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EDITORIAL

Pathobiology of the neutrophil-intestinal epithelial cell interaction: Role in carcinogenesis

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Abstract

The role of chronic inflammation, acting as an independent factor, on the onset of gastrointestinal carcinogenesis is now well accepted. However, even if there is an increase in the number of elements directly involving polymorphonuclear leukocytes (PMNL), as a major actor in digestive carcinogenesis, the different cellular and molecular events occurring in this process are still not completely understood. The transepithelial migration of PMNL, which is the ultimate step of the afflux of PMNL into the digestive mucosa, is a complex phenomenon involving sequential interaction of molecules expressed both on PMNL and on digestive epithelial cells. Chronic inflammatory areas rich in PMNL [so-called (chronic active inflammation)] and iterative transepithelial migration of PMNL certainly evoke intracellular signals, which lead toward progressive transformation of epithelia. Among these different signals, the mutagenic effect of reactive oxygen species and nitrates, the activation of the nuclear factor-κB pathway, and the modulation of expression of certain microRNA are key actors. Following the initiation of carcinogenesis, PMNL are involved in the progression and invasion of digestive carcinomas, with which they interact. It is noteworthy that different subpopulations of PMNL, which can have some opposite effects on tumor growth, in association with different levels of transforming growth factor-β and with the number of CD8 positive T lymphocytes, could be present during the development of digestive carcinoma. Other factors that involve PMNL, such as massive elastase release, and the production of angiogenic factors, can participate in the progression of neoplastic cells through tissues. PMNL may play a major role in the onset of metastases, since they allow the tumor cells to cross the endothelial barrier and to migrate into the blood stream. Finally, PMNL play a role, alone or in association with other cell parameters, in the initiation, promotion, progression and dissemination of digestive carcinomas. This review focuses on the main currently accepted cellular and molecular mechanisms that involve PMNL as key actors in digestive carcinogenesis.

Key words: Neutrophils; Intestinal epithelial cells; Carcinogenesis; Cytokines; Nuclear factor-κB pathway; MicroRNA; Reactive oxygen species

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INTRODUCTION

The link between a chronic active inflammatory process (i.e. chronic inflammation rich in neutrophils) and the onset of carcinoma, in association or not with another factor such as a pathogen, is now convincingly demon-

strated with epidemiological, experimental, and molecular data obtained for different tissues[1-10]. In particular, this relationship is well-established at the gastric and intestinal mucosal level[11-18]. Different factors are involved in digestive carcinogenesis, but the association of these factors and their importance in cancer onset are certainly variable from one disease to another and among individuals. Thus, predisposing genetic factors, infectious factors and inflammatory factors can be involved in digestive carcinogenesis[19]. Inappropriate innate immunity induces cellular infiltration of the digestive mucosa composed of polymorphonuclear leukocytes (PMNL), dendritic cells, natural killer cells, and then secondarily, an afflux of adaptive immune cells such as T lymphocytes. The intensity of this polymorphous cellular infiltrate varies according to the period of the active phases of the digestive disease[20]. In this regard, inflammatory infiltration can be present at variable time periods and at a variable frequency. Among the different populations of cells which migrate into the digestive mucosa, the PMNL play a central role in the pathophysiology of inflammatory digestive diseases[21]. Thus, previous epidemiological and histological studies have convincingly demonstrated a direct link between the clinical symptoms (pain and diarrhea) and the presence of PMNL in the digestive mucosa. More particularly, the periods of acute diarrhea certainly correlate with transepithelial migration of PMNL into the digestive lumen. It is noteworthy that during interaction between the intestinal epithelial cells (IEC) and PMNL different intracellular events are triggered, leading to neoplastic transformation of the digestive epithelia. The molecular phases involved in PMNL transepithelial migration are complex, but it is crucial to understand these phases to better comprehend the initial steps in digestive carcinogenesis. The progression from an *in situ* carcinoma to a microinvasive and invasive digestive carcinoma is associated with several molecular events, in particular, cytoskeleton modification, modulation of adherence molecules and metalloprotease production. Among these different events, some directly implicate PMNL. Currently, the pros and cons of the role of PMNL in tumor progression are debatable[22,23]. PMNL produce elastases[24], which favor tumor cell extracellular matrix invasion and release of pro-angiogenic factors, which creates a favorable microenvironment for tumor progression[25-30], but also produce defensins, which have an anti-tumor effect. Recently, a dual function of PMNL, in regard to their action on carcinoma cells, has been proposed[31,32]. Thus, two different populations of PMNL can be present in tumors, a population that favors tumour progression, the tumor-associated neutrophils 1 (TAN1) and a population that decreases tumor progression, the TAN2[31,32]. Accordingly to the proportion of TAN1 and TAN2 in a carcinoma the level of tumor progression can vary. This phenomenon can be present in colonic adenocarcinomas. Finally, previous studies implicate PMNL in the pathophysiology of metastases. This phenomenon can occur in colonic adenocarcinoma dissemination. In particular, PMNL allow transendothelial migration of tumor cells and then their migration into the blood stream.

