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Editorial

Caveolae-mediated Delivery of Therapeutic Nanoparticles across Blood-endothelial Barrier

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Nanomedicine is the nanotechnology application in pharmaceutics and medicine, and is a new frontier of inter disciplinary research including chemistry, materials science, pharmaceutical sciences, molecular biology and biomedical engineering [1]. Nanomedicine has shown the potential to transform the current medicine, for example personalized medicine will be designed based on genetic differences using nanotechnology tools.Thus, nanotechnology has enabled the design and manufacture of multifunctional nanoparticles which possess novel properties and biological functions [2]: 1) Increased tissue deposition and pharmacodynamics of water-insoluble drugs; 2) precisely targeted delivery of drugs into diseased tissues; 4) Combinational therapeutics based on co-delivery of multiple drugs in single nanoparticles; 5) imaging drug tissue accumulation and locations, and quantitatively monitoring drug pharmacodynamics; 6) controlled release of drugs; and 7) real-time readouts oftherapeutic efficacy *in vivo*.

Translation of nanomedicine in clinics still remains challenging because most of administered therapeutic nanoparticles are taken up by the reticulo-endothelial system of the liver rather than diseased organs resulting in systemic toxicity [3]. This poses a fundamental question of how these therapeutic nanoparticles move in the bloodstream. In other words, at the molecular level, how do therapeutic nanoparticles interact with endothelial cells lining the lumen of blood vessels? The endothelial monolayer presents a real barrier for the transport of nanoparticles because the openings of inter-endothelial junctions (the gaps between contiguous endothelial cells) have average size of 3 nm [4]. The restrictive junctions also depend on tissues, whether the endothelium is continuous or non-continuous, whether it is fenestrated or not [5]. The blood-brain barrier has been found a most restrictive layer based on its highly developed tight junctions consisting of claudins [6]. Nanotechnology cancer targeting therapeutics is based on a hypothesis that nanoparticles transport more readily across the leaky vasculatures of tumors because tumor blood vessels are permeable [2]. However, the experiments showed that tumor vessel endothelial junction was 12 nm wide [7] which is far smaller than widely-used therapeutic nanoparticles of 100 nm in diameter. Thus, the leakiest vasculature, such as tumor, still presents the barrier for nanoparticle transport across a layer of endothelial cells. Here we describe the transport of nanoparticles not through junctions but across the endothelial cells via a caveolar pathway. This trans cellular pathway regulates the transport of plasma proteins and nutrients in the endothelium and deep tissues [4], so it could be used to deliver therapeutic nanoparticles.

A caveolae is a flask-shaped in vagination on the plasma membrane and does not exhibit observable coating, unlike clathrin-coated vesicles [8]. The main protein made of caveolae is caveolin-1 [9] which helps to give rise to the caveolar flask-shape and also serves as a scaffold protein to regulate caveolae trafficking [10]. It is estimated that a caveolae consists of 144 caveolin-1 proteins. Cholesterol in a caveolae is also rich with 100 times greater than caveolin-1proteins [8]. Glycosphingolipids (such as, mono sialotetrahexosylganglioside) and sphingomylin are also enriched in caveolae compared to the plasma membrane proper [8]. Caveolae thus represent specialized, morphological sphingolipid-cholesterol compartment that is stabilized by caveolin-1 [8-10].

Caveolae occupy at least 70% of the total endothelial membrane in lung blood capillaries [4]. They can "bud" or "pinch" from the lumen side of the endothelial cell plasma membrane and transport their cargo to the basal side of the monolayer [8]. However, the signaling mechanisms regulating caveolae-mediated transcytosis are not well understood. It is believed that plasma proteins exploit the caveolae-mediated transcytosis to transport nutrients in the tissues. For example, albumin, an abundant plasma protein, could bind to a 60 kD a glycoprotein (gp60) on the endothelial cell surface [11, 12]. Binding to gp60 activated *Src* kinase resulting in phosphorylation of caveolin-1, gp60, and dynamin-2 (a "pin chase" associated with the neck of the caveolar in vagination) that initiated budding and release of caveolae [12]. The mechanism of trafficking of caveolae to the opposite side of vascular endothelial barrier and how caveolae avoid lysosomes are not investigated. On the basal membrane caveolae were shown to fuse to plasma lemma SNARE (soluble N-ethyl maleimide-sensitive factor attachment protein receptors) machinery where they discharged their contents [13].

The caveolar size is from 50 to 100 nm characterized using transmission electron microscopy (TEM) [4]. We recently demonstrated that caveolae of human lung micro vessel endothelial cells were able to internalize albumin-conjugated nanoparticles with the size from 20 to 100nm in diameter [14-16]. Using live cell co focal imaging [14] we observed the trafficking of caveolar loaded with albumin-conjugated nanoparticles and the caveolar pinched-off to form intra cellular vesicles and vectorially migrated to the basal membrane where they were released into the underlying tissues. An important aspect of caveolae-mediated transcytosis of nanoparticles was that it favored the transport of albumin because of the presence

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of albumin binding proteins present on the caveolar membrane [14]. We also showed that albumin nanoparticles of 20 nm in diameter preferentially utilized the caveolar pathway in contrast to particles made of 100nm [14]. These results offer a rationale for delivering drugs conjugated toalbumin nanoparticle to underlying tissue.

In conclusion, albumin-conjugated nanoparticles of 20 nm in diameterare effectively internalized by caveolar, suggesting that the caveolae pathway is a novel approach to deliver therapeutic nanoparticles across blood-endothelial barrier. However, there are many open questions to be addressed. Among them is whether this approach is effective in delivering therapeutic nanoparticles and whether pharmaco kinetics of drugs and proteins are enhanced by this mechanism. How do we design therapeutic nanoparticles to target to caveolar in vagination on the membrane? Another important question is whether albumin-conjugated nanoparticles can be modified to induce trans cellular delivery to specific organs such as the brain. Further studies are needed to identify the organ specific caveolar proteins that might be present and toassess the usefulness of exploiting the caveolae-mediated transport pathway for efficient delivery of drugs and biologics across the vascular endothelial barrier. To dissect these questions, it is needed to develop novel *in vivo* imaging tools, such as in travital microscopy [17], and using these tools we can real-time visualize the nanoparticle uptake by caveolar and trafficking of caveolar with their cargo in microvasculature of a mouse. These results will enable the design of therapeutic nanoparticles to target caveolar pathway of efficiently delivering drugs in cancer.

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