

# Metastatic components in colorectal cancer

Marjan Hajimoradi Javarsiani<sup>1</sup>, Shagayegh Haghjooy Javanmard<sup>2</sup>, Francesca Colonna<sup>3</sup>

<sup>1</sup>Department of Basic Sciences, School of Veterinary Medicine, Shiraz University, Shiraz, Iran, <sup>2</sup>Applied Physiology Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran, <sup>3</sup>Department of General Pathology, Cattolica del Sacro Cuore Largo Francesco University, Rome, Italy

Recent experiments have shown that cells with different genetic mutations can give rise to cancer transformation, both *in vitro* and *in vivo*, supported by the crosstalk between cancer cells and stroma. The stroma and the complex set of involved cells make up the tumor microenvironment that supports the engraftment of metastatic cells. In fact, environmental factors support colorectal cancer arise by formation and maintenance of cancer stem cells (CSCs). In this review, we discuss interactions between CSCs and their microenvironment that can provide better therapeutic opportunities in the metastatic cancer.

**Key words:** Cancer stem cells, colorectal cancer, metastasis, tumor microenvironment

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## INTRODUCTION

One of the most frequent types of cancer worldwide is colorectal cancer (CRC).<sup>[1]</sup> The intestine epithelium has a higher self-renewal rate than any other tissues in the body.<sup>[2]</sup> Classically, CRC pathogenesis has been characterized as the stepwise progression of cancerous lesions from potentially malignant precursors, predominantly tubular adenomas.<sup>[3]</sup>

Surgery, CRC therapeutic gold standard, is effective if tumor cells have not spread to distant organs. Colorectal-cancer stem cells (CR-CSCs) can metastasize in liver and lungs. Around the 30% of patients have a too late diagnosis of CRC.<sup>[4,5]</sup> In fact, in 20%–25% of patients with colon cancer, and in 18% of patients with rectal cancer, metastases are present at the time of the first diagnosis.<sup>[6,7]</sup> The most common metastasis localization in CRC patients is liver, but 2.1% of these patients show lung metastases,<sup>[8]</sup> with frequency about three times higher for patients with rectal cancer than for patients with colon cancer. In order to control and eradicate cancer, we need to focus not only on malignant cancer cells but also on the benign stromal cells useful indeed to cancer cells.

Metastasis, spreading of cancer cells to other organs, is an ability to regenerate a tumor at a distant site.<sup>[9]</sup> It is now recognized that the neogenesis of the tumor in a foreign organ is tightly bound to the gain of stem-like phenotype of cancer cells.<sup>[10]</sup> This feature critically depends on their interaction with microenvironment to migrate, survive in circulation, take root, and proliferate in a new organ [Figure 1].<sup>[9]</sup>

## COLORECTAL CANCER PATHOGENESIS

### The chromosomal instability pathway

The chromosomal instability pathway is known as the adenoma-carcinoma sequence, that establish a predictable progression of genetic mutations that involve histologic consequences and changes.<sup>[11,12]</sup> Colon cancer pathogenesis is carried out by mutations called “drivers,” necessary but not sufficient, and mutations called “passengers” contributing to tumor progression and that are witness to the multiple intra- and inter-patient heterogeneity. The genomic changes include inactivation of at least three tumor suppression genes (loss of adenomatous polyposis coli [APC], p53 and loss of heterozygosity for chromosome 18 [18q LOH]) and activation of proto-oncogenes (K-Ras).

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**Address for correspondence:** Dr. Marjan Hajimoradi Javarsiani, Applied Physiology Research Center, Isfahan University of Medical Sciences, Isfahan, Iran. E-mail: shagayegh.haghjoo@gmail.com

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Driver's mutations are:

- Inactivation of tumor suppressor APC (chromosome region 5q21, germline in FAP syndrome, or somatic in sporadic cases)
- Activation of proto-oncogene K-Ras
- Loss of p53
- 18q LOH, consequently loss of Deleted in colon carcinoma (DCC) and of some SMAD, transforming growth factor beta pathway signal transducer proteins.