Previous studies and reviews have focused on the role of the immune system during cancer development[33] but the impact of PMNL in the different phases of the natural history of cancer (Figure 1) has been poorly described to date. In this review, I describe the role of PMNL and the direct events induced by PMNL in the mechanisms of the different steps in digestive carcinogenesis (cancer initiation, progression and dissemination).

THE BIOLOGY OF THE NEUTROPHIL-INTESTINAL EPITHELIAL CELL INTERACTION

After transendothelial migration, following the crossing of the matrix of the lamina propria, which is mainly induced by a gradient of interleukin (IL) 8[34], PMNL adhere to the basal side of the glandular and crypt cell epithelium, and then transmigrate to the digestive lumen. This transepithelial migration is associated with sequential steps and with dynamic and transitory interactions between some surface molecules that are present on cytoplasmic membranes of PMNL and IEC[35,36] (Figure 2). Studies using *in vitro* models, such as the T84 model, have greatly improved our knowledge concerning these different cellular interactions. Thus, PMNL transepithelial migration can be induced by different stresses on epithelial cells, such as bacteria, bacterial products, toxins, or hypoxia[37,38]. Using this T84 model, the different steps of PMNL transepithelial migration and the different mechanisms involved in cell-cell interactions have been described[39-41]. Briefly, PMNL adhere to the basal side of the digestive epithelia through their CD11b/CD18 molecules (for which the ligand on epithelia is still unknown), then they migrate using a paracellular pathway through an homophilic CD47 interaction, which is expressed both on PMNL and IEC[42,43]. A more recent study showed that CD47 regulates neutrophil transmigration through close cross-talk with one toll-like receptor, TLR-2[44]. Other interactions occur at the desmosome and tight junction levels, which involve JAM and SIRPα[45-47]. After crossing the epithelial barrier PMNL interact with ICAM1 at the apical membrane through CD11b/CD18. During this transepithelial migration, the actin cytoskeleton of epithelial cells is reorganized[48]. Activated PMNL release 5'-adenosine monophosphate, which is secondarily cleaved by an epithelial membrane ectonucleotidase into adenosine, and finally produce chloride secretion on the epithelial apical side[49,50]. More recently, other molecular mechanisms have been described to occur during interaction between PMNL and the IEC[44,51]. Serine protease-mediated activation of epithelial protease-activated receptors has been shown to increase permeability. It has been demonstrated that transmigrating PMNL can regulate barrier function through epithelial protease-activated receptor activation[51]. Thus, transepithelial resistance decreased significantly after contact of PMNL with basolateral sur-

