Quantum-dots based simultaneous detection of multiple biomarkers of tumor stromal features to predict clinical outcomes in gastric cancer

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A B S T R A C T
Tumor microenvironment has been increasingly recognized as a complex and dynamic cancer society influencing tumor invasion and progression. The prognostic significance of this microenvironment is yet to be fully appreciated. A holistic approach to obtaining integrated information on key components in tumor microenvironment is essential. Here we reported on a quantum dots (QDs)-based simultaneous in situ detection of infiltrating macrophages, tumor microvessels density (MVD) and neovessels maturity, in gastric cancer tissues, to obtain integrated information on these components, termed as combined tumor stromal features. These stromal features had the comparable prognostic value for overall survival, and even better prognostic value for disease-free survival, compared with traditional tumor cell-based clinicopathological parameters. Subgroups of gastric cancer patients with favorable and unfavorable combined tumor stromal features were identified, with significantly different clinical outcomes. This study demonstrated the technical advantages of QDs-based simultaneous detection of multiple biomarkers in situ, revealed the important role of tumor stroma in cancer biology, and opened a new field to predict clinical outcome in gastric cancer from the perspectives of tumor microenvironment.

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1. Introduction

Gastric cancer (GC) is the fourth most common cancer and the third cause of cancer death worldwide [1]. Although primary tumor could be eradicated by surgical, chemo- or radio- therapeutic treatments, metastasis remains the most difficult problem and the major cause of death [2]. The clear causes of metastasis remain elusive despite vast information on cancer cells. While the tumor cell population has understandably received most attention, recent studies have shown that interactions between tumor and stromal cells create a unique microenvironment essential for tumor growth and metastasis [3]. Increasing evidence shows that the interactions between tumor cells and the surrounding stroma are critical factors to affect solid tumor growth, invasion and metastasis, but such complex interactions are largely unexplored [4].

Major contributors to the tumor microenvironment are inflammation and inflammatory mediators, now recognized as the seventh hallmark of cancer [5]. Tumor-associated macrophages constitute a significant proportion of the inflammatory tumor stroma, although neutrophils, immature myeloid cells, mast cells, T cells and NK cells are also present to variable numbers depending on the tumor type and grade [6]. Macrophages infiltration is a dramatic and common feature of cancer progression, and has recently been highlighted in an attempt to develop novel strategies against cancer [7]. It is suggested that cancer cell fusion with macrophages or other migratory bone marrow-derived cells (BMDCs) provides new explanation for cancer metastasis [8,9]. There is contradictory evidence on the prognostic significance of macrophages in cancer patients [10–13], and studies to define the prognostic role of macrophages in GC based on clinical samples are insufficient. In addition, macrophages have attracted considerable attention recently due to evidence demonstrating a pivotal role of these cells in promoting tumor angiogenesis. Endothelial-immune inflammatory cell cross-talk goes well beyond leukocyte and lymphocyte trafficking, since immune cells are able to intimately...