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Review

Friend or foe?
The tumour microenvironment dilemma in colorectal cancer

Tommaso Colangelo [a,b,1], Giovanna Polcaro [a,1], Livio Muccillo [a], Giovanna D'Agostino [a], Valeria Rosato [a], Pamela Ziccardi [a], Angelo Lupo [a], Gianluigi Mazzoccoli [c,*], Lina Sabatino [a,**], Vittorio Colantuoni [a,**]

[a] Department of Sciences and Technologies, University of Sannio, 82100 Benevento, Italy
[b] present address: Institute for Stem-cell Biology, Regenerative Medicine and Innovative Therapies (ISBReMIT), Casa Sollievo della Sofferenza-IRCCS, 71013 San Giovanni Rotondo (FG), Italy
[c] Department of Medical Sciences, Division of Internal Medicine and Chronobiology Unit, IRCCS Scientific Institute and Regional General Hospital "Casa Sollievo della Sofferenza", 71013 San Giovanni Rotondo (FG), Italy

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ABSTRACT

The network of bidirectional homotypic and heterotypic interactions established among parenchymal tumour cells and surrounding mesenchymal stromal cells generates the tumour microenvironment (TME). These intricate crosstalks elicit both beneficial and adverse effects on tumour initiation and progression unbalancing the signals and responses from the neighbouring cells.

Here, we highlight the structure, activities and evolution of TME cells considering a novel colorectal cancer (CRC) classification based on differential stromal composition and gene expression profiles. In this scenario, we scrutinise the molecular pathways that either change or become corrupted during CRC development and their relative prognostic value.

Finally, we survey the therapeutic molecules directed against TME components currently available in clinical trials as well as those with stronger potential in preclinical studies. Elucidation of dynamic variations in the CRC TME cell composition and their relative contribution could provide novel diagnostic or prognostic biomarkers and allow more personalised therapeutic strategies.

Contents

* Correspondence to: G. Mazzoccoli, IRCCS Scientific Institute and Regional General Hospital "Casa Sollievo della Sofferenza", 71013 San Giovanni Rotondo (FG), Italy.
** Corresponding authors at: Department of Sciences and Technologies, University of Sannio, Via Port'Arsa 11, 82110 Benevento, Italy.
E-mail addresses: sabatino@unisannio.it (L. Sabatino), colantuoni@unisannio.it (V. Colantuoni).
[1] These two authors equally contributed to the work.

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1. Introduction

Cancer is a genetic disease that arises through a multistep process whereby somatic cells acquire and accumulate multiple genetic and epigenetic changes that result in unrestrained proliferation [1]. A tumour is no longer depicted as a collection of relatively homogeneous cancer cells, whose biology could be understood only by elucidating the properties of these autonomously growing cells. A cancer is now recognised, instead, as a complex tissue composed of multiple distinct cell types, mainly derived from the neighbouring mesenchymal stroma with which tumour cells establish the so-called "tumour microenvironment" (TME) [1]. The functional interactions between tumour and stromal cells sustain growth and invasion. Neoplastic cells, in fact, emit a series of signals that convert the adjacent microenvironment into a pathological entity that continually evolves during cancer progression; the resulting TME, in turn, appears to dictate aberrant tissue functions and to play a critical role in the development of more advanced and therapy-refractory malignancies [1,2]. The orchestration of such events involves an array of cell types that contribute to the biology of tumours via individual and collective functions, greatly influencing disease initiation, progression and patient prognosis [2].

In this review, we define the biological landscape of the colorectal cancer (CRC) TME taking into account a recent CRC classification and highlighting the intricate network generated among the distinct cell types that participate in its construction. The functions that tumour parenchymal and stromal cells, specifically cancer-associated fibroblasts and immune cells, serve during the various steps of tumour progression are illustrated as well as mechanisms whereby conflicting signals may re-educate or corrupt single components culminating into a reshaped microenvironment that ultimately leads to a different outcome (Figs. 1–4, Table 1).

