



Cell Surface Membrane Lipid Rafts as Potent Regulators of Stem Cell Proliferation, Differentiation, Trafficking and Metabolism

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Published online: 17 December 2022

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Cell outer membranes contain glycosphingolipids and protein receptors, which are integrated into nanoscale glycoprotein microdomains ranging from 10 to 200 nm in size enriched with cholesterol and sphingolipids, known as membrane lipid rafts (MLRs). These structures float freely in the membrane bilayer and play an important role in assembling cytosolic signaling molecules together with surface receptors for growth factors, cytokines, chemokines bioactive lipids, extracellular signaling nucleotides, adhesion molecules and cell surface expressed enzymes, which together regulate several cell pathways. Therefore, MLRs behave as some type of sorting hubs for cell surface “*raftophilic*” receptors and play a role in their optimal signaling. Presence of MLRs on outer cell membranes explain at a novel level regulation and integration of microenvironmental signals that regulate cell behavior. To support this, cells much better respond to stimulation by ligands if corresponding receptors are included in MLRs.

MLRs cannot be directly visualized by conventional light microscopy, and other techniques serve to their visualization including super-resolution microscopy, such as stimulated emission depletion (STED) or structured illumination microscopy. Moreover, there also available other optical techniques for detecting the MLRs such as fluorescence correlation and cross-correlation spectroscopy (FCS/FCCS) or fluorescence resonance energy transfer (FRET). They can be also visualized by employing fluorescence microscopy after labelling of the cell surface with fluorescence-conjugated cholera toxin B subunit, which binds to a lipid raft constituent and marker, the ganglioside GM1.

In this January issue of Stem Cell Reviews and Reports there published two papers that address a biological importance of MLRs. The first paper is an excellent review submitted by Drs Roy and Patra that reviewed 225 papers published in the literature and deals with a role of MLRs in cell physiology and pathology (<https://doi.org/10.1007/s12015-022-10448-3>). Another original

research paper submitted by Abdelbaset-Ismail A, Ciechanowicz A et al. (<https://doi.org/10.1007/s12015-022-10481-2>) provides a novel view on MLRs formation in hematopoietic stem/progenitor cells (HSPCs). The authors report that NADPH oxidase 2 (Nox2)-derived reactive oxygen species (ROS) are required for a proper expression of enzymes regulating lipogenesis in these cells during inflammation, and that this occurs in a Nlrp3-inflammasome dependent manner. This data establishes a novel link between innate immunity including pattern recognition receptor Nlrp3 inflammasome and cell metabolic pathways that supply lipid components (cholesterol and sphingolipids) for proper assembly of MLRs involved in response to stimuli regulating HSPCs trafficking and proliferation.

We are living in very exciting times of stem cell research to understand biology of stem cells, and their potential applications in the clinic. Therefore, more work is needed in this promising area. Based on this it is important to better understand the molecular mechanisms involved in regulating stem cell proliferation and differentiation including involvement of MLRs in these processes. Evidence accumulates that these nanoscale microdomains in outer cell membranes are potent regulators of proliferation, differentiation, trafficking and metabolism and this intriguing novel view on stem cell biology requires further studies.

Going forward, Stem Cell Reviews and Reports will continue to publish the latest discoveries and to entertain challenging and provocative ideas. Therefore, we encourage you to submit your best work for our consideration, as we continue towards establishing our journal as the leading journal in stem cell research.

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