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Tumor phosphatidylinositol 3-kinase signaling in therapy resistance and metastatic dissemination of rectal cancer: Opportunities for signaling-adapted therapies

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Abstract

Locally advanced rectal cancer (LARC) comprises heterogeneous tumors with predominant hypoxic components, a hallmark of the tumor microenvironment and determinant of resistance to cytotoxic therapies, local recurrence, and metastatic progression. A rational integration of molecularly targeted agents in established combined-modality treatment regimens may improve local and systemic disease control, but will require a clear definition of functional biomarkers for patient stratification. In a prospective study of LARC patients given neoadjuvant chemotherapy and radiation, we applied a kinase substrate array technology to analyze the patients' tumor biopsies sampled at the time of diagnosis, and observed that receptor tyrosine kinase activities integrated by high phosphatidylinositol 3-kinase signaling were correlated both with poor tumor response to the neoadjuvant treatment and adverse progression-free survival. Conceptually, the specific tumor signature of phosphatidylinositol 3-kinase signaling activity may point to actionable therapy targets in LARC patients with unfavorable disease features. Clinical trial registration number NCT00278694.

Keywords: Rectal cancer; PI3K; Radiation; Angiogenesis; Metastasis; Biomarkers; Tumor hypoxia; Tyrosine kinase array

1. Introduction

1.1. Rectal cancer

With reference to the demography of colorectal cancer (CRC), owing to an aging population, this disease is common with a significant rise in incidence from the age of 60. In the European Union in 2012, more than 447,000 individuals were diagnosed with CRC; of these cases, about 30% were in the rectal anatomic site [1]. The management of rectal cancer is multidisciplinary, involving precision diagnostics within radiology and pathology and highly specialized expertise within oncology and surgery. Recognizing the therapeutic complexities, it is crucial to bridge the rapidly emerging knowledge from biology into the optimum care of patients.

As a result of systematic improvements that include multimodal therapy, primarily surgery and radiation, over the past few decades, long-term control of localized rectal cancer is commonly achieved. Locally advanced rectal cancer (LARC) comprises primary tumors that infiltrate within the mesorectal compartment or beyond to an extent that precludes primary surgical removal with sufficient microscopic margins. Randomized studies have highlighted the central role of neoadjuvant chemoradiotherapy (CRT) in macroscopic down-sizing and control of subclinical tumor manifestations within the pelvic cavity, to enable complete resection of the residual tumor within its entire extension for the ultimate improvement of outcome [2]. There is compelling evidence from large cohorts of patients given neoadjuvant CRT that histologic tumor down-staging translates into long-term survival benefits; however, on a closer look, this observation basically refers to subgroups of patients obtaining complete tumor response [3], suggesting that eradication of tumor clonogens is essential for favorable therapeutic results.

Even with successful local treatment outcome, a substantial number of LARC patients (30–40% of cases) will experience metastatic progression [4,5] as result of distant organ establishment of early disseminating tumor cells (DTC) [6,7] with clonogenic potential. Currently, no consensus exists to whether systemic therapy may reduce the risk of metastatic development in rectal cancer [5,8]. The use of postoperative adjuvant chemotherapy, as being given in colon cancer, has been adopted at a number of centers internationally despite the lack of evidence-based data [9]. In most Nordic countries, postoperative treatment is offered only on specific, individual-based indications.

Metastatic disease may be either organ-confined or extensively disseminated to the liver, lungs, peritoneum, multiple lymph node stations and skeletal locations, or even the brain. Metastasis limited to a single organ is increasingly considered potentially curable with multimodal approaches. Examples include disease confined to the liver [10], lungs [11], or the peritoneal cavity [12]. New insights into the biology of early systemic tumor dissemination may provide a direction to the next milestone in rectal cancer management, which will be the control of metastatic progression.

In line with these notions, and in the everyday clinical practice, it is recognized that rectal cancer presents with a high degree of biological heterogeneity [13]. The prevailing hypothesis is that in the primary tumor, expansion of distinct subclones under selection pressure within specific microenvironmental niches gives rise to such heterogeneity