Recently, mutations in the genes of tumor growth factor beta receptor (TGFβR) and PIK3CA has been also described for the adenoma-carcinoma sequence model.<sup>[11,13]</sup>

### Adenomatous polyposis coli and Wnt signaling pathway

Familial adenomatous polyposis (FAP) and others familial syndromes make APC-associated polyposis conditions. FAP is a CRC-predisposition syndrome that leads to the development of very numerous precancerous lesions or polyps in the last intestine tract. It represents <1% of all cases of colon cancer. In this disease, it is absolutely necessary to undergo a prophylactic colectomy to avoid the tumor, which occurs in 100% of cases.

Mutations in APC/Wnt/β-catenin are the main actresses in CRC carcinogenesis in both sporadic (80% APC mutated) and hereditary cases. Moreover, in sporadic tumors, where the APC gene is not mutated, mutations in other pathway components, such as β-catenin, regulated by APC, are found.<sup>[14,15]</sup>

Normally, APC blocks the transition from G to S stages of the cell cycle. In the cytoplasm, APC binds some proteins such as axin, glycogen synthase kinase-3β and β-catenin; the latter is so phosphorylated, ubiquitinated, and degraded through the proteasome. If there is no APC complex, β-catenin can move into the nucleus. Here, it activates the transcription of proliferation's genes such

as Myc and Cyclin D1. Furthermore, β-catenin stabilizes intercellular junctions and contact inhibition, important factors involved in the metastatic process.<sup>[11,16]</sup>

### Epidermal growth factor receptor pathway and K-Ras

In the epithelium, epidermal growth factor receptor (EGFR) represents a transmembrane tyrosine kinase that performs its activity of cellular proliferation and survival through two intracellular pathways. Its ligand, epidermal growth factor (EGF), binds the extracellular domain of the receptor leading to its dimerization. Hence, the intracellular domain is autophosphorylated and activates some proteins such as Ras/Raf/Mitogen-activated protein kinases (MAPK) for one pathway and PI3K/AKT for the other pathway [Figure 2]. The first pathway regulates cell proliferation, differentiation, senescence, and apoptosis. The gene that encodes for Raf protein is an oncogene that includes also the H-Ras, N-Ras, and K-Ras isoforms.<sup>[17]</sup> The last one was the most mutated in 40% of sporadic CRCs. Furthermore, BRAF, a member of Raf family, acts in this pathway and is mutated in sporadic CRCs. After the bond between ligand and receptor, the downstream mechanism includes the activation of cascade signal through PI3K mediated by Ras. This activation inhibits apoptosis, whereas RAF activation stimulates cellular proliferation. For this reason, is clear that K-Ras mutations increase cell proliferation and survival independently of EGFR receptor activation.<sup>[11,18]</sup>

### TP53 mutation

TP53 is the guardian of the genome, involved in the control of apoptosis and cell cycle. It is often mutated in several neoplastic diseases included CRC. P53 induces G stage cell-cycle arrest when there are some DNA damages, so enables DNA repair before the DNA replication process. Unsuccessful repair induces cell apoptosis. In general, TP53 mutation occurs at the time of transition from adenoma