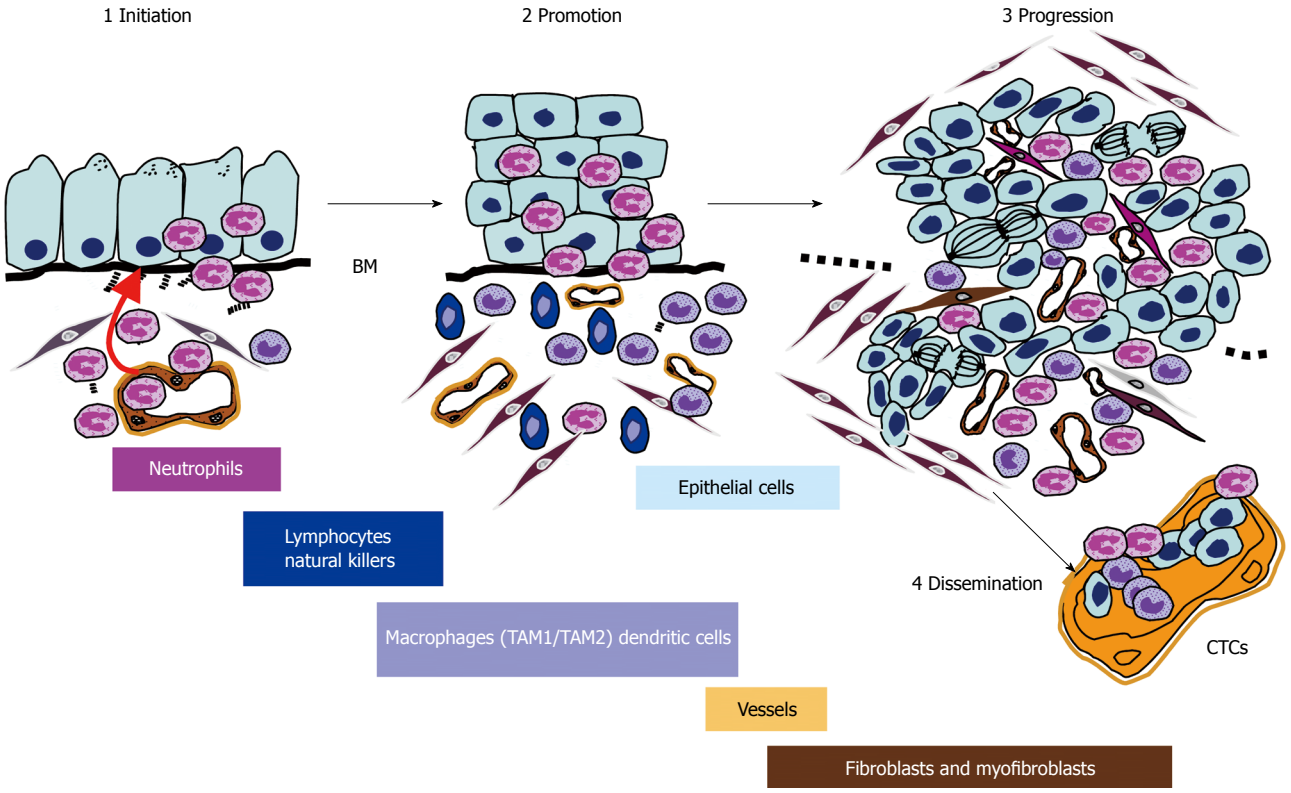

Figure 1 Involvement of a neutrophil-rich microenvironment in the different steps of digestive carcinogenesis including initiation, promotion, progression and dissemination of tumor. BM: Basement membrane; TAM: Tumor-associated macrophages; CTCs: Circulating tumor cells.

faces of T84 monolayers or after incubation with PMNL elastase and proteinase-3[51].

ROLE OF CHRONIC ACTIVE INFLAMMATION IN INITIATION OF DIGESTIVE CARCINOGENESIS

Beside these different events, which are associated with rapid paracellular migration of PMNL, different studies using the T84 model demonstrated the modulation of different molecules expressed on epithelial cells, which may be potentially involved in the initiation of carcinogenesis in direct or indirect pathways, by inducing an amplified inflammatory response rich in PMNL[52,53]. Moreover, paracellular migration of PMNL induced the onset of apoptosis, and, then potentially increases turnover of epithelium regeneration[54]. Thus, there is certainly a tight association between this chronic active inflammation and the onset of digestive carcinoma. An increased level in oxidative stress is present in the mucosa of inflammatory bowel diseases[55-57]. In this regard, an inflammatory microenvironment rich in PMNL can increase the rate of mutation, in addition to enhancing the proliferation of mutated cells[58]. Activated PMNL serve as sources of reactive oxygen species (ROS) and reactive nitrogen intermediates that are capable of inducing DNA damage and genomic instability[59]. Interestingly, release of ROS can occur during epithelium adhesion, but also during transepithelial migration and during post transepithelial migration of PMNL[60]. Alternatively, activated PMNL may use cytokines such as tumor necrosis factor (TNF)-α, which is implicated in carcinogenesis, to stimulate ROS and nitric oxide accumulation in neighboring epithelial cells[61,62]. Moreover, nitric oxide synthase can activate cyclooxygenase-2 in epithelial cells[63]. Different studies focus primarily on the effect of early mediators of inflammation, such as TNF-α, in stimulating tumor cell growth by activating nuclear factor (NF)-κB[64]. Conversely, decreased production of TNF-α in mice can reduce digestive carcinogenesis associated with chronic colitis[65]. However, chronic inflammation involves many other cytokines in the host microenvironment, which may also affect tumor growth in an NF-κB-dependent manner. While most inflammatory cytokines are released from activated macrophages following stimulus-induced transcription, others are secreted from intracellular pools and display later kinetics during the inflammatory response. Furthermore, the fact that NF-κB inhibition does not completely prevent tumor formation in these studies suggests that cytokines could also promote tumorigenesis *via* alternative pathways[66]. Mutations in p53, caused by oxidative damage, were found in both cancer cells and in a non-dysplastic epithelium in cancer associated colitis, suggesting that chronic inflammation causes genomic changes[67]. Finally, ROS can also cause direct oxidative inactivation of mismatch repair enzymes[5].