2. A new microenvironment-based CRC classification

CRC has provided a paradigm for studying tumourigenesis since the development of the Fearon-Vogelstein model [3–5]. CRC arises via clonal expansion of colonic crypt cells bearing loss-of-function mutations in *APC* or gain-of-function mutations in *CTNNB1*. These mutations foster the persistent activation of the Wnt pathway that regulates the stem cell compartment and cell fate along the crypt-villus axis. This results in β-catenin translocation to the nucleus and its interaction with TCF/LEF and YAP/TEAD transcription factors, promoting cell proliferation and stemness. These initial events are followed by subsequent mutations in oncogenes (e.g. *KRAS*, *BRAF*) and/or tumour suppressors (e.g. *SMAD4*, *TP53*) leading to the transition of adenomatous polyps into overt adenocarcinomas and the onset of metastatic disease [5]. The sequential acquisition of mutations correlates with typical morphological alterations that define the adenoma-carcinoma sequence or the classic form of CRC characterised by genomic instability of the CIN (Chromosomal INstability) type, such as chromosomal rearrangements and numerical abnormalities. These are manifested as aneuploidy, frequent loss-of-heterozygosity (LOH) at tumour suppressor gene loci, gene deletions or duplications [5,6]. This group represents about 85% of all CRCs and underscores that genomic instability events are recognised as a hallmark of cancer [1]. When the surveillance systems that normally monitor genome integrity fail, further mutations occur and the resulting mutation-bearing cells undergo selection and clonal expansion [1]. Comprehensive gene expression analyses in several

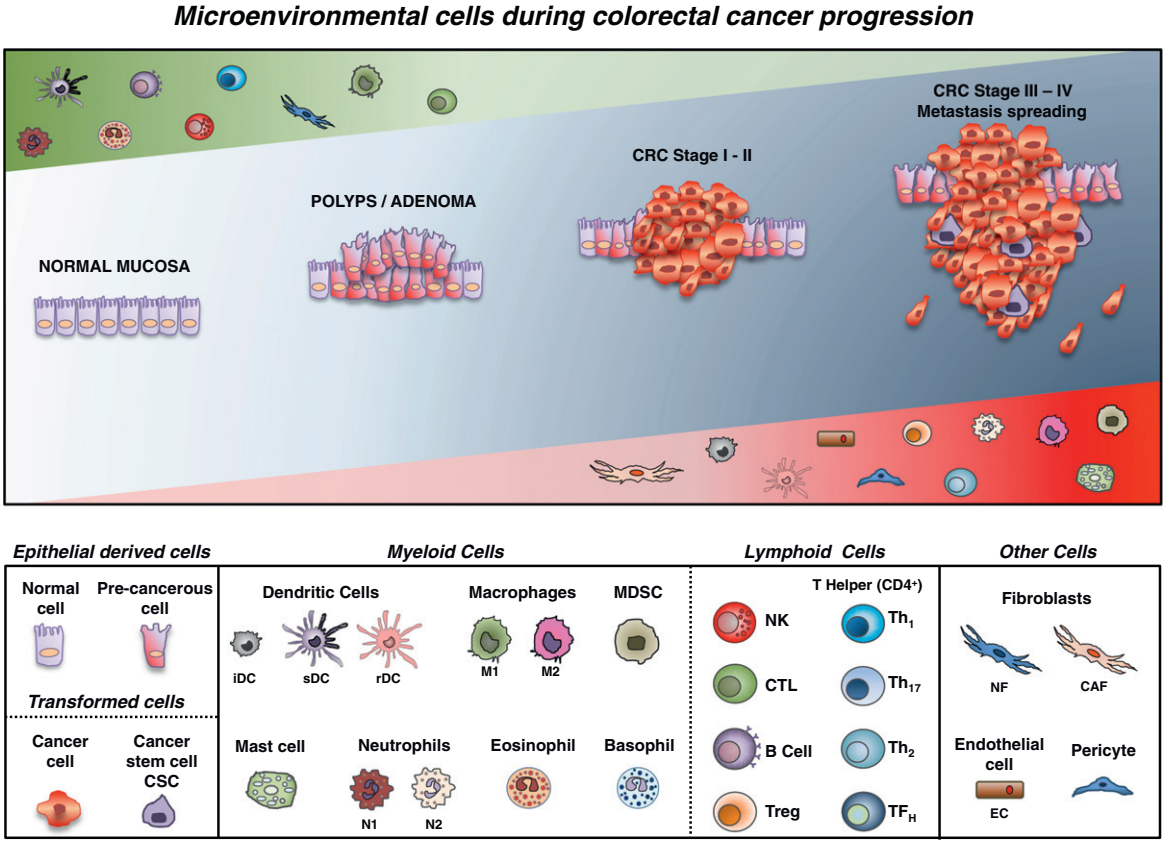

Fig. 1. Microenvironmental cells during colorectal cancer progression. The picture depicts the cell populations that contribute to establish the CRC microenvironment along with their variations during progression reported as decrease (green triangle) or increase (red triangle). The cells implicated are listed in the legend below. iDC: immature Dendritic Cell; sDC: stimulatory Dendritic Cell; rDC: regulatory Dendritic Cell; MDSC: Myeloid-Derived Suppressor Cell; NK: Natural Killer; CTL: Cytotoxic T Lymphocyte; Treg: Tregulatory cell; NF: Normal Fibroblast; CAF: Cancer Associated Fibroblast.