Nanomaterial's interfacial stimulation of vascular endothelial cells and divergent impacts on vasculature associated diseases

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The blood vasculature, one the most important circulatory systems, acts to transport vital nutrients and signals such as oxygen, ions and cells, simultaneously removing waste products as well as transmitting endogenous substances. Most exogenous substances (such as nanomedicine and nanomaterials for applications in disease diagnosis and therapeutics) in the body rely on the systemic circulation of blood vasculature to arrive their destinations. Upon the transportation by blood vasculature, nanomaterials with tunable physicochemical properties have shown a series of therapeutic benefits for nanomedicine, such as improved pharmacokinetics, enhanced bioavailability, and reduced toxicity. Given that vascular endothelial cells (VECs) line the inner surface of the vessel wall, nanomaterials in circulation have numerous possibilities of interacting with VECs, thus establishing unique boundaries between VECs and nanomaterials. Such a bio-nano interface is responsible for the majority of the physicochemical reactions, kinetics and thermodynamic exchanges, which highly correlates to a variety of VEC's biological responses. Among multifarious nanomaterials, two-dimensional lamellar materials (LMs) have generated considerable interest for biomedical applications. They are generally modified with hydrophilic moieties, the most common of which is polyethylene glycol (PEG), to increase their duration in the blood circulation, which was thought to elude the body's defense against intruding particles in blood vasculature. During this process, the interaction between VECs and nanomaterials lacked deep understanding, impeding the development of safe and efficient nanomedicine.

To clarify interaction between VECs and nanomaterials, the investigation of cellular responses and nano-bio interfacial interaction after PEGylated lamella nanomaterial (PLM)'s stimulation was explored. Inspired by previous study, the nano-bio interaction between PLMS with similar architecture and VECs was initially explored for exploring the potential cell effect. Human vascular endothelial cell (HUVEC) was chosen as the representative vascular cell for detecting the internalization and cytokine secretion level after PLM's stimulation. The mechanism of interfacial interaction between PLM and cell was further investigated by computational simulation, contact angle analysis, protein screening and siRNA interference to reveal the PLM's stimulated mechanotransduction. The i*n vivo* impact on vasculature-associated diseases were assessed in two models, including the $ApoE^{-/-}$ mice and patient-derived tumor xenograft (PDX) mice as atherosclerosis and cancer model, respectively.

Here, we discover that VECs can be significantly stimulated by various two-dimensional PLMs, including PEGylated copolymer material poly(lactic acid) (P-PLA), PEGylated MXenes material (P-Ti_3C_2), PEGylated graphene oxide (P-GO) and PEGylated transition metal dichalcogenide material (P-MoS_2), without being internalized. Similar trends are observed on the VECs in response to different PLM-induced stimulation including restricted internalization, promoted inflammatory cytokine secretion, increased membrane fluidity, and elevated stiffness. Additional experiments and computational simulations suggest that the unique VEC stimulation can be ascribed to the interaction between the PLMs and the membrane phospholipids in the horizontal and vertical modes, which induces ion-transport-related conformational change of L-type calcium ion channel $Ca_v1.3$ and the activation of Ca^{2+} related signal pathway. Additionally, the *in vivo* studies demonstrate that PLMs- stimulated VECs have divergent impacts on two types of vasculature-associated diseases: exacerbating the development of atherosclerosis while magnifying the accumulation of nanomedicine within tumors. Thus, the current study not only advances our understanding of how specific proteins on VEC membranes could be stimulated by PLMs but also guides the rational use of promising PLMs in nanomedicine.

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