Other mechanisms have been described, which involve PMNL in the early steps of initiation of carcino-

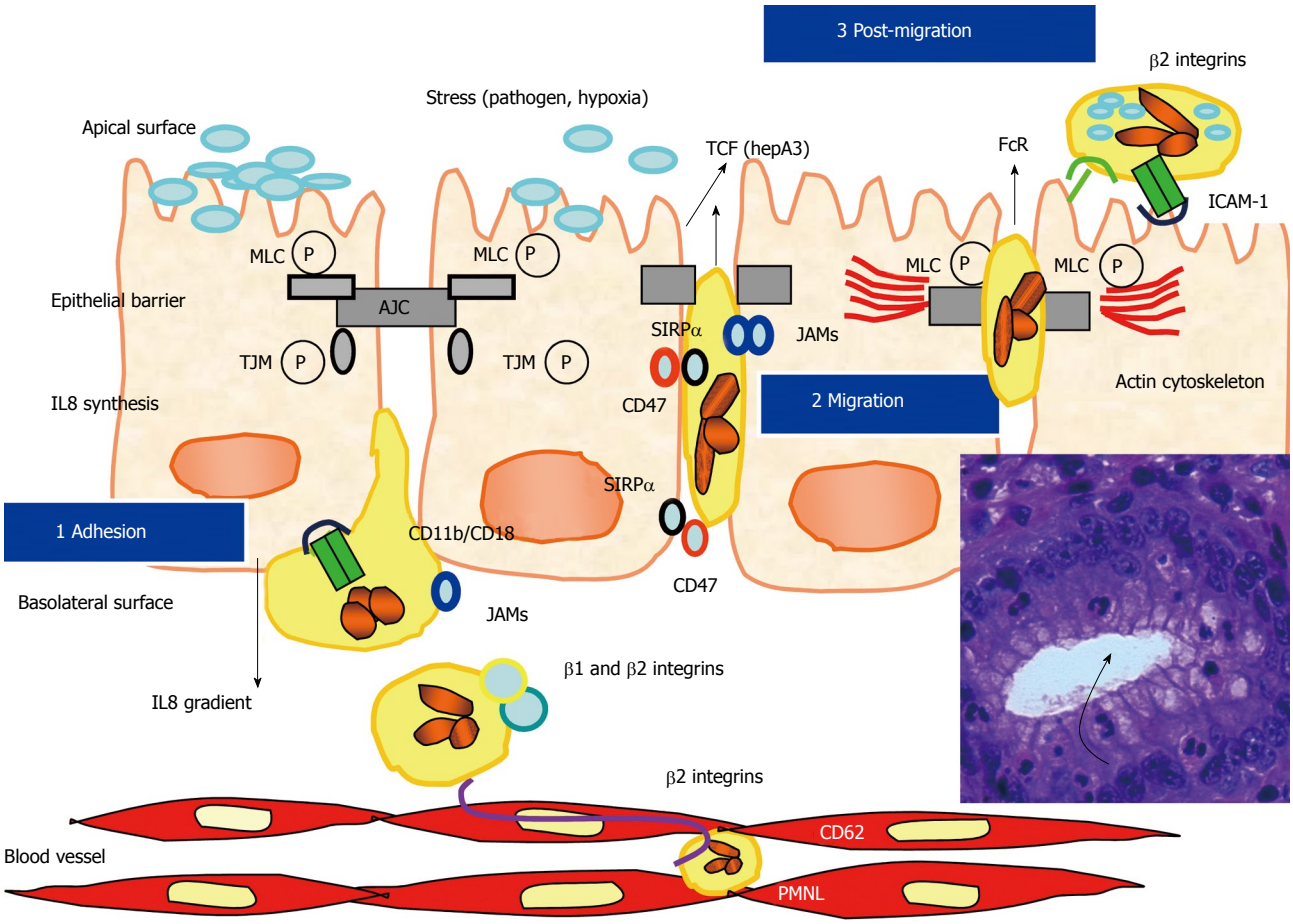

Figure 2 Cross-talk between polymorphonuclear leukocytes and intestinal epithelial cells. Different steps and molecules involvement in polymorphonuclear leukocytes transepithelial migration. The microphotograph shows polymorphonuclear leukocytes (PMNL) in an intestinal epithelium. TJM: Tight junction molecules; AJC: Apical junction complex; MLC: Myosin light chain kinase; JAM: Junctional adhesion molecules; TCF: Transcellular chemotactic factor; SIRP: Signal regulatory protein; IL: Interleukin.

genesis. Using animal models that reproduce digestive carcinogenesis linked to colitis, the molecule vanin 1 has been recently implicated in the onset of carcinoma[68]. Interestingly, it has been described that protein expression of cyclooxygenase-2 and the hypoxia-inducible factor-1 is up-regulated and associated with inflammation in early steps of digestive carcinoma[69]. The role of ROS and nitrates, largely suggested by previous studies, has been highlighted by different recent studies[70-76]. Interestingly, the myeloperoxidase (MPO) released by activated PMNL can inhibit nucleotide excision repair in certain epithelial cell lines[77]. In this regard, mutagenic products of MPO such as 5-chlorouracil and 5-bromouracil are released into inflammatory tissues. Moreover, the role of PMNL in initiation of carcinogenesis is probably more complex[78-80].

