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Commentary

Inflammation, Aging and Colorectal Cancer

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Ageing is associated with mental and physical deterioration and decreased physiological reserves. Acquired and genetic factors may contribute to the diseases, commonly associated with ageing. Non-familial manifestations of cancer, atherosclerosis, demyelinating disorders, type II diabetes are the most common disorders associated with ageing. Increased levels of circulating inflammatory cytokines are present in age-related diseases [1-3].

The relationship between ageing and related disorders can be explained by the obvious prolonged exposure to noxious factors. Many gene mutations correlated to colorectal cancer evoke inflammatory responses. Mutations in these genes can bring to activation of pro-inflammatory mediators [4,5]. Inflammation is a physiological, defense response, to contrast pathogens. When the stimuli for inflammation persist, or the reparative action is out of control a condition of chronic inflammation can be established. Chronic inflammation is now a well-recognized risk factor for tumor development and progression [6]. Colorectal tumor cells can induce either directly or through activation of T and B lymphocytes, the release of several inflammatory cytokines like IL1, IL2, IL6, IL18 and Tumor Necrosis Factor alfa. These inflammatory cytokines stimulate cells growth and are fundamental for the inflammatory status to persist. The increased metabolism related to colorectal tumor cells accelerated proliferation determines significant oxygen consumption. The resulting acidification and hypoxia induce the production of cytokines and angiogenic growth factors, which give rise to neo-angiogenesis and lymph-angiogenesis, supporting the persistence of chronic inflammation [7,8] (Figure 1). Tumor necrosis is a well-established marker of poor prognosis in colorectal cancer, and it might represent a trigger for the presence of an immune-cell infiltrate.

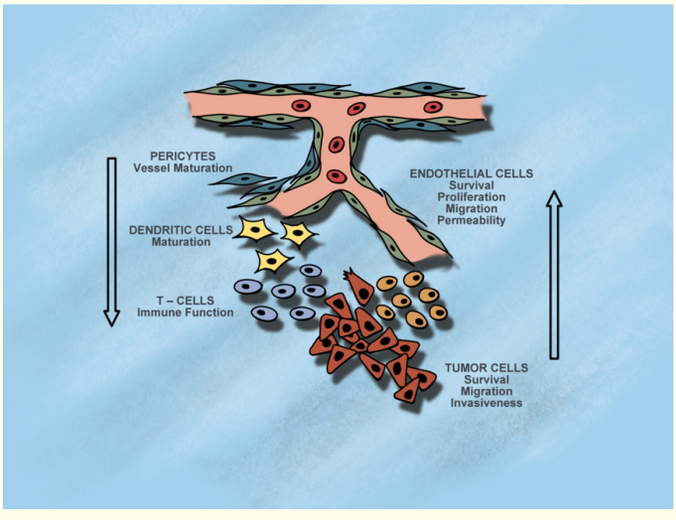

Figure 1: *Original prototype (Design Dr. J Sanguinetti).*

Inflammatory cytokines can exert their action locally, stimulating cell growth, apoptosis, reduced removal of necrotic tissue; conceptually it is possible that elevated levels of inflammatory cytokines might lead to a de-regulation of the immune system through a systemic effect [9] (Figure 2). Both the innate and the adaptive arm of the immune system undergo marked changes with age, a phenomenon to which has been given a general unspecific definition of "the process of immune-senescence".

