Reviewer’s report

Title: Extracellular vesicles: potential applications in cancer diagnosis, prognosis, and epidemiology

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Reviewer: Vilma Martins

Reviewer’s report:

In this paper, the authors have pointed the recent progress in understanding extracellular vesicles (EVs) biology and the role of them in cancer, discussing the utility of EVs for cancer diagnosis, prognosis, epidemiology and therapeutic opportunities. Although the subject is interesting, I found that the manuscript is a bit preliminary and skinny. The following issues will need to be adequately addressed prior to acceptance for publication.

Major Concerns:

(1-) In introduction part, the authors have cited 29 references; however 20 of them are literature review. It is suggested that the authors include high impact research articles. For example, in the second paragraph, the authors could cite different manuscripts describing the extracellular vesicles secretion by platelets, neutrophils, reticulocytes, macrophages, megakaryocytes, monocytes, B and T cells, mast cells, and endothelial cells.

(2-) At the beginning the second paragraph, the authors summarized the cancer development and progression; however, they did not cite any reference.

(3-) In the third paragraph of the introduction, for the sentence “These changes include the development of EVs and release of cargo that may serve as biomarkers for disease diagnosis, prognosis, and epidemiology”, the authors cited references related to circulating tumor cells not to EVs (references 12 - 16).

(4-) About EV biogeneration, the authors have not described the endocytic and exocytic pathways. It is important describe the proteins involved in the different steps of endocytic and exocytic pathways, such as Alix, Tsg101, Rab5, Rab7, Vps4, Vps36.

(5-) In EV biogeneration part, the authors could describe in a separate paragraph the role of E6/E7 proteins in MVs composition and secretation. Moreover, they could present other proteins that are involved in the regulation of EVs releasing. Recently, Ostrowski et al. (2010) showed that Rab proteins (Rab27a and Rab27b) control the exosome secretion pathway.

(6-) In EV biogeneration part, the authors mentioned that lung cancer cells release MVs into circulation and into lung pleural effusion. The authors could develop a separate paragraph about this issue, including more research articles.

(7-) In using EVs to determine cancer aggressiveness part, the authors could describe the participation of exosomes in the formation of primary tumors and
metastases (Peinado et al. 2012).

(8-) In the page 4, line 3, the authors describe the content of EVs, and did not cited the Thakur, 2014 paper in Cell Research, where is described the presence of double-strand DNA inside EVs. Theory described by Lee in Biochemical and Biophysical research communication, 2014.

(9-) In page 9, lines 17 to 23 and page 10, lines 1 to 4, authors back talk about EVs as a biomarkers in a paragraph intended to describe the therapeutic purposes of the EVs. These sentences need to be relocated.

(10-) Is there reference to support the propose to remove vesicles to prevent metastasis and tumorigenesis (in page 11, line 2 and 3)?

(11-) In page 16, during figure description, in line 5 authors say that “exosomes also can be formed directly from the plasma membrane”, without reference. The current literature show that microvesicles can be formed directly from plasma membrane, not exosomes.

(12-) The title of the Figure 1, does not describe the entire content of the figure. The figure does not explain the process of generating EVs, and comprise others aspects not related with the title.

Minor Concerns

(1-) Page 4, line 17, maybe the authors would like to write about the involvement of EVs in intercellular communication not intracellular communication.

(2-) In figure 1B, C and D the proportions of the organelles (Golgi and Endoplasmic Reticulum), nucleus, MVB and EVs are not correct

Level of interest: An article of insufficient interest to warrant publication in a scientific/medical journal

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests' below.