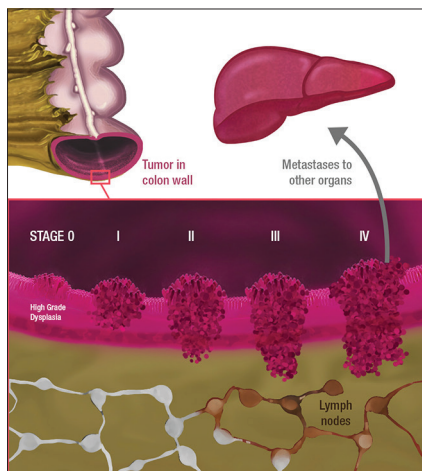


Figure 1: Colorectal Cancer stages

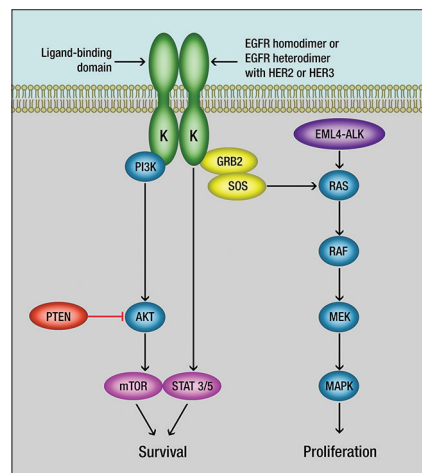


Figure 2: Epidermal growth factor receptor Pathway and its two pathways: Ras/Raf/Mitogen-activated protein kinases or PI3K/AKT

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to cancer lesion where it is overexpressed in 60% of the tumors.<sup>[11]</sup>

### Loss of heterozygosity for chromosome 18

LOH represents the loss of one of the two gene's copies. This LOH in 18q21 is seen in advanced CRC and involves some proteins such as SMAD proteins or DCC. The DCC is a transmembrane protein encoded by a "conditional tumor suppressor gene." This one, in the absence of netrin-1, its ligand, can block cell growth. This ligand is produced in the colon crypts where its concentration decrease when cell differentiates and moves toward the surface. This gradient contributes to the physiological process of apoptosis and sloughing of epithelial cells. So when the gene is mutated, in the 70% of CRCs cases, netrin-1 will not bind its receptor resulting in abnormal cell survival.<sup>[11,19]</sup>

### PI3K/AKT pathway and tumor growth factor beta receptor II

As mentioned earlier, EGFR activates 2 pathways. The second one involves PI3K/AKT/mTOR. PI3K phosphorylates AKT that, once activated, phosphorylates several proteins such as mTOR. PI3KCA gene encodes the catalytic subunit of PI3K and is mutated in over 25% of CRCs.

Another protagonist is the TGF $\beta$  family that includes several multifactorial proteins involved in many cellular processes. TGF $\beta$  receptors have some isoforms: type I (I), type II (RII), and type III (RIII). The type II is mutated in 90% of CRCs with microsatellite instability. In early stages of carcinogenesis, this receptor mediates some suppressive effects, whereas in late stages, it promotes tumor development by inhibiting tumor cell death. It participates also in epithelial-to-mesenchymal transition (EMT) that induces tumor invasion and metastasis. It has been shown that TGF $\beta$  RII activates downstream PI3K/AKT. The activation of this pathway can make cells resistant to growth factor deprivation and stress-induced apoptosis and promote cell motility.<sup>[11]</sup>

## TUMOR-STROMA INTERACTION

Nonmalignant cells and tumor microenvironment (TME) interact with each other. Immune cells,<sup>[20]</sup> endothelial cells and fibroblasts<sup>[21]</sup> are the main factors of the TME that support the engraftment and self-renewal of CR-CSCs. Therefore, the different tumor-associated cells together with the extracellular matrix (ECM) support tumor formation. On the other hand, tumor cells strongly transform the nature and content of the stroma and TME in general. For these reasons, TME is an important factor in the cancer development and so in metastatic colonization. The understanding of the mechanisms established between tumor cells and TME is of strong scientific interest and could provide potential targets for the development of new anticancer therapies [Figure 3].

### Cancer-associated fibroblasts

Cancer-associated fibroblasts (CAFs) have a morphology similar to myofibroblasts. They are large spindle-shaped cells activated during the wound healing process.<sup>[22]</sup> CRC-associated fibroblasts show specific markers including fibroblast surface protein-1, alpha-smooth muscle actin, vimentin, prolyl-4-hydroxylase, chondroitin sulfate proteoglycan neuron-gial antigen-2, fibroblast-activated protein (FAP), and platelet-derived growth factor receptor.<sup>[23]</sup> CAFs origin is heterogeneous and still under study. This is to be found in different cell types, such as mesenchymal stem cells derived from bone marrow, resident tissue fibroblasts, hematopoietic stem cells, endothelial cells (mesothelium-endothelial transition [EndMT]) and epithelial cells (EMT).<sup>[24,25]</sup> In the liver, for example, activated CAFs are responsible for the production of different factors such as hepatic growth factor (HGF), some cytokines and chemokines, EGF, IGF1 and 2, prostaglandin E2 (PGE2) and the vascular endothelial growth factor (VEGF) that contribute to the tumor metastasization.<sup>[26]</sup> CAFs increase self-renewal of CR-CSCs and their invasion by specific cytokine and chemokine secretion after chemotherapy treatment such as the interleukin-17 (IL-17A).<sup>[21]</sup>

