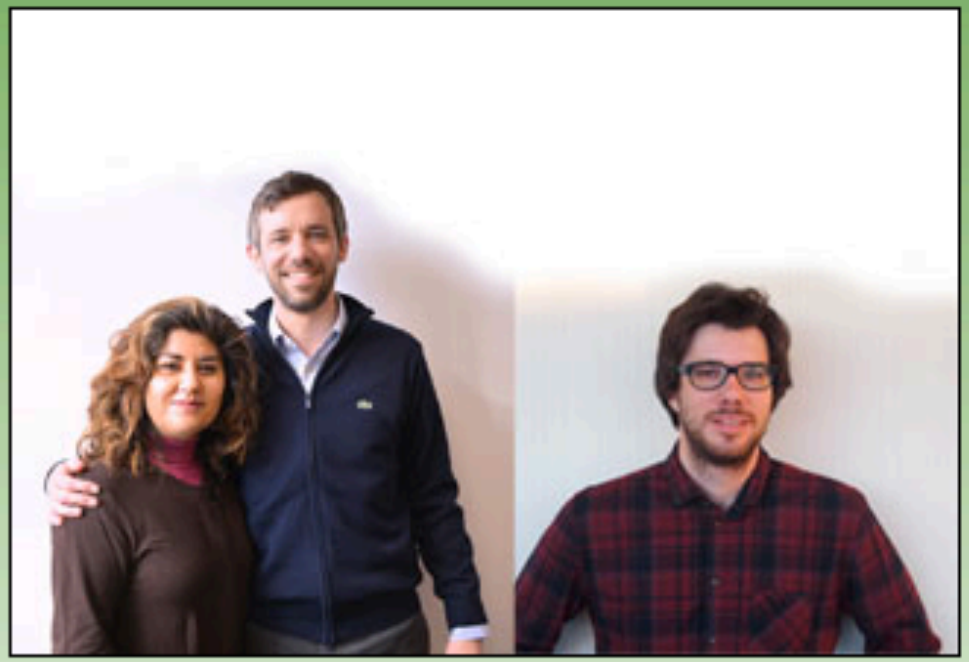
Excerpts from the Current Issue



Virna Cortez-Retamozo, Mikael Pittet, and Martin Etzrodt

HIGHLIGHTS

Angiotensin II drives tumor-promoting macrophages

Article by **Pittet and colleagues**. Preview by **Gabrilovich**.

of IL-1R1-mediated proinflammatory responses. The relevance of these findings to explain the mechanistic underpinning for various pathological conditions associated with sustained inflammation in humans now appears as a manageable challenge. Thus, what can make necrosis "silent" by keeping a lid on IL-1α? Now, the answer is clear—it is IL-1R2.

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Applying Pressure on Macrophages

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In this issue of *Immunity*, Cortez-Retamozo et al. (2013) demonstrate that the increased production of angiotensin II in tumor-bearing mice induces the expansion of macrophage progenitors and the supply of macrophages.

Macrophages contribute to all facets of tumor progression and thus are an important component of the tumor microenvironment. Their role in tumor development, angiogenesis, tumor cell invasion, and metastases is well established (Qian and Pollard, 2010) (Qian et al., 2011). For a number of years, these cells have been considered to be important negative regulators of immune responses in cancer (Mantovani and Sica, 2010) (Gabrilovich et al., 2012). In a preclinical model, the blockade of macrophage recruitment improved the survival of mammary tumor-bearing mice by slowing primary tumor development and reducing pulmonary metastasis (DeNardo et al., 2011). There is now ample evidence demonstrating that tumor-derived factors drive an increased production of macrophages in cancer. It is believed that different growth factors, such as M-CSF (CSF-1), play major roles in this process. In this issue of *Immunity*, Cortez-Retamozo et al. (2013) demonstrate that peptide hormone angiotensine II (AngII) might contribute to the increased production of macrophages in cancer by amplifying self-renewing hematopoietic stem cells and macrophage progenitors.

AngII is an oligopeptide that belongs to the renin-angiotensin system, which regulates blood pressure. Its precursor, angiotensin I (Ang I,) is derived from α2-globulin angiotensinogen produced by the liver after cleavage of a 10 amino acid peptide by renin. Ang I is converted to AngII by the angiotensin-converting enzyme (ACE). Ang II acts as a hormone to affect blood pressure via many mechanisms, including cardiovascular, renal, adrenal, and other systems. ACE inhibitors are major drugs used in the treatment of high blood pressure. Previous studies have demonstrated that AngII might promote inflammation and that it interacts with monocytes and mobilizes these cells from the splenic reservoir. In the current study, Cortez-Retamozo et al. used a mouse model of lung adenocarcinoma caused by the activation of oncogene *Kras* and inactivation of the tumor suppressor gene *p53*. These mice developed lung cancer after an intranasal infection with *Cre*-recombinase-containing adenovirus. The authors found that tumor-bearing mice had a significantly higher concentration of AngII in plasma than did control mice. Treatment of naive mice with AngII resulted in increased colony-forming activity of splenocytes, suggesting that AngII might have an effect on myelopoiesis. This conclusion was further supported by the fact that AngII-treated mice had a higher proportion of myeloid progenitors. The expansion of progenitor cell numbers occurred in the spleen but not in bone marrow. AngII is a potent regulator of hemodynamics. Thus, it might have an effect on cell mobilization and the expansion of myeloid cell numbers. To address this concern, Cortez-Retamozo et al. used vasodilator hydralazine and demonstrated that this did not affect the AngII-inducible expansion of myeloid progenitor cell numbers. Furthermore, the effect of AngII on myeloid cells was found to be mediated by its interaction

