Role of Extracellular Vimentin in Cancer-Cell Functionality and Its Influence on Cell Monolayer Permeability Changes Induced by SARS-CoV-2 Receptor Binding Domain

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The cytoskeletal protein vimentin is secreted under various physiological conditions. This extracellular vimentin can be primarily categorized into two types: one which is intact to the cell surface and another which is secreted into the extracellular space. While surface vimentin has been shown to be involved in processes such as viral infections and cancer progression, secreted vimentin controls inflammation by reducing the neutrophil infiltration, helps in bacterial elimination in activated macrophages and promotes axonal growth in astrocytes by activating IGF-1 receptor in the same signaling pathway as IGF-1. IGF-1R is overexpressed in cancer cells and IGF-1/IGF-1R pathway plays significant role in general cellular functions. In this study, we demonstrate the functional role of extracellular vimentin in cancerous and non-cancerous cells by evaluating parameters such as cell migration, proliferation, adhesion and membrane permeability. Our findings show enhanced migration, proliferation and adhesion in cancerous cells (MCF-7) than the non-cancerous cells (MCF-10a) upon extracellular vimentin treatment. Whereas membrane permeability is reduced in monolayers of MCF-7 compared to MCF-10a upon extracellular vimentin treatment. RBD domain of the SARS-CoV-2 spike protein alters blood-brain barrier integrity and surface vimentin has been shown to act as a co-receptor between SARS-CoV-2 spike protein and the cell-surface angiotensin-converting enzyme 2 (ACE2) receptor. Here, we checked for membrane permeability in MCF-7 and MCF-10a monolayers upon SARS-CoV-2 RBD treatment in presence of extracellular vimentin. Our finding suggests that extracellular vimentin bound to the cell surface enhances membrane permeability on both cell lines. But extracellular vimentin directly bound to SARS-CoV-2 RBD inhibits this effect in MCF-7 monolayers.

Further we also aimed at the verification of cell surface and secreted vimentin using macrophage activation as a model. Results showed that activated macrophages do express vimentin on their cell surface and that its structure is distinctly different from intracellular filamentous vimentin. Further investigation revealed cell surface vimentin is expressed in a polarized manner on macrophages. This polarization effect is also strongly promoted on activation. Analysis with macrophages expressing GFP tagged vimentin also confirmed the secretion of vimentin in the extracellular surrounding on activation. A higher amount of vimentin was observed in the environment when activation was performed for longer periods. Furthermore, we would like to check if this secreted vimentin has any influence on phagocytosis and migration of the macrophages.