Some factors secreted by stromal cells such as HGF, OPN, and stromal-cell-derived factor-1 (SDF-1)<sup>[27]</sup> increase the CD44-v6 protein required for cell migration. The remodeling of the ECM takes place with the intervention of the matrix metalloprotein family members (MMP). MMP-2 and MMP-9 constitute the basal membrane and contribute to tumor proliferation by degrading type IV collagen and laminin. MMP-9 is activated by MMP-3 and MMP-13.<sup>[28]</sup> The expression of MMP-9 in fibroblasts is induced by tumor necrosis factor-alpha (TNF-alpha) and TGF- $\beta$ .<sup>[29]</sup> CAFs activated with TGF- $\beta$  secrete IL-11, which leads to increased STAT3-dependent survival<sup>[23]</sup> thus promoting the onset of liver metastases.<sup>[30]</sup> For this reason, TGF- $\beta$  signaling may be therapeutically relevant in the context of CAFs and liver metastases.<sup>[31]</sup>

Furthermore, CAFs can alter their energy metabolism, which can promote tumor growth. They use aerobic glycolysis as an energy source. This metabolism generates lactate and ketones which, when secreted in the intracellular space, act as paracrine oncometabolites that feed the oxidative mitochondrial metabolism in cancer cells.<sup>[32]</sup> This aerobic glycolysis is referred to as "Warburg's inverse effect." The acid environment generated by this metabolic switch not only activates the MMPs, but it also prevents the attack of the growing tumor mass by the immune cells.

### Tumour growth factor-beta

Endothelial cells may be involved in the formation of the metastatic niche transforming into cells similar to CAF,

