Reviewer's report

Title: Targeting surface nucleolin with multivalent HB-19 and related Nucant pseudopeptides results in distinct inhibitory mechanisms depending on the malignant tumor cell type

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Reviewer: Yongzhang Luo

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This manuscript demonstrates that cell surface nucleolin could associate with several clients and form a 500-kDa complex. Together with these client proteins, nucleolin regulates the adhesion, migration, survival, and autoimmunity of tumor cells. Moreover, HB-19 and the Nucant pseudopeptides, two surface nucleolin antagonists, show different interference effects on epithelial tumor cells and leukemia. While this is an interesting scenario, but what is still lacking is a clear indication of the relevance for this complex in a tumor situation.

The key piece of data in the manuscript is the identification of the nucleolin-containing complex. This complex is purified by affinity chromatography via HB-19. As the author mentioned, HB-19 is a pseudopeptide that could bind the GAR domain of nucleolin, thus could compete the GAR domain-dependent interaction. Moreover, Dumler et al. demonstrate a specific association of uPAR with nucleolin and casein kinase 2 in VSMCs (Current Biology 1999). Since all of these three proteins are highly expressed on tumor cells, this complex should also been detected in the immunoblotting aliquots. However, the author did not identify this complex, indicating that the limitation of the HB-19 based affinity chromatography. It is also intriguing that only the surface nucleolin complex has been found. The nucleolin in the cytoplasm also binds with many clients. If possible, the authors should use nucleolin monoclonal antibodies as a bait to capture the complex. Or at least, the uPAR-CK2-NL complex should be examined in the lysate of the CEM cells.

Regarding the nucleolin associated proteins in the complex, the author clearly demonstrate the detail function of each protein. However, the 500 kDa complex is quite stable, indicating a specific interaction pattern. Although the binding domain has not been mapped, a more detail mechanism should been demonstrated, e.g. if one client protein was knocked-down, would the binding partten change? Krust et al. also report that surface nucleolin antagonists exert distinct inhibitory mechanisms on various tumor cell types. Since the expression profile of these nucleolin associated proteins has not been mentioned, the author should present evidence that the existence of the 500 kDa complex is universal in the different types of tumors, and especially endothelial cells.
Level of interest: An article of importance in its field

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.