MicroRNA have been mainly investigated in oncology. However, microRNA are also implicated in inflammatory mechanisms, and their deregulation during some inflammatory diseases, in particular at the digestive level, could be associated with the molecular events that link chronic inflammation to cancer development[81-87]. The action of PMNL in this process is currently difficult to define, but through ROS release, and/or by the production of different enzymes, PMNL probably participate in deregulation of the RNA network in digestive epithelial cells.

IMPLICATION OF NEUTROPHILS IN PROGRESSION OF DIGESTIVE CARCINOMA

Recent studies have demonstrated that the presence of intratumoral PMNL can be associated with shorter disease specific survival in certain cancer patients[88]. Following the initiation of digestive carcinoma, processes allow the tumor to grow from a single initiated cell into a developed primary adenocarcinoma. In this context, tumor growth depends on increased cell proliferation and reduced cell death, both of which can be stimulated by PMNL-driven mechanisms. This inflammation-induced tumor promotion may occur early or late in tumor development and leads to activation of premalignant lesions that have been dormant for many years. As for tumor-associated macrophages[89-91], PMNL probably promote tumor growth but the putative mechanisms have not yet been determined. However, it has been shown that accelerated intestinal epithelial cell turnover caused by chronic active inflammation and epithelial damage might predispose the mucosa to DNA damage, resulting in an elevated risk of mutation, which is in line with dysplasia and carcinoma development in patients with ulcerative

