Reviewer 1: Minor revision

Dear Reviewer:

Thank you for your revisions and suggestions which add value to the manuscript. Please find below line by line answers to your queries (in blue). In the revised document, your revisions are highlighted in YELLOW for your convenience.

In this paper, Dr. Vaiselbuh reviewed the roles of exosomes in cancer niche development, cancer diagnosis and prognosis as well as exo-therapy. It is a timely, helpful and detailed review of exosomes in cancer research; however, some questions need to be discussed:

1. Exosomes in the body fluid are accessible biomarkers for cancer diagnosis. However, what about their specificity, do they have markers indicating their origins and targets?

Answer: Page 10, line 5 from bottom: Reference # 74 added.

Proof of concept that exosomes represent the signature of the cancer of origin was shown in a xenograft mouse model of human lung cancer cells, labeled with human CD63-green fluorescent protein (GFP). hCD63-GFP exosomes were identified in blood and saliva of tumor bearing mice, suggestive of the link between distal tumor progression and biomarker discovery in saliva (Yang).

The reviewer raised a good point regarding specific markers indicating the origin of exosomes. The field of downstream RNA profiling of exosomes isolated from biofluids of patients with solid tumors as well as hematological malignancies is blossoming, and thus far, RNA profiles seem to be cancer-specific without common pattern for marker identification. One marker profile in metastatic melanoma patients is currently in Phase-I clinical trial (see page 9 line 6 (Peinado et al)), which might indicate a promising precedent. See also Table 2

Answer: Page 10, bottom line: Reference # 75-77 added.

Entry into target cells seems not to be an at random event either. Human brain tumors (gliomas) express an oncogenic form of the epidermal growth factor receptor, known as EGFRvIII. EGFRvIII can be 'shared' by glioma cells via horizontal transfer by oncosomes with transfer of oncogenic activity and promotion of the cancer phenotype. (AL-Nedawi). However, identification of the exosomes-target anchorage and internalization remains greatly elusive, although heparin-glycan proteins and integrins on the exosomal membrane surface have been suggested to play a role (Christianson, Clayton)

2. The methods how to isolate exosomes as well as how to analysis their contents are important for investigating exosomes in cancer research. They might be included in this review if possible.

Answer:

Page 5, line 10 from bottom: Reference # 1, 33 added.
Several detailed protocols are readily available that describe exosome isolation methods using different techniques: ultracentrifugation, OptiPrep density gradient centrifugation, ExoQuick and total exosome isolatin precipitation (Thery, Van Deun).

Page11, bottom line: Reference# 84-86, 33 added.

A consensus need to be reach on dependable isolation methods for exosome biomarker research (Van der Meel). Reproducable protocols that obtain the purest exosome fractions for downstream RNA profiling with lack of contaminating Arg02-complexes would meet the standards of clinical care (Van Deun, Mestagh, Kalra 2013).