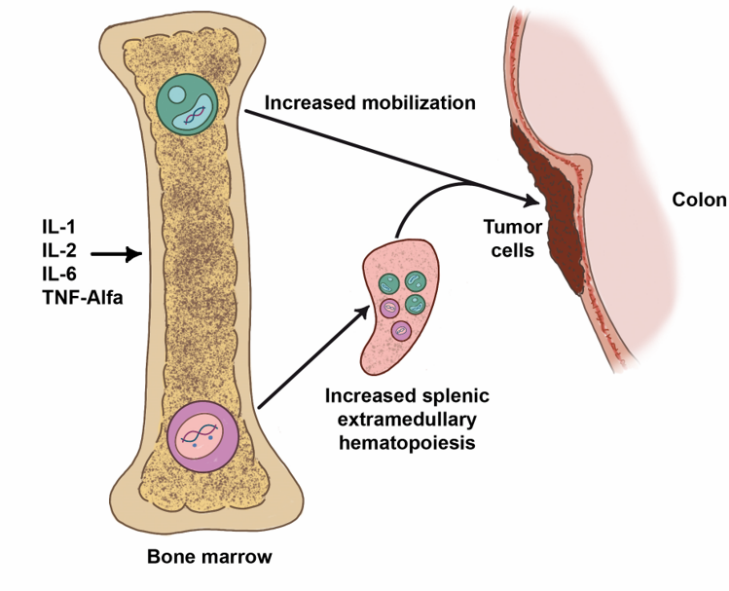

Figure 2: *Altered immunological response related with inflammatory cytokines leads to progression of colorectal cancer.*

Despite the obvious deterioration of the immune system with ageing, the innate immune system seems hyper-active in most age-related diseases as evidenced by increased serum levels of inflammatory cytokines such as IL-6, TNF-α, and acute phase proteins. Hypothetically, systemic chronic inflammation not only de regulates the central immune system, but also activates a probable genetic predisposition to an innate auto-immune system.

Chronic inflammation stimulates the hematopoietic stem cell, with the possibility of proliferation of selected clones of genetically modified cells. Most patients with colorectal cancer may host hematopoietic cell clones: this condition has been named clonal hematopoiesis of indeterminate potential (CHIP). Chronic inflammation may be a driver for ageing per se and for ageing consequences, through the general de regulation of the immune system, including the activation of specific genes devoted to promote local, un physiological cell growth and cell apoptosis [10,11].

Reduced levels of inflammatory cytokines after therapy

It has been shown that reduced systemic levels of inflammatory cytokines after therapy is a valid prognostic factor for better clinical outcomes in patients with age-related disease [9]. Persistence of elevated levels of inflammatory cytokines determines a poor clinical

outcome in patients with colorectal cancer, treated by chemotherapy and/or surgery [12,13]. There is the possibility that the activation of genetically-determined hemopoietic clones, by prolonged chronic inflammation, has a cut-off limit, which once it has been overcome, there is no possibility for regression.

Anti-inflammatory therapy for age-related diseases.

Globally, the regional incidence of colorectal cancer varies over 10-fold. These geographic differences appear to be attributable to dietary and environmental exposures. Death rates for colon-rectal cancer have declined progressively since the mid-1980s in the United States and in many other western countries [14,15]. This improvement in outcome can be attributed to detection of diseases at an earlier stage, screening programs and more effective primary and adjuvant treatments. However, in the United States and western countries, the decline in cancer mortality, adjusted for age and sex, started well before the widespread implementation of screening and before effective adjuvant therapy became widely used. Mortality rates continue to increase in countries with limited resources and health infrastructure, particularly in Central and South America and Eastern Europe. Theoretically, part of this reduced mortality in western countries, might be related with the widespread use of anti-inflammatory drugs and antibiotics, with reduced rates in the population of low grade inflammatory stimuli.

Aspirin and non-steroidal anti-inflammatory drugs have been shown to reduce the prevalence of colorectal cancer [16]. Both drugs have a generic anti-inflammatory action. A reduced risk of colorectal cancer is evident in inflammatory bowel disease-related colorectal cancer for patients treated with statins [17-20]. New targeted drugs, with a more selective action, have been developed and applied in the clinical setting not rarely with unexpected findings [21-23].

At the present the hypothesis that anti-inflammatory drugs might have a systemic action in preventing the age-associated immune deregulation is attractive, and the subsequent questions include a potential role for anti-inflammatory drugs to prevent ageing per se. The possibility that activation of mutated clones and CHIP, after a while, can be irreversible, implies the need for an aggressive treatment of any form of inflammation, especially after 40 years of age.

Declaration of Interest

The author has no conflicts of interest to declare.

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