Milk exosomes for drug delivery

The need to effectively deliver drugs to target site has employed a multitude of substances varying from biological to a chemical nature and solid metals for the preparation of tiny drug delivery vesicles called nanoparticles. However, factors such as high costs, difficulty in reproducibly manufacturing them in sufficient quantities, and/or toxicity concerns have limited use in clinics for many or most of them. To overcome these limitations, we have recently used natural cell-secreted nano-carriers called exosomes. Exosomes are natural tiny lipid particles secreted by many cells types and are found is almost all bodily fluids. The exosome-based drug delivery gained much momentum after successful demonstration of nerve cell-derived exosomes for increasing immunity in cancer patients and for specifically targeting cancer genes. Other cell types that have been used as exosome factories include stem cells, human and mouse cancer cells, etc. Exosomes from these cells were shown to deliver small RNAs for gene silencing and small drugs (e.g., doxorubicin and curcumin). Although exosomes produced by few cell types have favorable properties for human use, the workload required to scale up the production of these cells and the resulting yield of exosomes are nowhere in the vicinity for clinical use. The safety and cancer-stimulating properties of exosomes derived from the stem cells and cancer cells is also of much concern. Exosome-like particles and lipids derived from fruits (e.g., grapes and grapefruit) were recently examined as an alternative drug carrier.

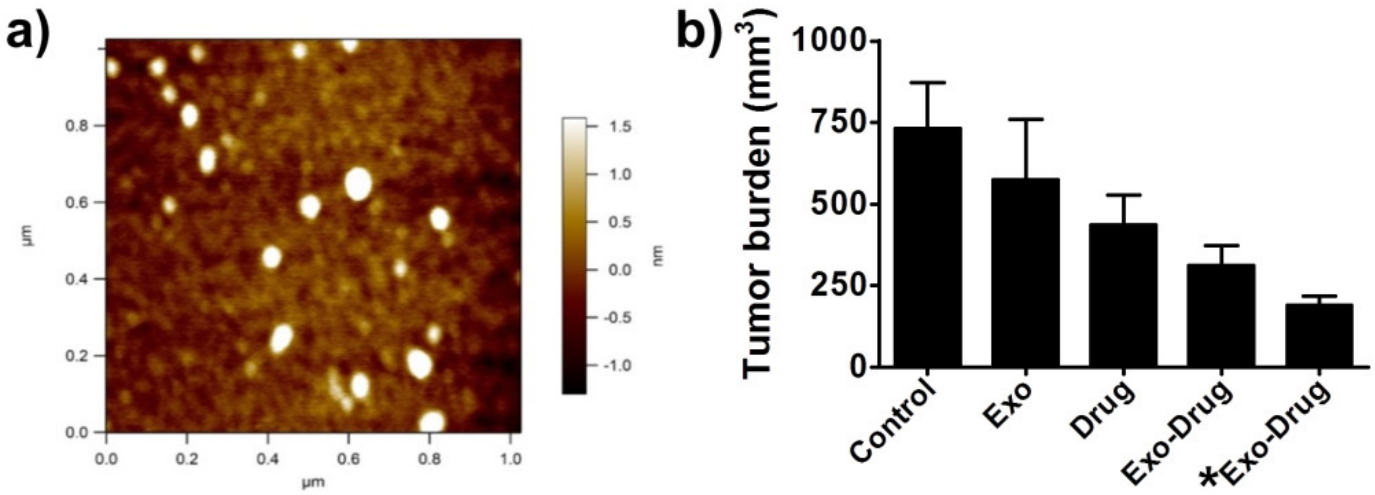

Fig.1. a) Milk exosomes observed under atomic force microscope. b) Treatment of lung tumors established in mice with drug (Withaferin A) loaded exosomes or *Exo-drug (with tumor-targeting ligand) showed significant reduction in tumor growth compared to free drug.

Thus, for exosomes to be accepted as a drug carrier in clinics, the development of biocompatible and economically-viable exosomes, which are effective and well-tolerated, must be demonstrated.

Our systematic efforts have led to the identification of cow milk as a natural source of exosomes that could serve as a drug carrier. Milk has been in the human environment from the ancient times, and a great majority of people consume milk for nutritional purposes. We have shown that exosomes from milk can serve as a vehicle to deliver both natural (plant-derived) compounds used as supplements as well as cancer drugs. We observed higher drug reaching at target site and enhanced effectiveness of the drug given orally via exosomal formulations in animal studies. This effect was further increased by the addition of a tumor-targeting tag, such as folic acid that help drug to reach specifically to tumors (Fig. 1). Therefore, milk exosomes could represent the most useful drug-carriers that can be exploited to deliver all kinds of agents ranging from small molecule drugs to nucleic acids to proteins (Fig. 2). The simplicity and versatility of our approach for delivery of drugs and the tremendous potential of this 'platform' technology will have a broad-based impact not only in the field of cancer but also in other diseases.

