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World J Gastroenterol 2005;11(44):7054-7056
World Journal of Gastroenterology ISSN 1007-9327

Immunosurveillance function of human mast cell?

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Received: 2005-05-24 Accepted: 2005-07-08

Abstract

Mast cell (MC) is so widely recognized as a critical effector in allergic disorders that it can be difficult to think of MC in any other context. Indeed, MCs are multifunctional and recently shown that MCs can also act as antigen presenters as well as effector elements of human immune system. First observations of their possible role as anti-tumor cells in peri- or intra-tumoral tissue were mentioned five decades ago and a high content of MCs is considered as a favorable prognosis, consistent with this study. Believers of this hypothesis assumed them to be inhibitors of tumor development through their pro-apoptotic and -necrolytic granules e.g., granzymes and TNF-α. However, some still postulate them to be enhancers of tumor development through their effects on angiogenesis due to mostly tryptase. There are also some data suggesting increased MC density causes tumor development and indicates bad prognosis. Furthermore, since MC-associated mediators have shown to influence various aspects of tumor biology, the net effect of MCs on the development/progression of tumors has been difficult to evaluate. For instance, chymase induces apoptosis in targets; yet, tryptase, another MC protease, is a well-known mitogen. MCs with these various enzyme expression patterns may mediate different functions and the predominant MC type in tissues may be determined by the environmental needs. The coexistence of tryptase-expressing MCs (MC_T) and chymase and tryptase-expressing MCs (MC_{TC}) in physiological conditions reflects a naturally occurring balance that contributes to tissue homeostasis. We have recently discussed the role and relevance of MC serine proteases in different bone marrow diseases.

Key words: Mast cell; Immunosurveillance; Tryptase-chymase; Cytotoxicity; Tumors

Özdemir Ö. Immunosurveillance function of human mast cell? *World J Gastroenterol* 2005; 11(44): 7054-7056
http://www.wjgnet.com/1007-9327/11/7054.asp

LETTER TO THE EDITOR

I read the article by Tan *et al*[1] describing `prognostic significance of cell infiltrations of immunosurveillance in colorectal cancer with great interest. My interest in this study is that we have recently demonstrated human mast cell (MC) mediated cytotoxicity against different human leukemia and lymphoma tumor cells *in vitro*[2-4]. Our *in vitro* results seem to support their study conclusion of MC cytotoxicity against tumor cells that might contribute to immunosurveillance *in vivo*. The genuine role of MC in tumor stroma has been a very controversial topic for the past five decades and needs still further clarification. Here, I have discussed further primarily the anti-tumor effects of MC in the light of recent literature and our findings.

MC is so widely recognized as a critical effector in allergic disorders that it can be difficult to think of MC in any other context. Indeed, MCs are multifunctional and recently shown that MCs can also act as antigen presenters as well as effector elements of human immune system. First observations of their possible role as anti-tumor cells in peri- or intra-tumoral tissue were mentioned five decades ago and a high content of MCs is considered as a favorable prognosis, consistent with this study[1,5,6]. Believers of this hypothesis assumed them to be inhibitors of tumor development through their pro-apoptotic and -necrolytic granules e.g. granzymes and TNF-α. However, some still postulate them to be enhancers of tumor development through their effects on angiogenesis due to mostly tryptase. There are also some data suggesting that increased MC density causes tumor development and indicates bad prognosis[7,8]. MCs with these various enzyme expression patterns may mediate different functions and the predominant MC type in tissues may be determined by the environmental needs. Furthermore, since MC-associated mediators have shown to influence various aspects of tumor biology, the net effect of MCs on the development/progression of tumors has been difficult to evaluate. For instance, chymase induces apoptosis in targets; yet, tryptase, another MC protease, is a well-known mitogen. We have recently discussed the role and relevance of MC serine proteases in different bone marrow diseases[9]. The coexistence of tryptase-expressing MCs (MC_T) and chymase and tryptase-expressing MCs (MC_{TC}) in physiological conditions reflects a naturally occurring balance that contributes to tissue homeostasis.

In the past two decades, it was believed that murine MC has natural cytotoxicity in the long term (>24 h) against murine tumor cells (WEHI-164, L929, etc.) by different mechanisms e.g. TNF-α dependent and non-TNF-α dependent[10]. Recent studies suggested that MC

can kill targets through degranulation of serine proteases, cathepsin G, leukotrienes and NO. Lately, MCs have been shown to contain granzyme B[11] and express Fas ligand[12], which are the most important components of cell mediated cytotoxicity. Chymase was also demonstrated to induce apoptosis in neonatal rat cardiomyocytes and human vascular smooth muscle cells[13]. Thus, MC mediated cytotoxicity seems to be operated by at least 2 pathways: by secretory pathways via exocytosis of granules containing serine proteases such as granzymes, chymase and soluble TNF-α; and nonsecretory (cell-to-cell contact) pathways via membranous TNF-α and FasL. We are the first to show human MC cytotoxicity against NK-sensitive/resistant human leukemia/lymphoma cells in short and long term by our established flow cytometric method[2-4]. Our studies suggested that increased chymase content of MCs in long-term culture could have played a role to mediate cytotoxicity.

Tan *et al*[14] demonstrated in this study that both MCT and MCTC may equally proliferate or infiltrate in colorectal cancer similar to hepatocellular carcinoma and intrahepatic cholangiocarcinoma, consistent with some earlier literature. In contrast to these reports, in some malignant lesions, MCT`s were found to be concentrated at the tumor edge, i.e., the "invasion zone," whereas MCTCs were not increased in this area[15-17]. For instance, a significant increase of MCT phenotype was observed in the invasive carcinoma of the cervix throughout the different stages of malignant transformation. Furthermore, an abundant MCT (but not MCTC) increase was detected infiltrating the tumors in sections of invasive carcinoma although the number of MCT was shown to be similar to that of MCTC in benign lesions. Malignant tumors had 2 to 3 times more MCT than MCTC and the number of MCT was noted to be significantly higher in malignant than benign lesions.

Our studies and past literature review suggest that increase of MC density in tumor stroma is as important as the phenotypic change[18,19] causing predominance of one phenotype. Consistent with this study, if chymase containing MCs (MCTC/MCC) were dominant over MCT in tumor stroma, this would usually be predictor of good prognosis such as in localized bronchioloalveolar carcinoma[20] and human renal tumors[21]. In contrast to this opinion, there are a few data suggesting that MCTC/MCC are related to a bad prognosis e.g. lip and some gastrointestinal cancers[22,23]. Nevertheless, overall chymase content of granules in MCs as well as timing of biopsy and other factors could be also important in these exceptional cases. If MCT`s were dominant over MCCT/MCC, this would be a bad prognostic factor such as in cervix cancer, B-cell non-Hodgkin's lymphoma and others[24,25]. Mounting evidence certainly indicates that MCs accumulate around the tumors and could either promote or inhibit tumor growth depending on the local stromal conditions[26]. These findings overall emphasize the role of MCT type in the tumor development rather than chymase containing MCs (MCC and/or MCCT) but this requires further studies and clarification. My personal conclusion is that inhibitory or proliferative effects of MCs depend on multiple interactions among MC, tumor type and the environment.

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