Reviewer 1:

Overall, this review article is very well-written and will provide readers of this new journal a very good review for tumor associated macrophages. However, as pointed out in the title, TAM serves as multi-tasking cells in the tumor microenvironment, the review majorly focus on the pro-tumor function of TAMs, neglecting the anti-tumor function of macrophages. It will be better if the authors can add a separated paragraph to describe the anti-tumor function of TAMs and discuss the possible mechanisms. Recently, some excellent studies have provided such evidence, such as PMID:21215706, PMID:24713431, and PMID:24704833.

Reviewer 2:

This review article briefly summarizes our current knowledge on the origin, phenotype and tumor-promoting functions of tumor-associated macrophages. The article also discusses some of the most important advances made in the recent years towards finding effective therapies that could target these cells in order to inhibit or delay tumor progression.

The manuscript is well-written in general, has a clear structure and cites many important papers of the field from the previous years. I could find only a few typos, however the style and vocabulary could be improved in some parts of the text that I am sure will be done after a few rereading.

I have a few further suggestions the authors may consider.

- I would change the title of the second paragraph “Tumor-associated macrophages (TAMs)” to one that is more informative, e.g. “Origin and phenotype of tumor-associated macrophages”.

- I would move the section on M1-M2 macrophages (between lines 63-85) to the second paragraph discussing the phenotype of TAMs.

- It is not clear from the text and should be more accentuated that the surface markers, cytokine/chemokine secretion, immune-suppressive activity etc. is highly dependent on the intratumoral localization of TAMs. TAMs from hypoxic/normoxic, central/peripheral/perivascular regions comprise distinct subpopulations, characterized by different marker sets and functional properties. Accordingly, it is generally true that TAMs are MHClow, however, especially in the early stages of tumor progression, we can find a significant number of MHChigh TAMs in many tumors, that have an M1-like phenotype and reside in normoxic regions. This phenomenon is highlighted by the paper of Casazza et al. Cancer Cell 2013, in which the authors showed that inhibition of the entry of macrophages into hypoxic tumor areas will keep them from acquiring many of their pro-tumoral activities. I would be glad to see this paper among the references as well.
Reviewer 3:

The manuscript of Marelli et al reviews different roles macrophages can play in cancer. In general, the review is readable, and usefully describes some new approaches being tried to boost macrophage defenses against cancer.

There are some significant suppositions about macrophages and T cells in cancer where evidence is lacking. Many statements are difficult to find origins for because they are not referenced, or the authors reference reviews that reference other reviews.

Line 23: replace “immune” with leukocyte; macs aren’t necessarily “immune”

Lines 44-46: How does one know that macrophages are “profoundly” affected by the tumor environment versus just not receiving signals that activate a killer “M1” function? Reference needed.

It is posited (line 49) that initially a host “actively eliminates antigen-expressing tumor cells”. But, references that directly support this postulate are not given. Please provide appropriate references. The authors might be reminded that long ago it was observed that “Nude” mice did not display a general increase in cancer. These and other observations do not support a normal role for so-called “immunosurveillance” in human cancer.

As mentioned, trying to trace the origins of statements about leukocytes and cancer was difficult for this reviewer. For example, the first 5 references (lines 43 and 58) are all reviews. The authors of these reviews do not seem the origin of results/beliefs that there is chronic inflammation in cancer or that the presence of macrophages in cancer is associated with progression. In particular, though Mantovani and some co authors are oft-quoted (as by the authors) as associated with pro tumor macrophages, from what this reviewer could surmise, such a view seems based in review articles, not on original results by this author. Actually, R. Prehn was an important contributor to the concept of “immunostimulation” (e.g., Science 1972) Following that, studies inside wounds and progressing tumors established that macrophages promote tumor growth. I believe Mills et al recently reviewed such studies (e.g., Frontiers 2014).

Line 59: Why is it surprising that the immune system favors tumor growth? Tumors seem to closely resemble healing wounds where macrophages are required to help repair/replace lost cells, etc. (e.g., Dvorak, NEJM 1986).

Lines 63-67: Since this article concerns cancer, it is not clear how “alternative activation” occurs. There is little or no evidence of any IL-4 inside tumors that this reviewer could find. Instead it seems that macrophages remain in their “M2” state because of lack of “M1” activation signals and/or products from the tumor environment (e.g., TGF-b, as mentioned). What is the evidence that M1-polarized macrophages produce a lot of IL-1? No references given for M1/M2 macrophages so this reviewer could not locate evidence that IL-1 is an “M1” associated product.

Line 72: References 6 and 7 are reviews/opinions; they do not provide results about suppression of Th1 inflammation, tissue remodeling or wound healing.

Line 73: The authors describe macrophages as having “several functional states”, but again without references. What are these different postulated states?
Line 118: What is the evidence that macrophages are “immune activated” early in cancer. Only a review was referenced (#29), and that did not provide clear evidence of activation either.

Line 120: In a related vein, what is the evidence that there is a switch from a type 1 to a type 2 response during tumor growth. Provide a reference please.

Line 122: As mentioned earlier, it does not appear that IL-4 is present normally in tumors. The reference cited for CD4+ T cells in cancer is a review; evidence is not provided in that review that IL-4 is actually present in tumors.

Line 128: The authors cite reference #35 as supporting that TAM simultaneously express both “M1 and M2 characteristics”. This reviewer could not find such evidence in this reference.

Lines 141-157: Somehow the authors forgot to mention the original TAM “M2” type marker, arginase. Perhaps an oversight.

Line 171: Typo “box” next to TGF-b

Line 188: I believe Hypoxia alone is an “M1” type of stimuli, but something in the tumor environment prevents this. The authors might note this.

Line 215: One can certainly understand how NO could inhibit T cells because it is a non-specific killer molecule. However, how would arginase do this in vivo. It is not clear.

Line 285: Typo, remove “the”

As I said at the outset, the review of Marelli et al is generally well presented, and provides some new information about what is going on in the macrophage/tumor immunology area. But, I believe the authors should study the sources of their information in several areas because one cannot locate supporting information from looking at many of their review-type references. This should aid the authors in restating several areas noted above so they are accurate and backed by traceable results.