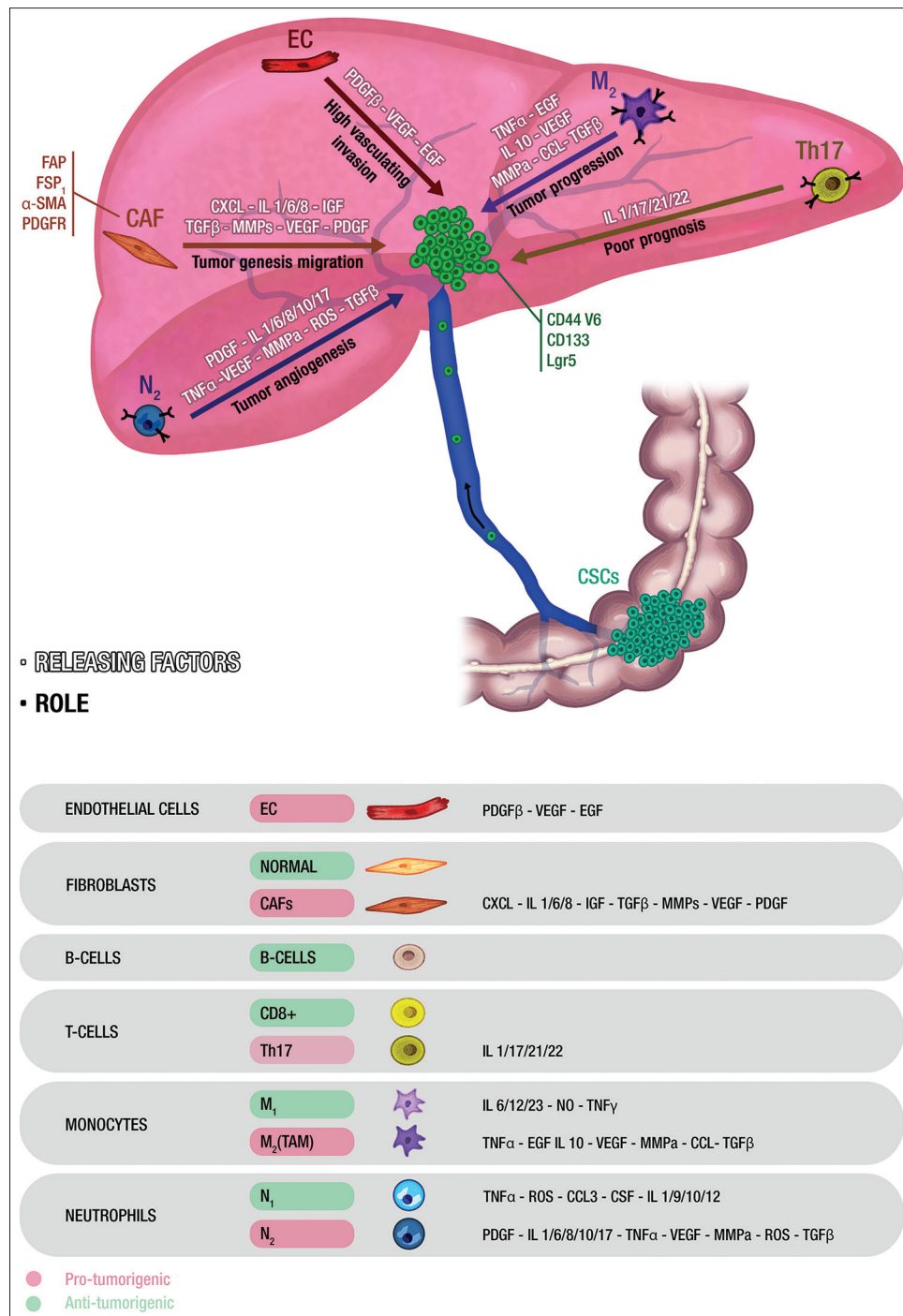


Figure 3: The factors released and their role in tumor suppression

through a mechanism driven by TGF-β called EndMT.<sup>[31]</sup> TGF-β is an important factor for the interactions between metastatic tumor cells and the microenvironment in CRC. This acts as a tumor suppressor during initial tumor formation and instead has a predominant oncogenic role during tumor progression. This switch appears to occur after the acquisition of further mutations involving, for example, P53<sup>[33]</sup> or SMAD4.<sup>[34]</sup> In advanced tumors, the increase in TGF-β levels is induced by a prometastatic program activated by cross-talk between tumor cells and stromal cells. Indeed, the TGF-β level increases

the survival of metastatic cells and therefore, their organ colonization.<sup>[23]</sup> CRC cells capable of initiating metastases possess the ability to raise TGF-β levels in the environment by secreting TGF-β or recruiting TGF-β-producing cells such as macrophages, CAFs, or platelets.<sup>[23-27]</sup>

#### Endothelial cell

The transformation of endothelial cells leads to pathological disorders. In normal tissues, these form a continuous and uniform monolayer but, in TME, endothelial cells have an



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atypical shape and size with ruffled margins and promote a stem cell phenotype.

Numerous cell types referred to as TME.<sup>[35]</sup> Angiogenesis is one of the hallmarks of cancer. It is necessary for the development of malignant tumors and is mediated by a group of angiogenic factors such as VEGF and the placental growth factor. Many types of tumor cells in a hypoxic environment secrete VEGF.<sup>[36,37]</sup> Furthermore, CAFs upregulate the release of IL6 in the presence of tumor cells which increases angiogenesis.<sup>[38]</sup> Angiogenesis induced with VEGF and IL-6 is further enhanced by the production of VEGF by the same fibroblasts.<sup>[38]</sup>