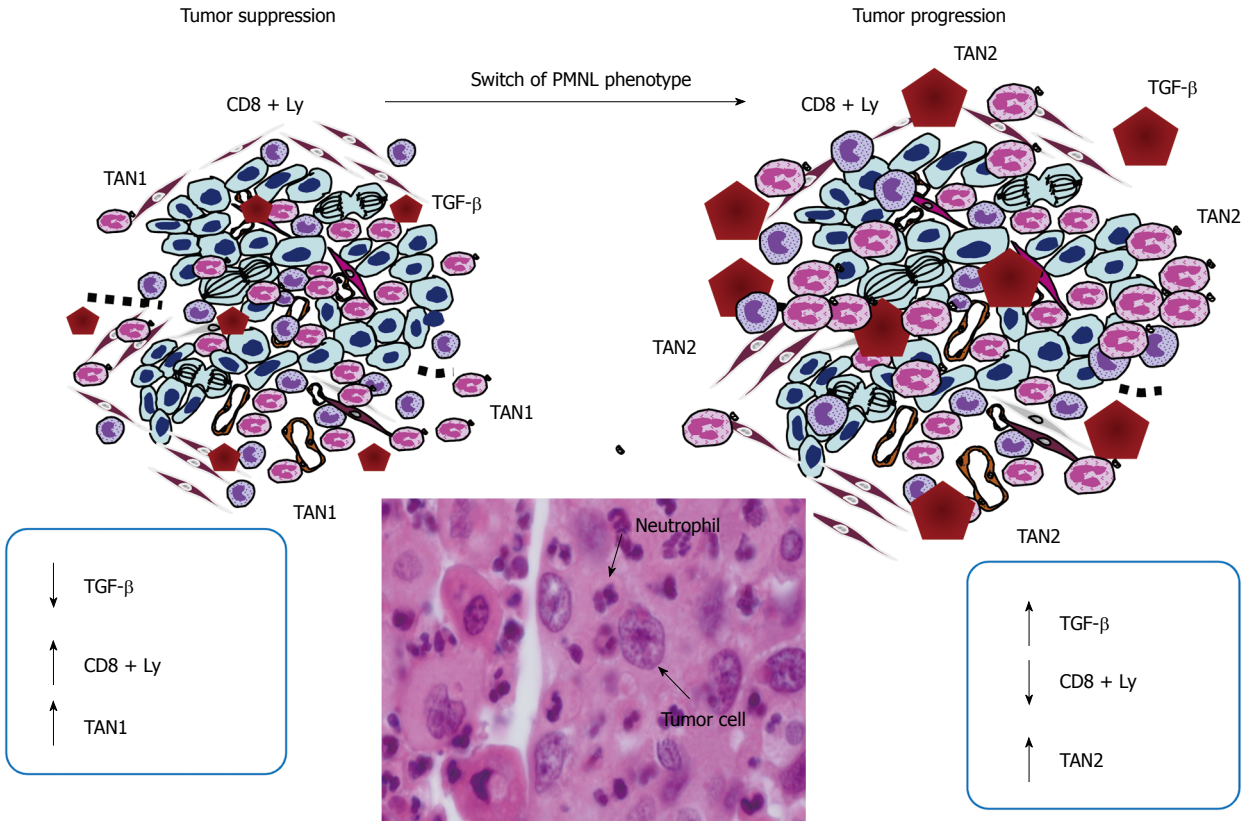

Figure 3 Speculative role of tumor-associated neutrophils in progression of digestive carcinoma. The microphotograph shows neutrophils tightly associated with digestive carcinoma cells. TAN: Tumor-associated neutrophils; TGF: Transforming growth factor.

colitis[92]. In parallel, the repeated inflammatory process could act on COX-2 expression which is down-regulated by the adenomatous polyposis coli (APC) gene and up-regulated by nuclear beta-catenin accumulation, and additionally implicate the Wnt signaling transduction pathway in colon carcinogenesis[93].

Secreted PMNL factors, such as human neutrophil peptides 1-3 (HNP1-3), have been found to be elevated in patients with digestive carcinoma, both in tissues and plasma, and to correlate with Dukes' stages[94]. Other molecules such as neutrophil gelatinase-associated lipocalin or neutrophil elastase are able to suppress or to increase the invasion of carcinoma cells[95-97]. Among the cytokines involved in carcinoma progression, Transforming growth factor (TGF)-β is certainly one of the most studied, to date. It has been reported recently in a mouse model of carcinoma that TGF-β controls maturation of a sub-type of PMNL, the so-called TAN-2. TANs could function in parallel with tumor-associated macrophages (TAMs)[98,99]. Conversely, inhibition of the TGF-β activity leads to the differentiation of PMNL in anti-tumor TAN-1 cells (Figure 3). While TAN-2 inhibit the cytotoxic response of CD8+-T lymphocytes, which infiltrate the intestinal mucosa and thereby allow tumor cells to circumvent immune surveillance, TAN-1 enhance the anti-tumor action of CD8+ T-lymphocytes. TGF-β blockade not only activates CD8+T cells, but also increases the recruitment of hypersegmented neutrophils, their NI polarization (high expression of TNF-α, ICAM-1 and FAS) and their anti-tumor activity. Moreover, N1 neutrophils produce T cell-attracting chemokines including CCL3, CXCL9 and CXCL10. By contrast, TGF-β stimulation polarizes PMNL to the so-called N2 state with increased expression of arginase and chemokines such as CCL2 and CCL5. N1 are cytotoxic for tumors, whereas N2 display pro-tumor properties.

We may speculate that this mechanism is universally found in carcinomas arising in different organs. Finally, it is noteworthy that the prognostic value of a high number of PMNL in different carcinomas correlates with poor outcome in previous studies[100].

In addition to TGF-β, other cytokines produced by PMNL may be involved in carcinoma progression. Thus, TNF-β secreted by PMNL can stimulate a positive loop of inflammation by inducing production of chemokines such as IL8 and Groα by epithelial tumor cells and probably inducing renewed recruitment of PMNL[101]. Moreover, other mechanisms may exist such as carcinoma cell stimulation of PMNL to produce oncostatin M[102].

Although it is not yet established, we can speculate that some miRNA expressed by PMNL, in particular mir-223, may also play a crucial role in modulating progression of digestive tumors. Mir-223 was found to possess a crucial role in regulating neutrophil proliferation and activation[103]. Moreover, the expression of mir-223 may be modulated by some cytokines released by tumor cells and may influence the phenotype of TAN-1 or