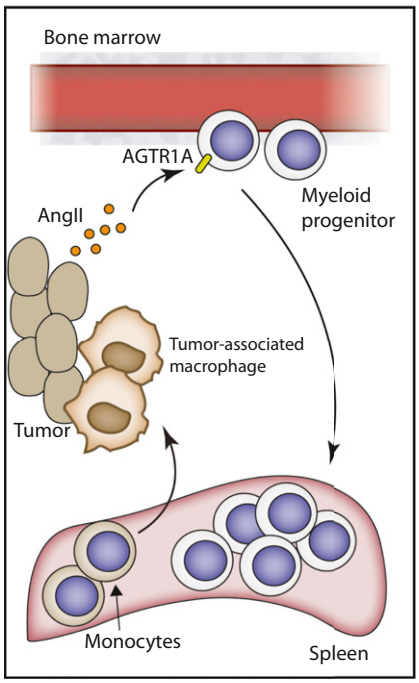

Figure 1. AngII-AGTR1A Signaling Promotes Tumor-Associated Macrophages
Bone marrow myeloid progenitors interact with tumor-produced AngII, which downregulates $S1P_1$ and causes its entrapment in spleens, where it proliferates and differentiates to monocytes. After migration to the tumor site, monocytes become tumor-associated macrophages.

with a specific receptor, AGTR1A, on hematopoietic cells but not on nonhematopoietic cells. Using an elegant parabiont experimental system, the authors demonstrated that AngII causes retention of myeloid progenitors in the spleen. This effect was mediated by downregulation of the sphingosine-1-phosphate receptor 1 ($S1P_1$), which was down-stream of AGTR1A signaling. $S1P_1$ plays a major role in regulating leukocyte egress from peripheral lymphoid organs. Thus, the inhibition of $S1P_1$ by AngII can explain the sequestration of myeloid cells in the spleen. To block AngII production, the authors used the ACE inhibitor enalapril, a drug that is commonly used in the treatment of high blood pressure. A 5 day treatment of tumor-bearing mice with enalapril did not affect tumor burden, but it did decrease the expansion of myeloid progenitor numbers. An extended 3 week treatment decreased the expansion of myeloid progenitor numbers in the spleen but not in bone marrow, and it reduced both the amplification of monocytes in the spleen and macrophage accumulation in the lungs. The number of tumor lesions in the lungs decreased significantly, and animal survival thus increased, in mice treated with enalapril but not in mice treated with hydralazine. The authors also observed the increased production of angiotensinogen in 16 out of 44 samples of non-small-cell lung cancers (NSCLCs) and found the increased expression of angiotensinogen mRNA in the publicly available data set of NSCLC tumor tissues.

This study suggests a mechanism by which tumors might control the expansion of macrophage numbers. This mechanism involves AngII mediation of the redistribution of myeloid progenitors and their increased expansion in the spleen (Figure 1). Because of the role of AngII, the study also suggests that ACE inhibitors might have a role in cancer treatment. However, as with any good research, many questions remain unanswered. The significance of these findings for cancer patients needs to be demonstrated. If a substantial proportion of cancer patients have an increased level of AngII, this should result in increased blood pressure in those patients. This would be especially evident in patients with a substantial tumor burden. However, at this moment, there is no evidence that even advanced stages of cancers are associated with high blood pressure. Moreover, large cohort studies that have involved treatment of cancer patients with ACE inhibitors have not provided clear evidence supporting the antitumor effect of these drugs (Wilop et al., 2009). It is important to point out that macrophage number expansion was not studied in those trials. In addition, the described mechanism of redistribution of myeloid progenitors to the spleen might not be directly applicable to humans because there is little evidence that the spleen in cancer patients plays as important a role as a site of extramedullary hematopoiesis does in tumor-bearing mice. The issue of the association between blood pressure and macrophage expansion also needs clarification. The authors showed that the effect of AngII was not associated with blood pressure. However, in a recent study, Jun et al. came to the opposite conclusion (Jun et al., 2012). In that study, Jun et al. showed that chronic AngII infusion resulted in a 250% increase in bone marrow inflammatory cells. This effect was substantially reduced by the attenuation of AngII-induced hypertension. Interestingly, targeted expression of ACE in monocytes and macrophages increased resistance to the growth of melanoma via enhanced immune responses (Shen et al., 2008). This suggests that accumulation of AngII in monocytes might actually promote antitumor immunity as opposed to their being an effect of AngII on myeloid progenitors. Future studies will clarify what role AngII might play in the regulation of macrophage accumulation in cancer. This report provides evidence supporting the interplay between renin-angiotensin and the immune system and provides a unique mechanism by which a tumor might control the expansion of myeloid cell numbers.

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