Genes & Diseases (2021) 8, 115–116

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PERSPECTIVES

Is circulating exosome carry Staphylococcal nuclease domain-containing protein 1, a component of RNA-induced silencing complex?

The RNA induced silencing complex (RISC) is a major eukaryotic cellular machinery which plays pivotal role in gene regulation. Argonaute-2 (Ago2) and Staphylococcal nuclease domain-containing protein 1 (SND1) are key functional components of this complex and have RNA binding ability and ribonuclease activity. Circulating Extracellular Vesicles (EVs) have high importance in cancer research and studies have shown that presence of Ago2 in EVs regulates gene expression in recipient cells. Secretion of miRNAs, mRNAs and Ago2 in extracellular vesicles or exosomes is a newly recognized mode of gene regulation and intercellular communication. However, there is no experimental evidence on possible presence of SND1 protein in EVs. This commentary discusses about the possible presence of SND1 in EVs along with Ago2 during circulation in blood.

It is very well-known fact that Ago2 or SND1 proteins are present in almost all types of eukaryotic cells and RISC complex is one of the very important cellular machinery of these cells.[1,2] It is also known that cancer cell over-expresses RISC complex proteins including SND1, Ago2 and Astrocyte Elevated Gene-1 (AEG-1).[3] Many studies have also reported that Ago2 may present either inside or outside of EVs and regulates various gene expression.[4–6] SND1 is also present in ER/Golgi vesicles, lipid droplets and milk secreting cells.[7] This predicts that SND1 protein may also present in EVs along with Ago2. Number of reports have shown that Ago2 and SND1 directly interact with each other in RISC complex.[1,3] These studies support the hypothesis of possible SND1 protein presence in EVs.

Ago2 present in EVs may have very important functional significance, as fusion of these EVs with recipient cell membranes deliver all the content to the recipient cytoplasm, including miRNAs, mRNAs and Ago2.[8,3] Cancer cells express and secretes high level of oncogenic miRNAs such as miR-221, miR-21, miR-155.[9–11] Expression and secretion of these miRNAs is regulated by SND1.[3] These miRNAs may also present in EVs and may fuse with normal cells present in the vicinity of tumor microenvironment or distant part of the same organ or different organs in the body.[6,12,13] These Microvesicles (MVs) from cancer cell may transform normal cells to become cancer cell or MVs from normal cell may secrete tumor suppressor miRNAs and these miRNAs may suppress tumor growth in the cancer patients.

It is already known fact that presence of vesicular and non-vesicular Ago2 and growth factors in serum and cell culture supernatants shows that they may have some very important function in cell–cell communication, gene regulation, oncogenesis. Various studies have also shown that *Ago2*, *SND1* and *AEG-1* are well known oncogenes.[3] Presence of SND1 in Endoplasmic reticulum/Golgi vesicles, lipid droplets and milk secreting cells clearly show that it is not an experimental artefact it's an evidence-based fact. Cell–cell communication is very important mechanism in eukaryotic gene regulation as well as growth and development of normal and cancer cells. Normal cells show contact inhibition during growth and cancer cells escape this mechanism and they have anchorage independent growth ability. EVs may have various cellular origin and biogenies mechanisms but they may finally merge or integrate with different cell types and delivers their cargoes (miRNAs or Ago2 containing RISC complex) to recipient cells. Therefore, integration of EVs with other cell or cell types effectively helps in cell–cell communication, growth and maintenance. As the known matter of fact SND1 directly interacts with Ago2 and other members of RISC complex including AEG-1. If EVs from cancer cell merges with normal

Peer review under responsibility of Chongqing Medical University.

https://doi.org/10.1016/j.gendis.2020.03.007

cell, this may result in transformation of normal cell to cancer cell due to the presence of SND1 and AEG-1 or vice versa (due to low expression of SND1 and AEG-1). Therefore, Ago2 along with its main partner SND1 may present in EVs and it is theoretically and practically possible. This Ago2 and SND1 containing RISC may be help in cellular adaptation to either promote any disease condition (tumor growth) or suppress any disease condition (tumor growth). Finally, more and more experimental evidences are needed to prove the presence of SND1 in EVs or Exosomes. Detecting all the components of RISC including SND1 in EVs and their cargoes may lead to greater understanding of EVs functions in cellular communication and gene regulation as well as therapeutically targeting them for the treatment of various diseases including metabolic syndrome and cancers.

Authors contribution

Varsha D. Shiragannavar: Contributed intellectually to this perspective.
Nirmala G. Sannappa Gowda: Contributed intellectually to this perspective.
Prasanna K. Santhekadur: Contributed intellectually and wrote this perspective.

Acknowledgements

This work was supported by Ramalingaswami Re-entry fellowship, Department of Biotechnology (DBT), Govt. of India to PKS and salary support to VDS.

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23 December 2019
Available online 15 May 2020