation.

Substantial evidence now exists implicating the role of tumor hypoxia in the development of an aggressive phenotype. Many studies have established hypoxia as an independent and adverse prognostic variable in patients with tumors of the head and neck, cervix or soft tissue [8,9]. For instance, in one cervical cancer study, tumor oxygenation surpassed age, menopausal status, size, clinical stage and histology as the most important prognostic variable for survival [8]. These studies underscore the importance of elucidating the effects of hypoxia at the molecular level and the mechanism by which such conditions lead to a more aggressive phenotype and their contribution to tumor progression.

Tumor progression has been specifically correlated with genetic instability [10]. Furthermore, it has long been argued that the large number of mutations found in malignant cells cannot be accounted for by the low rate of mutation observed in somatic cells, leading to the suggestion that cancer cells assume a mutator phenotype during tumorigenesis [11]. We and others have proposed that the tumor microenvironment contributes to such genetic instability [12], and research over the past several years has focused on cell stresses induced by the microenvironment that may cause this instability. Specifically, hypoxia has been proposed to be a key microenvironmental factor involved in the development of genetic instability, as it is associated with increased DNA damage, enhanced mutagenesis and functional impairments in DNA repair pathways. Collectively, these phenomena constitute a significant source of genetic instability induced by hypoxia, thus potentially accelerating the multi-step process of tumor progression. In this review, we describe the role of the tumor microenvironment in the induction of genetic instability, and we highlight recent insights into the mechanisms by which this process may occur.

2. DNA damage, mutagenesis and genetic instability in the tumor microenvironment

Numerous studies have established that endogenous-reactive metabolites, replication errors and spontaneous decay result in a significant amount of