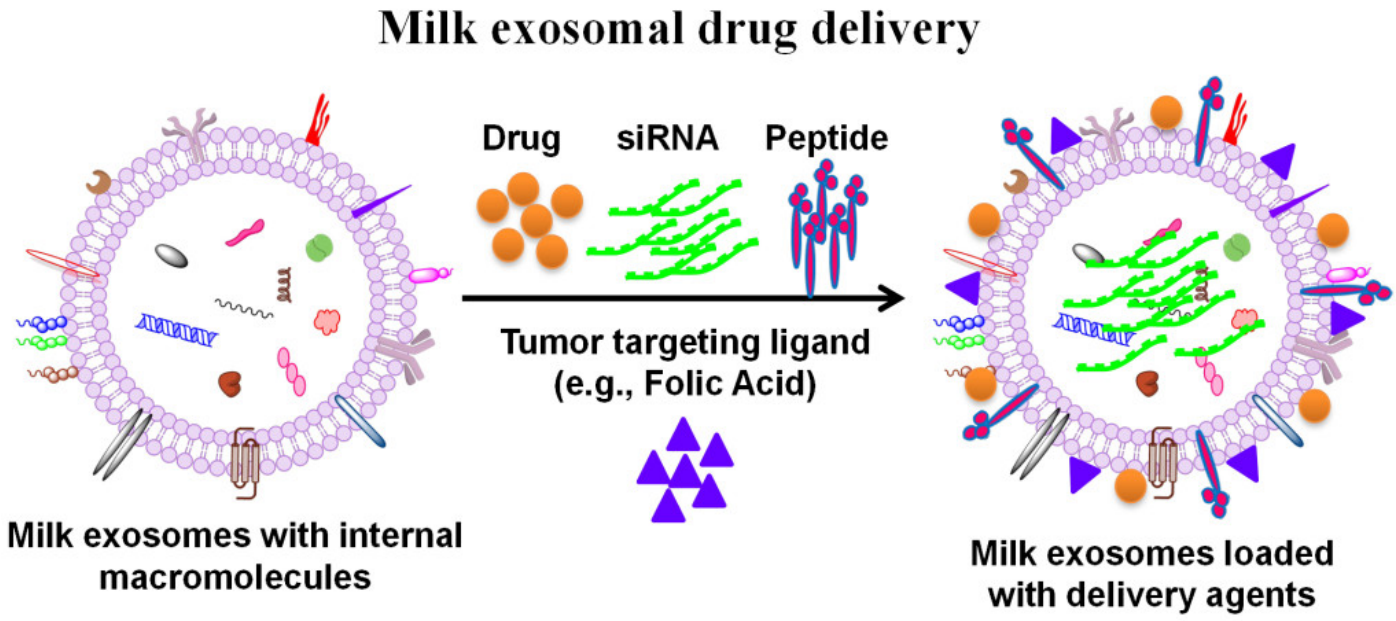

Fig. 2. Schematic representation of versatile delivery agents that can be loaded into/onto milk-derived exosomes for disease prevention and treatment applications.

In addition, we observed protective effects of milk exosomes (in absence of drugs) – a 'bonus' effect - which could be attributed to the internal as yet undetermined macromolecules. This opens up an entirely new avenue for the use of milk/colostrum exosomes alone as immune booster, which is the subject of ongoing studies. Oral administration of the exosomes and exosomal drug formulations was well tolerated with no adverse immune and inflammatory response in our short-term studies; in fact, some anti-inflammatory molecules were enhanced. Our goal is to focus on oral drug delivery as this is highly patient friendly and could prevent hospital visits otherwise required for intravenous infusions of cancer drugs.

Our findings suggest that milk exosomes could be a well-suited and inexpensive means to enhance oral absorption of drug (bioavailability), improve efficacy and safety of drugs. In addition, the physical and biological stability, well tolerability, simplicity of preparation process, possibility of facile scale-up of manufacturing process, and amenability of drying and sterilization process makes milk-derived exosomes as ideal nanoparticle for drug delivery with wide therapeutic applications.

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Publication

Bovine milk-derived exosomes for drug delivery.
Munagala R, Aqil F, Jeyabalan J, Gupta RC.
Cancer Lett. 2016 Feb 1