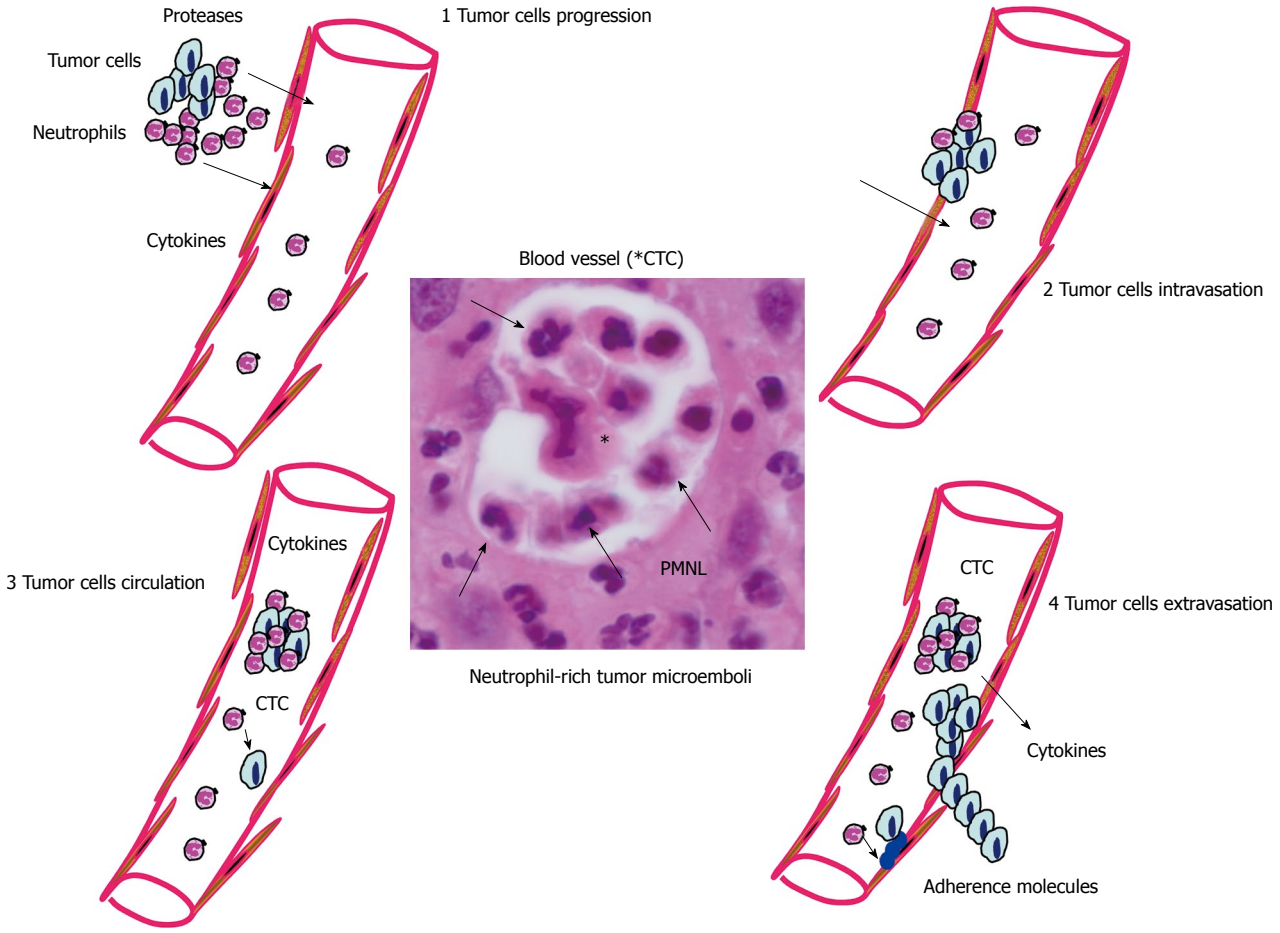

Figure 4 Speculative role of polymorphonuclear leukocytes in digestive carcinoma dissemination. The microphotograph shows circulating tumor cells associated with polymorphonuclear leukocytes (PMNL). CTC: Circulating tumor cells.

TAN-2. In this regard, different molecules have recently been reported as markers and/or promoters of inflammation-associated cancers[104]. Thus, we can speculate that the level of expression of mir-223 in carcinoma might be a marker of tumor progression.

THE NEUTROPHIL AS AN ACTOR OF THE PATHOBIOLOGY OF DIGESTIVE CARCINOMA METASTASIS

Inflammation is a key actor of metastasis onset[105]. In this regard, different studies have demonstrated the role of PMNL in tumor metastasis through different steps[106,107]. PMNL can participate in the transendothelial migration of adenocarcinoma cells, as well as their dissemination into the blood (Figure 4)[108,109]. Cytokines produced by PMNL can increase vascular permeability and upregulation of certain adhesion molecules located on endothelial cells[110]. In addition, PMNL are important sources of proteases that degrade the extracellular matrix and may alter the vascular barrier allowing entry of tumor cells into the blood stream. Interestingly, in a model of invasive colon cancer, CCR1+ myeloid cells, the recruitment of which is driven by the chemokine CCL9 produced by cancer cells, promote invasiveness through secretion of the matrix metalloproteinases MMP2 and MMP9[111]. It has been demonstrated that extracellular ATP can be released by activated PMNL[112]. This release of ATP occurs through a conformational opening of membrane Cx43 hemichannels in response to PMNL activation[113]. Moreover, the extracellular ATP released by activated PMNL may act both on epithelial cells, through activation of some purinergic receptors expressed by epithelial cells[53], and on endothelial cells[112]. More specifically, ATP released by activated PMNL is auto-hydrolyzed to AMP through CD39 on the surface of PMNL. CD39 may function as an immunomodulatory control point, requiring a close and special relationship with CD73-positive cells, such as endothelial cells. In addition to regulating the endothelial barrier function, a role for PMNL-dependent ATP release in directed movement of PMNL has been reported[114]. ROS released by activated PMNL can generate mitochondrial DNA mutations that regulate tumor cell metastasis[115].

