Gastric Cancer (2017) 20:215–216
DOI 10.1007/s10120-016-0596-2

LETTER TO THE EDITOR

Tumor-associated macrophages in gastric cancer: more than bystanders in tumor microenvironment

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Received: 4 December 2015 / Accepted: 20 January 2016 / Published online: 19 February 2016

Dear Editor,

Two very interesting articles recently published in *Gastric Cancer* [1, 2] added new light to the relevance of tumor-associated macrophages, not only for tumor biology but also for the prognosis of gastric cancer patients.

The results published by Zhang et al. [1] demonstrate the prognostic significance of polarized tumor-associated macrophages (TAMs) for gastric cancer patients, and when combined with the TNM staging system may provide a useful tool for prognosis. Additionally, Yamaguchi et al. [2] reported that intraperitoneal TAMs of gastric cancer patients with peritoneal dissemination were polarized to the M2 phenotype, thus contributing to tumor progression.

Macrophages are a crucial switch in the tuning machinery of inflammatory and host immune response, and they are present in most, if not all, solid tumors. Both clinical and experimental evidence suggest that TAMs have emerged as a critical regulatory cell type in the tumor microenvironment, supporting tumor growth and metastasis.

In analogy to the dichotomic states used to initially classify mouse T-helper cells into Th1 and Th2 phenotypes, macrophages are known to undergo a polarization process resulting in two extreme phenotypes, the M1, or "classically activated," macrophages, and the M2, or "alternatively activated," macrophages. TAMs display several characteristics of the M2 phenotype, which, by contrast to M1, are associated with immunosuppression, promotion of tumor growth, angiogenesis, and metastasis [3, 4].

Data recently published by our group [5] are consistent with the general conclusions stated in both articles. Our data showed how the alarmin HMGB1, highly abundant in the tumor microenvironment and particularly relevant for gastric cancer [6], enhances the protumoral activities of M2 macrophages, promoting the invasiveness capacity of cocultured MKN-45 gastric cancer cells and increasing the production of both metalloproteinase-9 and mucin-1 in these tumor cells. Additionally, culture supernatants of HMGB1-stimulated M2 macrophages increased the formation of new blood vessels. All these activities are mediated by a mechanism dependent on the expression of the receptor for advanced glycation end products (RAGE), as RAGE targeting knockdown abrogated all these activities.

Of note, Murray et al. [7] have recently highlighted that M1 and M2 polarized phenotypes represent only two extreme phenotypes in macrophage heterogeneity spectrum, and therefore it is imperative to unify experimental standards for diverse experimental scenarios. Although the results obtained by Yamaguchi and our own findings have some limitations because both were attained using the biased two extreme phenotypes (M1 and M2) approach, the significance of TAMs in gastric cancer should be equally considered.

For many years, many attempts to correlate tumor-associated macrophages and prognosis have failed. Most of these studies have considered the intratumoral macrophage population as a whole, without any distinction of the relative abundance of macrophage/phenotype populations.

However, these new data, independently published, clearly support that we must consider TAMs as very active

This comment refers to the article available at doi:10.1007/s10120-015-0488-x.

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factors in tumor biology, where immune status based on TAM phenotype does correlate with both progression and prognosis of gastric cancer. Finally, and not less important, is that this tumor-infiltrating cell population phenotype may also contribute to the outcome of many of the current therapeutic approaches in cancer [8].

Acknowledgments This work was supported by Grant 1130337 from Conicyt, Chile.

Compliance with ethical standards

Conflict of interest The authors have declared no conflicts of interest.

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