ImmunoTools *special* Award 2015

Adriana Bonomo, MD, PhD

FIOCRUZ, FIO-CÂNCER PROGRAM,
Laboratório de Pesquisa sobre o Timo
Av. Brasil, 4365. Pavilhão 26/ SALA: 506 Manguinhos
CEP 21040360 Rio de Janeiro Brazil

Adaptive Immunity and its influence on the metastatic niches

The role of the immune system in controlling cancer was first hypothesized more than one hundred years ago (*reviewed in Schreiber et al., 2011*). However, the concept of Immunosurveillance as a response of the adaptive immune system came up with the proposition of the Clonal Selection Theory by Burnet (*reviewed in Schreiber et al., 2011*) and the demonstration that tumor specific antigens in fact exist (*Old and Boyse, 1964*). More recently, experiments in which tumor cells originally grown in immunocompromised hosts were transplanted into syngenenic immunocompetent animals showed that part of these tumor cells were eliminated, but not the whole tumor mass, indicating a role for the immune system in "selecting" malignant cells (*Matsushita et al., 2012; DuPage et al., 2012*). This confirms the proposition that, besides immunosurveillance, the immune system could shape the tumor in a process named "immunoediting" (*Dunn et al., 2002; Schreiber et al., 2011*). Immunoediting comprises elimination (surveillance), equilibrium (selection), and escape, adding the possibility of a pro-tumoral activity to the previously proposed immunosurveillance role. Once the tumor is "shaped" by the immunoselection mechanisms, it will be in equilibrium with the host immune system, until it can escape.

Regarding modulation of the immune system, tumor cells might express co-inhibitory molecules and secrete cytokines that will eliminate or subvert the immune response (*Zitvogel et al., 2006; Schreiber et al., 2011; Pardoll, 2012*). Tumor associated macrophages (TAM), had been shown to play important pro-tumorigenic and lung metastatic activity as M2 subtype (*Lin et al., 2001; Joyce and Pollard, 2009*) and are associated with a poor prognosis in breast cancer (*DeNardo et al., 2011*) shown to be critical for lung metastasis establishment,

Regarding bone metastasis, it is clear that osteoclasts (a specialized bone macrophage), play important role in creating a hospitable environment for tumor cell colonization of the bone, configuring a vicious cycle (*Mundy, 2002; Roodman, 2004*). However, if T cells play any role, in cancer induced bone disease is not known (*Noonan et al., 2010; Fournier et al., 2006*).

The presence of T cells in the bone cavity has been well documented. Bone marrow $CD4^+$ T cells are involved in the control of normal hematopoiesis (*Monteiro et al., 2005*) and are present in the hematopoietic stem cell niche (*Fujisaki et al., 2011*), which is also occupied by cancer metastasis (*Shiozawa et al., 2011*). As an active component of the bone marrow microenvironment (*Di Rosa, 2009; Pacifici, 2010*), $CD4^+$ T cells have also been found to have an impact on the bone remodeling process through the induction or the regulation of molecules involved in bone metabolism (*Wong et al., 1999; Kong et al., 1999; Takayanagi et al., 2000; Takayanagi, 2009*).

Having the above in mind, we asked if T cells from mice bearing a bone metastatic tumor would play any role in the osteolytic bone disease and/or bone and bone marrow colonization. Our results showed that cancer induced bone disease starts before metastatic colonization and is mediated by RANKL expressed by tumor specific T cells (Monteiro et al, 2013), placing T cells in the center of the bone metastatic colonization process. Other cells from the adaptive and innate immune response are being studied as means to understand these mutual micro-environmental regulation of tumor growth and the immune system in order to be able to interfere with the distant disease that threatens host quality of life and survival.