Once metastatic cells enter the circulation, they need to survive in suspension and resist detachment-induced cell death or anoikis. The survival of circulating cancer cells is affected by inflammatory mediators released by immune cells in response to cancer-derived stimuli[116]. In the same way, the presence of a variety of cytokines

released by activated PMNL present in the tumor microenvironment, including TNF-α, can promote the survival of circulating metastatic seeds[117]. PMNL can also favor the circulation in the blood of tumor cells, in a similar way to that of platelets or blood macrophages which can be physically linked to cancer cells, allowing them to travel together through the circulation[118]. Thus, single circulating tumor cells (CTC), which are no longer present in an immunosuppressive environment, may be targeted again by immunosurveillance. In this regard, the interaction of circulating cancer cells with PMNL may protect them from cell death, thereby overcoming immunosurveillance[119]. The journey of CTC ends upon integrin-dependent arrest on the endothelium, followed by extravasation. In this regard, systemic inflammation enhances attachment of CTC to endothelial cells, and this process is governed by neutrophil-dependent upregulation of adhesion molecules[120]. Thus, the production of high levels of proinflammatory cytokines by the PMNL can upregulate expression of certain adhesion molecules on endothelial cells and thereby increase the probability of metastatic cell attachment and potentialize the passage of tumor cells from the circulation into the extracellular space and then to develop micrometastases[90,105].

CONCLUSIONS AND PERSPECTIVES IN THERAPIES TARGETING NEUTROPHILS

Different proinflammatory molecules and inflammatory cells have been suggested to be potential candidate targets for therapeutic strategies for cancer[99,121,122]. One study has shown that different drugs that prevent inflammation can inhibit carcinogenesis[123].

The role of PMNL in the onset and progression of digestive carcinoma, in particular those occurring in inflammatory bowel diseases, is complex. However, recent studies highlight new aspects of the pathophysiology of the PMNL-epithelial cells interaction, in particular, the effect of ROS release by activated PMNL on digestive epithelial cells at the molecular level or the effect of different TAN on tumor progression. Interestingly, these novel findings on the role of PMNL in the initiation and progression of carcinogenesis open up therapeutic avenues for the treatment of digestive cancers[124]. It is noteworthy that immunotherapy against cancer has been explored as a coadjuvant and has been based mostly on the properties of the adaptative immune system (i.e. B and T lymphocytes, dendritic cells) and of some components of the innate system (macrophages, NK cells, or complement proteins)[125,126]. PMNL have been rarely considered as a weapon against cancer. However, studies highlighting the anti-tumor efficacy of PMNL have been published. For example, suppression of the secreted protein acidic and rich in cystein, which is associated with the capacity of tumor cells to migrate and invade tissues, in malignant cells, led to the promotion of PMNL recruitment and induced tumor rejection[127]. However, the mode of action of PMNL that leads to the killing of tumor cells is not fully understood. It probably depends on the maturation of PMNL since in an animal model of lung tumors, only a subpopulation of PMNL i.e. TAN2 had an anti-tumor effect[31]. PMNL produce cytotoxic agents such as proteases, ROS, and defensins, all of which can directly damage the target cells. However, the cytotoxic effect of PMNL on tumors is greatly enhanced in the presence of target-specific antibodies. Finally, another strong argument for the anti-cancer effect of PMNL comes from studies using animal models in which tumor cells were genetically engineered to release immunoregulatory molecules (cytokines and chemokines). These molecules did not affect the proliferation of the tumors directly, but activated a host immune reaction that was strong enough to overcome their oncogenic capacity. For instance, G-CSF-releasing colon adenocarcinoma cells were found to lose their tumorigenic activity through the massive attraction of PMNL to the tumor injection site[128]. These PMNL distinguished between G-CSF-producing and nonproducing cancer cells. Moreover, tumor inhibition *in vivo* was accompanied by intimate physical contact between PMNL and G-CSF-producing tumor cells[129]. However, future research should be done in order to better target the different subpopulations of TAN, since only one population of PMNL would have an anti-tumor effect and should be considered.

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