

# Innate Inflammation and Cancer: The Colorectal Carcinoma Paradox

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## Editorial

Among innate immune cell populations, Natural Killer (NK) cells and macrophages have an important cytotoxic potential against tumor cells. Numerous papers often define NK cells as potent cytotoxic cells playing an important role in the host defence against tumor and viral infected cells. In autologous or HLA-matched setting, NK cell cytotoxicity is triggered by a series of full or accessory, activating, receptors [1-4] while is inhibited by killer inhibitory receptors. Killer inhibitory receptors bind group of host's HLA-class I antigens preventing NK cell autoimmunity. Based on their anti-tumor activity, NK cells are considered powerful candidate for adoptive cancer immunotherapy [5].

Tumor Associated Macrophages (TAMs) are functionally divided in two major populations: 1) M1 macrophages, producing pro-inflammatory cytokines; exerting strong cytotoxic properties and anti-tumor activity and 2) M2 macrophages are anti-inflammatory cells stimulating tumor cell proliferation, progression and angiogenesis [6,7].

Often NK and TAMs are components of the inflammatory infiltrates of the tumor microenvironment of epithelial malignancies and although, some reports support the idea that NK cell infiltration of malignant microenvironment positively affects the prognosis of solid tumor bearing patients [8-10], a clear evidence of a clinicopathological role of NK cells in common epithelial malignancies has not been demonstrated. In contrast, literature data strongly suggest that TAMs infiltration in the solid tumor microenvironment is prevalently composed of M2 macrophages. Thus, inflammation is involved in the pathogenesis of solid tumors. In some situations, inflammation is present in the tumor microenvironment and contributes to tumor progression or actively interferes with its development. In other situations, inflammation is present in pre-cancerous lesions and may contribute to increased cancer risk [11].

The inflammation of Colorectal Carcinoma (CRC) microenvironment, in virtue of its particular organ microenvironment, rich of bacterial flora, may strongly influence CRC pathogenesis. Thus, the question to be asked is: What is the clinicopathological role of innate inflammation in CRC? Based on the literature data and our clinical and laboratory experiences gained within the last 5 years, it is possible to state that, among common epithelial tumors, inflammation of the CRC microenvironment represents a curious exception since NK cell infiltration is negligible and, when it is present it does not affect CRC growth while TAMs infiltration is an extremely favourable and independent prognostic factor [12].

As mentioned above, a few studies have shown that NK cells infiltration in colorectal, gastric and lung carcinomas was a favourable prognostic factor [8-10]

However, at least in CRC, NK cells were barely detectable in the tumor milieu [12] or even in the presence of NK cells; there was no impact on CRC patients' survival [12]. Lack of NK cell infiltration was not limited to CRC but was also present in other common malignancies including renal cell [13], breast and hepatocellular carcinomas (Sconocchia et al. [2] unpublished results).

The idea that TAMs in CRC have a completely different behaviour than that observed in other solid tumors, was supported by Forssell et al. [14] who showed that a rich infiltration of CD68+TAMs in the tumor front correlated with survival in colon cancer and by Zhou et al. [15] who showed that the density of macrophages in the invasive front inversely correlated to liver metastasis of colon cancer [15]. Further studies have attempted to investigate whether the protective effect of macrophages in CRC was dependent on a generic or a specific macrophage subpopulation infiltration. Phenotypic analysis of CRC microenvironment, obtained in our laboratory, showed that rich macrophage infiltration composed of CD16+HLA-DR-CD11c+CD11b+CD68+ cells subpopulation was a favourable, independent, prognostic factor predicting survival of CRC patients while the presence of a generic CD68+CD16- cell population without a specific area of CRC infiltration was not. These results were also confirmed by an institutionally independent study [12]. As a consequence of this finding, it is possible to consider that, in virtue of the unique tissue situation in which CRC develops, a specific population of CD16+ TAMs may be recruited and expanded. Interestingly, the indicated hypothesis could not be confirmed since CD16+ TAMs are widely demonstrated in several solid tumor microenvironments of renal cell, breast, and hepatocellular carcinomas as well as in melanoma. More importantly, at least in renal cell carcinoma [13] and breast carcinoma the presence of CD16+ TAMs is a negative or indifferent prognostic factor. To date, the reason why CD16+TAMs infiltration of CRC is a protective factor is unknown. Currently, my laboratory is actively involved in the characterization of these cells. To be noted, in the CRC microenvironment, CD16+TAMs do not express HLA-DR antigens and morphologically do not resemble polymorphonuclear cells. The comparison between CD16+TAMs of CRC with CD16+TAMs of melanoma and breast carcinoma show that CD16+TAMs of CRC were HLA-DR- while CD16+ TAMs of melanoma and breast carcinoma were generally HLA-DR+.

Thus, these cells derived from granulocytes or monocytes? The correct answer to this question may open up a window for future translational studies whose objective will be to target CRC microenvironment by recruiting and expanding CD16+ TAMs utilizing granulocytes colony stimulating factor or monocyte colony stimulating factor in patients with early and advanced CRC.

In conclusion, the clinicopathological role of innate immune cells in the CRC microenvironment is becoming clearer since, the role of

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NK cells is marginal while the role of at least CD16+ macrophages is critical either as prognostic marker or as potential tool for targeting CRC. The remaining question would be whether or not CD16+ TAMs are functionally M1 macrophage however, for answering this question further studies are necessary.

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