Foreign Body Reactions-Induced Cancer Metastasis

Lanxiao Wu, Cheng-Yu Ko, Liping Tang
Bioengineering Department, University of Texas at Arlington

Statement of Purpose: Inflammatory responses have been implicated to play an important role in cancer metastasis.(1) On the other hand, biomaterial implants have been shown to trigger different extent of localized inflammatory responses. We thus assumed that foreign body reactions may be used as a means to attract metastatic tumor cells. Indeed, our pilot studies have shown that large numbers of migrating tumor cells are recruited to the tissue surrounding biomaterial implants. This work is aimed at determining the mechanisms of foreign body reactions-mediated cancer cell recruitment.

Methods: To trigger different extent of foreign body reactions, PLLA particle (8.23 ± 2.12 μm in diameter), aluminum hydroxide particle (10 μm in diameter, Alhydrogel 85, Superfos Biosector A/S Corporation), and glass beads (450-500 μm in diameter, Glasperlen, B. Braun Melsungen Corporation) were used in the study. Specifically, microparticles were subcutaneously implanted on the back of C57BL/6 mice for 24 hours. Metastatic melanoma cells (B16F10) were then transplanted into peritoneal cavity. After cell implantation for different periods of time, microparticle implants and their surrounding tissue were recovered for immuno-hiostochemistry (IHC) analyses of immigrated cancer cells (HMB-45+) and imflammatory cells (CD11b+). Based on the results shown in recent literatures, we have hypothesized that cancer cells migrate from peritonea to lymphatic system via CCR7/CCL21 pathway. Thereafter the circulating cancer cells are recruited to the implantation sites via CXCR4/SDF-1 pathway. To test these hypotheses, particle implanted animals were injected intraperitoneally with either AMD3100 (CXCR4 antagonist, 250 μg/0.1 ml/mouse) or CCL21 neutralizing antibody (1 mg/0.1 ml/mouse) 1 hour prior and 12 hours post tumor injection. At the end of the study, lymph nodes, microparticle implants, and their surrounding tissue were recovered for IHC analyses. Statistical analyses between different groups were carried out using Student t- test.

Results: To directly test the influence of inflammatory responses on melanoma cell migration, studies were carried out using particles with different tendencies to prompt inflammatory responses. Very interestingly, we found that the number of tumor cell around PLLA particle implants was more than those around aluminum hydroxide and glass bead implants (Figure 1). Furthermore, we found an excellent correlation (R^2=0.92) between the extent of inflammatory reactions (reflected by the accumulation of CD11b+ cells) and melanoma cell recruitment. These results lend strong support to our hypothesis that inflammatory responses play an important role in melanoma cells migration and, perhaps, metastasis. Further studies were carried out to determine the molecular mechanism of foreign body reactions-induced cancer metastasis as described in the "Methods" section. As expected, the CCL21 neutralizing antibody treatment substantially reduced melanoma cell accumulation in lymph node (Figure 2A), but not in the skin, indicating that CCR7/CCL21 is essential to cancer cell migration in lymphatic system. Furthermore, CXCR4 antagonist is found to effectively reduce (>50%) cancer cell accumulation in the implantation site (Figure 2B) suggesting that CXCR4/SDF-1 is required for cancer cell migration into particle implantation sites.

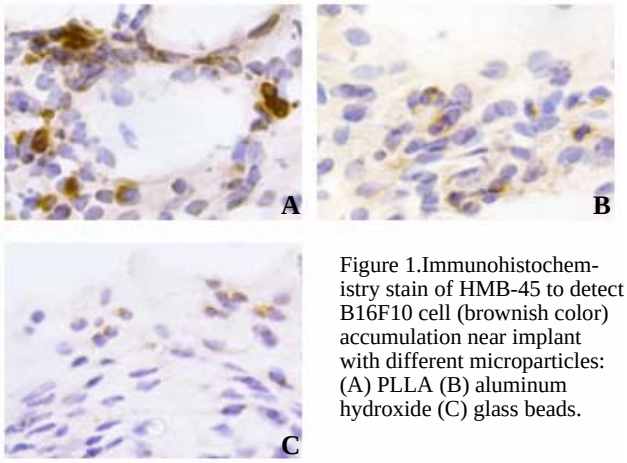

Figure 1.Immunohistochemistry stain of HMB-45 to detect B16F10 cell (brownish color) accumulation near implant with different microparticles: (A) PLLA (B) aluminum hydroxide (C) glass beads.

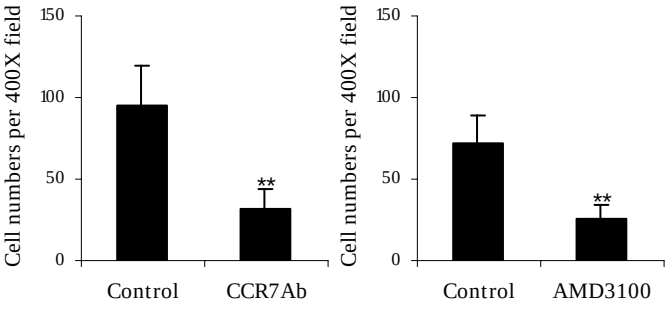

Figure 2. Effect of (A) CCL21 neutralizing antibody, and (B) AMD3100 on melanoma cell recruitment. **: P<0.01.

Conclusions: Our results presented here demonstrate that biomaterial-mediated inflammatory responses may trigger the migration of cancer cells from distal area (periotoneal cavity) to the implantation site (subcutaneous space). Our results suggest that cancer cells migrate from peritonea to lymphatic system via CCR7 receptor and from circulation to particle implantation site via SDF-1 chemokine. It is our belief that these new findings may allow us to develop novel therapies to reduce or eliminate cancer metastasis by removing migrating metastatic cells from circulation.

References:

1. Aggarwal BB. Biochem Pharmacol. 2006;72(11):1605-1621.