Chymase is a protease found in mast cell granules with a variety of enzymatic functions. Chymase converts angiotensin I to angiotensin II, which is closely involved with angiogenesis by activating vascular endothelial growth factors (VEGF) and matrix metalloproteases (MMP).

As suggested by Akgul and Noon, chymase-positive mast cells may be closely involved with fibrosis of the heart [1]. We previously reported that chymase converted the precursor of transforming growth factor (TGF-β) to its active form in cultured fibroblasts [2]. In addition, using hamsters with myocardiopathy, we confirmed that the number of chymase-positive mast cells increased as cardiac fibrosis advanced and that chymase inhibitors suppressed cardiac fibrosis. Since TGF-β is known to facilitate cardiac fibrosis, we also believe that chymase-positive mast cells facilitate cardiac fibrosis via TGF-β activation [2].

However, in hamsters grafted with a sponge, chymase facilitated angiogenesis via angiotensin II production [3]. Akgul and Noon suggested that, in general, angiogenesis and fibrosis are opposing phenomena. Tumor cells produce basic fibroblast growth factor (bFGF), which aids fibroblast proliferation and angiogenesis in stage I non-small cell lung cancer [4]. Increased MCD might be a reflection of generalized inflammatory reaction, e.g., in breast cancer. Could any MC subtype have a specific role? Increased MCD may not associate with proportional changes of subtypes, which could be modified by their environment. In contrast with this study, no proportional change was detected in hepatocellular carcinoma. Authors demonstrated MCCT as a prognostic indicator, e.g., in lip cancer, as opposed to renal colorectal carcinoma. Chymase also induces apoptosis in endothelial cells and the accumulation of tumor-associated macrophages indicating MC cytotoxicity besides its effect on matrix metalloproteinase-9, similar to our findings [2].

Increased MCD is neither always associated with bad prognosis nor angiogenesis. It can also indicate a better survival such as in soft tissue sarcomas. Earlier studies showed increased tumor development in MC-deficient mice as well as no significant difference between MC-deficient and sufficient mice for the angiogenesis. Recent studies also found no significant association between angiogenesis and MCD such as in ovarian cancer, even with NSCLC [3]. If MC always induces angiogenesis, how do authors explain the lack of correlation between angiogenesis and systemic MC diseases.

Although it is hard to explain these conflicting results, they may be due to variations in the timing of the study, tumor types as well as methodologies. No standardized scheme is yet available to assess the angiogenesis. Heterogeneity of endothelial cell marker expressions even in a tumor is well known. CD105, proliferation marker, proved to be superior to pan-endothelial marker (CD34) in NSCLC [4]. Utilizing these markers facilitates the vascular status estimation but may not show the angiogenic status. Some tumors are vascularized without significant angiogenesis by vascular mimicry. Authors did not mention microvessel density (MVD) of the normal region in this study. Also, since given standard deviations are so high, the assumed MVD...
increase raises a suspicion. Moreover, mean MVD was reported to be 80 in NSCLC using same methodologies [5]. Choosing an evaluation zone in a tumor stroma is another dilemma. Recently, increased tumor islet MCD in NSCLC noticed as favorable.

Finally, anti-angiogenic effect of tranilast occurs not by simply MC stabilization rather via its overall inhibiting effect on macrophage cytokine release, fibroblast, and smooth muscle proliferation. Only observing increased MCD in a tumor with bad/good prognosis on pathological specimens seems to be far behind to explain the role of MCs.

References


Reply to Ozdemir

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The fact that mast cells are present in large numbers around cancers is well known; further, mast cells contain many angiogenesis factors. Many reports have indicated the involvement of mast cells in cancer angiogenesis. In our report, we demonstrated that chymase-positive mast cells are involved in angiogenesis around stage-1 non-small cell lung cancers suggesting the possibility that chymase is involved in cancer angiogenesis [1]. However, Ozdemir et al. [2] found that mast cells which were differentiated from bone marrow mononuclear cells inhibited tumor cell growth in vitro and concluded that mast cells have antitumor activities.

Although Ozdemir cited reports that found no tumor suppression in mast cell-deficient mice, many reports, to the contrary, documenting tumor suppression in mast cell-deficient mice have been made. Also, he mentioned reports that, unlike our study, found no correlation between the number of vessels and the concentration of mast cells. These differences in outcome may suggest that the roles of mast cells differ depending on tumor type and progression. We have reported, using animal models, that local chymase injection strongly facilitates angiogenesis [3]. Recently, we documented that there was a strong correlation between the number of vessels and the concentration of chymase-positive cells around stomach cancers and that the postoperative survival rate for patients with high chymase-positive cell concentrations was lower when compared to patients with low chymase-positive cell concentrations [4]. These results strongly suggest the possibility that chymase facilitates angiogenesis, thus subsequently advancing cancer growth.

The functions of mast cells around cancers cannot be ascertained based solely on our results. However, based at least on our past studies, chymase-positive cells are involved in cancer angiogenesis. Yet, as stated by Ozdemir, mast cells contain many substances that facilitate angiogenesis and substances that are toxic to cancer cells. Hence, the roles of mast cells may differ depending on cancer differentiation and progression. Not all mast cells contain chymase, and its expression is seen in only about half the cells. Therefore, we would like to strongly emphasize that whether or not mast cells contain chymase is a very important point. However, clarifying the role of chymase-positive mast cells in angiogenesis and cancer growth will require clinical study using a chymase inhibitor.

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Letter to the Editor

Early removal of chest drainage and outpatient program after videothoracoscopic lung biopsy

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