**Title : The Multifaceted Nature of Oncogenes: A Story of Endocan**


## Abstract

Oncogenes often exhibit multifaceted roles beyond their initially identified functions, contributing to cancer progression through diverse mechanisms. Many oncogenic proteins function as moonlighting proteins, possessing multiple physiologically relevant biochemical or biophysical functions within a single polypeptide chain. We have identified endothelial cell-specific molecule 1 (ESM1), also known as endocan, as a moonlighting protein with distinct oncogenic properties beyond its well-established role in angiogenesis. Our findings reveal that secreted ESM1 directly interacts with both EGF and EGFR, enhancing their interaction and potentiating EGFR signaling in non-small cell lung cancer (NSCLC) cells. Even NSCLC cells harboring EGFR mutations require ESM1 to sustain elevated EGFR phosphorylation levels and cell proliferation. Unexpectedly, we also observed nuclear localization of ESM1 in prostate cancer cells, particularly within the cancer stem cell (CSC) population. Functional analyses suggest that nuclear ESM1 promotes CSC stemness by interacting with and stabilizing the β-catenin–TCF4 complex. Moreover, a positive regulatory loop exists between β-catenin and ESM1, where β-catenin facilitates ESM1 nuclear translocation. These findings highlight ESM1 as a moonlighting oncogenic protein, executing distinct functions in different cellular compartments—acting extracellularly as a ligand-like enhancer of EGFR signaling while also functioning intracellularly as a nuclear co-transcriptional regulator of WNT signaling. Furthermore, ESM1-derived peptides have demonstrated promising potential in disrupting EGF/EGFR or WNT signaling activation in NSCLC and prostate cancer cells, respectively. Understanding and targeting the moonlighting functions of oncogenic proteins like ESM1 could provide novel therapeutic strategies and insights into cancer treatment.