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Review

Colorectal cancer defeating? Challenge accepted!

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ABSTRACT

Colorectal tumours are actually considered as aberrant organs, within it is possible to notice a different stage of cell growth and differentiation. Their origin is reported to arise from a subpopulation of tumour cells endowed with, just like the healthy stem cells, self-renewal and aberrant multi-lineage differentiation capacity likely to be called colorectal cancer stem cells (CCSCs). Cancer stem cells (CSCs) fate, since their origin, reflects the influences from their microenvironment (or niche) both in the maintenance of stemness, in promoting their differentiation, and in inducing epithelial–mesenchymal transition, responsible of CSCs dissemination and subsequent formation of metastatic lesions. The tumour cells heterogeneity and their immuno-response resistance nowadays probably responsible of the failure of the conventional therapies, make this research field an open issue. Even more importantly, our increasing understanding of the cellular and molecular mechanisms that regulate CSC quiescence and cell cycle regulation, self-renewal, chemotaxis and resistance to cytotoxic agents, is expected to eventually result in tailor-made therapies with a significant impact on the morbidity and overall survival of colorectal cancer patients.

Contents

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1. Introduction

Colorectal cancer (CRC) is one of the major causes of death worldwide (Jemal et al., 2011). Despite the prompt surgical removal followed by adjuvant therapy, often suitable in the early stages of the disease, the majority of patients undergo to recurrences and metastases. This phenomenon frequently correlates with an acquired resistance to conventional therapies such as chemo- and radio-therapy (Jänne and Mayer, 2000).

Increasing evidences recently claimed that tumours are structured by heterogeneous populations of cells hierarchically organized, with CSCs at the top of this pyramid model. The concept that this subset of cells may arise from normal stem cells (or progenitor cells), as a result of genetic and/or epigenetic mutations (Barker et al., 2009) is appealing for several reasons. Healthy stem cells and CSCs share many properties, including the self-renewal and aberrant multi-lineage differentiation capacity, altered DNA repair machinery, high expression levels of anti-apoptotic genes and ATP-binding cassette (ABC) transporters, which could explain the failure of current anti-cancer treatments (Todaro et al., 2007). Moreover, the CSCs are highly clonogenic and can generate a serially transplantable phenocopy of the primary malignancy in immuno-compromised mice (Clarke et al., 2006), highlighting their tumourigenic capacity.

The amazing cellular turnover of the colon epithelium makes this tissue the ideal subject for the study on the healthy stem cells biology, and then on cancer stems cells during tumour progression. Under physiological conditions, colon homeostasis is highly regulated, and it is the result of a perfect balance between stem cells, differentiated cells and the microenvironment. Sometimes, however, this balance is missing, so throwing the foundations for the emergence and progression of the tumour.

It has been noticed that the colon stem cells (SCs) reside at the base of the intestinal crypts, where the microenvironment seems to orchestrate the stemness status, the proliferation and the resistance to apoptosis of stem cells, regulating different signaling pathways. This network of signals link up different stromal cells, such as mesenchymal cells with immune cells, blood vessels, soluble factors and extracellular matrix components (Kosinski et al., 2007) building the complex tumour architecture. Likewise the CSCs are strictly dependent from their residing environment, the tumour niche, which not only play a role in determining the cell type, but also provides protection by sheltering CSCs from diverse genotoxic insults, contributing to their enhanced therapy resistance (Sun and Nelson, 2012).

Most conventional therapies affect differentiated cells, which constitute the bulk of tumour mass, thus saving CSCs. This phenomenon seems to be the cause of the initial tumour shrinkage followed by relapses, often more aggressive of the primary tumour of origin (Al-Hajj et al., 2004).

Nowadays, thanks to new quick and low-cost technologies, it is possible to achieve genomic and proteomic analysis to better characterize the tumour patient "phenotype" considering that the "one-size-fits-all" approach for cancer treatment is not longer sufficient. These "omics" analyses have pushed a new personalized approach in the cancer field, trying to optimize the treatment options, to avoid the resistance phenomena, bypassing unnecessary side effects (Chang et al., 2009; Wilson et al., 2007).

The origin and tumour progression are tightly regulated by aberrant oncogenic pathways activation, in concert with an inactivation of tumour suppressor signals. This phenomenon, however, seems to follow a branched trend, rather than linear, thus generating a large clonal diversity, and contributing to the intra-tumoral genetic heterogeneity (Marusyk et al., 2012). The huge inter-tumour variability depends from several aspects, first of all the variables related to the host (age, hormonal status), while the intra-tumour cellular organization is differentially influenced by several stimuli coming from the contiguous microenvironment (differences in vascularity, infiltration degree, connective tissue components). Last but not least it is also important to consider the cellular state diversity, as the cell cycle, the exposure to antigens, and the membrane composition (Heppner, 1984).

This great heterogeneity poses a considerable number of questions on how to address the issue of tumour, both from the point of view of diagnosis and of the possible treatment suggested (Gerlinger et al., 2012), as we will discuss later in this review.

We recent demonstrated the role of different components of the immune system against the tumours (Tallerico et al., 2013; Todaro et al., 2009). Although there is strong evidence of how the cells of the immune system can limit tumour