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Preface

Ivan Robert Nabi[1]

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Caveolin-1 expression is associated with a poor prognosis in breast, prostate, and other cancers, and specifically with highly aggressive triple-negative basal-type breast cancers. However, caveolin-1 has also been ascribed tumor suppressor functions, and in some tumor types, caveolin-1 expression is associated with improved prognosis. Despite almost 2000 publications on caveolin and cancer, defining the contribution of this multifunctional protein to cancer progression remains a challenge. Caveolins are key regulators of cholesterol and sphingolipid-rich membrane domains or lipid rafts. Lipids, lipid metabolism, and lipid domains also play key roles in cancer. However, defining lipid domains and their function has proven to be complex and controversial. This issue of *Cancer Metastasis Reviews* provides an analysis of lipid domains and caveolin, with a particular focus on the varied and diverse roles of caveolin in cancer.

Skotland, Kavaliauskiene, and Sandvig provide a comprehensive overview of lipid species in membranes, and discuss what is a lipid raft and the changes in lipid composition and lipid rafts that are associated with cancer. Gauthier-Rouvière and colleagues review the role of lipid raft-associated flotillins that upregulate a raft endocytic pathway associated with tumor cell invasion and metastasis. Johannes and Billet then discuss the role of raft-dependent endocytosis, and how it is impacted by glycosylation, in the internalization of cancer-related receptors. The proposed connection between raft-dependent endocytosis and receptor glycosylation via the galectin lattice may have significant implications for development of receptor-based targeted therapeutics.

Subsequent reviews in this issue focus on the complex and varied role of caveolin in cancer. Volonte and Galbiati describe the central role of caveolin-1 in cellular senescence and the impact of this tumor suppressor function of caveolin-1 on cancer biology. Nassar and Parat focus on caveolins and cavins, both required for caveolae formation, in prostate cancer, discussing the tumor promotor role of caveolins and tumor suppressor role of cavins and the value of plasma/serum caveolin as a diagnostic tool for prostate cancer detection. Quest and colleagues comprehensively describe both the canonical role of caveolin-1 at the plasma membrane and non-canonical roles of caveolin-1 in exosomes and intracellular organelles and on cancer cell metabolism, the contribution of which to caveolin-1 function in cancer remains less well understood.

Caveolin-1 plays key roles as both mechanosensor and mechanotransducer in response to the tumor microenvironment. Caveolin-1 is phosphorylated by Src kinase in response to oxidative and mechanical stress and a review from my lab focuses on the role of Src-dependent tyrosine-14 phosphorylation on caveolin-1 function in cancer progression, hypothesizing a potential functional interaction between tyrosine-14 phosphorylation and the highly conserved caveolin scaffolding domain. Bernatchez focuses on the role of caveolin-1 and its scaffolding domain in endothelial cells, describing their regulation of signaling events in tumor stroma and how they impact vascular permeability, angiogenesis, and mechanotransduction. Del Pozo and colleagues further discuss the role of caveolin-1 in the reciprocal biomechanical crosstalk between tumor cells and stromal fibroblasts and how it is impacted by the extracellular matrix stiffening that is closely associated with cancer progression. Singh and Lamaze discuss membrane tension buffering by caveolae, in which caveolae flattening protects cells from rupture in response to mechanical stress, such as that encountered in the tumor microenvironment, providing new perspectives into caveolin function in cancer.

Finally, an editorial by Thompson and colleagues reminds us of the NIH workshop over 25 years where his clinical data challenged the accepted notion of caveolin-1 as a tumor suppressor. Work since that time, as outlined in this issue, has highlighted the central and complex roles of caveolin-1 and lipid domains in cancer biology, encompassing receptor endocytosis, metabolic reprogramming, mechanobiology, and the tumor microenvironment, and invoked novel concepts, analytical approaches, and technology that have led to new insights and improved perspectives for cancer diagnostics and therapy.

✉ Ivan Robert Nabi
ivan.robert.nabi@ubc.ca

[1] Life Sciences Institute, Department of Cellular and Physiological Sciences, University of British Columbia, 2350 Health Sciences Mall, Vancouver, BC V6T 1Z3, Canada