Other angiogenic factors are PDGF, FGF, and SDF-1; in human colon carcinomas, among these factors, PDGF-R is mainly expressed by tumor-associated stromal cells and by pericytes of tumor vasculature.<sup>[39]</sup> The expression of PDGF-R on CAFs, in a dependent stanniocalcin-1 manner, is associated with metastasis and poor prognosis in CRC.<sup>[40]</sup> A particular cytokine, IL-33, is secreted by endothelial and epithelial cells for the activation of NF- $\kappa$ B and MAPK signaling and it may have therapeutic interest in the reprogramming of endothelial cells and in the normalization of tumor vasculature in CRC. Most data showed that IL-33 increases endothelial cell proliferation, migration, and differentiation in blood vessels improving neo-angiogenesis.<sup>[41]</sup>

### Immune cells

The immune system acts as an effective protector against cancer and has a dual role, in fact, it is able both to promote and suppress the development of tumor.<sup>[42]</sup> The immune system counteracts tumor cells with innate immunity cells (e.g. macrophages, neutrophils, and dendritic cells) and adaptive immunity cells (B and T lymphocytes). This system recognizes specific tumor antigens (neo-antigens) expressed by malignant cells. Cancer cells produce PGE2 which plays a key role in the tumor escape phase as it suppresses immunity and induces inflammation. This mechanism is necessary for tumor growth in immunocompetent hosts. This effect has been observed in breast, melanoma, and CRC.<sup>[43]</sup> Chemokine signaling plays an important role in the recruitment and communication of CRC cells with other TME residents. Finally, it often promotes both the progression of cancer and the spread of metastases.<sup>[44]</sup> As previously described, tumor and stromal cells secrete chemokines, cytokines, and angiogenic factors. These act as TME immunological modulators. For example, microbial products and interferon- $\gamma$  attract monocytes to tumor sites that differentiate into alternative mature macrophages (M2 instead of the classic macrophage, M1). Macrophages, one of the most abundant tumor infiltrating

cell types, have many tumor-suppressor roles in CRC.<sup>[45]</sup> The macrophage polarization depends on TME and is a process involving TGF- $\beta$ , ILs, and chemokines that convert them into alternative macrophages M2.<sup>[46]</sup> These release IL12, IL23, and nitric oxide increase the expression of the major histocompatibility complex (MHC) which leads to T-cell differentiation and promotion of angiogenesis. During inflammation, the environment stimulates neutrophil migration to the site. In particular, N1 neutrophils have antitumor effects, and N2 neutrophils have pro-tumor effects. In addition, in this case, TGF- $\beta$  plays an important role in converting N1 neutrophils to N2 and produces arginase to inactivate the effector functions of T cells. Nevertheless, tumor-associated macrophages and dendritic cells are all sources of CAF for stromal TGF- $\beta$ .<sup>[31]</sup>

Regarding T cells, there are three types – CD8+ T cells (cytotoxic T lymphocytes [CTLs]), CD4+ T cells (helper T cells), and regulatory T cells. CTLs recognize specific antigens by mediating immune surveillance and are effective in CRC metastasis.<sup>[31]</sup> T helper lymphocytes interact directly with MHC Class II molecules on cells, which can influence the behavior of some types of cells, namely macrophages, CTLs, and B cells. All immune cells, in particular, CD4+ T cells, influence self-renewal of CR-CSCs through IL-22 secretion. They in fact activate the methyltransferase DOT1 L responsible for the transcription of genes associated with stem cells.<sup>[20]</sup> Finally, B lymphocytes differentiate into plasma cells by recognizing the antigen directly or interacting with T helper cells. They release cytokines such as IL10/17/35, IFN- $\gamma$  and TNF- $\alpha$  for immune system signaling. They also make up long-lived memory B cells. The accumulation of plasma cells or memory B cells is a specific antitumor immune response.

## CONCLUSIONS

In this review, we try to explain the CRC metastatic microenvironment. Although many factors and signaling pathways have been described as responsible for tumor progression, a better understanding of microenvironmental factors is essential to improve or design new therapeutic approaches that allow good prognosis even in the CRC advanced stages.

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