References

DeNardo, D. G., D. J. Brennan, E. Rexhepaj, B. Ruffell, S. L. Shiao, S. F. Madden, W. M. Gallagher, N. Wadhwani, S. D. Keil, S. A. Junaid, H. S. Rugo, E. S. Hwang, K. Jirström, B. L. West, L. M. Coussens. 2011. Leukocyte complexity predicts breast cancer survival and functionally regulates response to chemotherapy. *Cancer Discov.* 1, 54-67.

Di Rosa, F. 2009. T-lymphocyte interaction with stromal, bone and hematopoietic cells in the bone marrow. Immunol. *Cell Biol.* 87, 20–29.

Dunn, G. P., A. T. Bruce, H. Ikeda, L. J. Old and R. D. Schreiber. 2002. Cancer immunoediting: from immunosurveillance to tumor escape. *Nat. Immunol.* 3, 991-998.

DuPage, M., C. Mazumdar, L. M. Schmidt, A. F. Cheung and T. Jacks 2012. Expression of tumour-specific antigens underlies cancer immunoediting. *Nature* 482, 405-409.

Joyce, J. A. and J. W. Pollard. 2009. Microenvironmental regulation of metastasis. *Nat. Rev. Cancer* 9, 239-252.

Lin, E. Y., A. V. Nguyen, R. G. Russell and J. W. Pollard. 2001. Colony-stimulating factor 1 promotes progression of mammary tumors to malignancy. *J. Exp. Med.* 193, 727-740.

Matsushita, H., M. D. Vesely, D. C. Koboldt, C. G. Rickert, R. Uppaluri, V. J. Magrini, C. D. Arthur, J. M. White, Y. S. Chen, L. K. Shea, J. Hundal, M. C. Wendl, R. Demeter, T. Wylie, J. P. Allison, M. J. Smyth, L. J.

Old, E. R. Mardis and R. D. Schreiber. 2012. Cancer exome analysis reveals a T-cell-dependent mechanism of cancer immunoediting. *Nature* 482, 400-404.

Monteiro, J. P., A. Benjamin, E. S. Costa, M. A. Barcinski and A. Bonomo. 2005. Normal hematopoiesis is maintained by activated bone marrow $CD4^+$ T cells. *Blood* 105, 1484-1491.

Monteiro AC, Leal AC, Gonçalves-Silva T, Mercadante AC, Kestelman F, Chaves SB, Azevedo RB, Monteiro JP, Bonomo A. 2013 T cells induce pre-metastatic osteolytic disease and help bone metastases establishment in a mouse model of metastatic breast cancer. *PLoS One.* 2013 Jul 18;8(7):e68171. doi: 10.1371/journal.pone.0068171

Mundy, G. R. 2002. Metastasis to bone: causes, consequences and therapeutic opportunities. *Nat. Rev. Cancer* 2, 584-593.

Old, L. J. and E. A. Boyse. 1964. Immunology of experimental tumors. *Annu. Rev. Med.* 15, 167-186.

Pardoll, D. M. 2012. The blockade of immune checkpoints in cancer immunotherapy. *Nat. Rev. Cancer* 12, 252-264.

Schreiber, R. D., L. J. Old and M. J. Smyth, 2011. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. *Science* 331, 1565-1570.

Shiozawa, Y., E. A. Pedersen, A. M. Havens, Y. Jung, A. Mishra, J. Joseph, J. K. Kim, L. R. Patel, C. Ying, A. M. Ziegler, M. J. Pienta, J. Song, J. Wang, R. D. Loberg, P. H. Krebsbach, K. J. Pienta, R. S. Taichman. 2011. Human prostate cancer metastases target the hematopoietic stem cell niche to establish footholds in mouse bone marrow. *J. Clin. Invest.* 121, 1298-1312.

Takayanagi, H. 2009. Osteoimmunology and the effects of the immune system on bone. *Nat. Rev. Rheumatol.* 5, 667-676.

Zitvogel, L., A. Tesniere and G. Kroemer. 2006. Cancer despite immunosurveillance: immunoselection and immunosubversion. *Nat. Rev. Immunol.* 6, 715-727.