Sequence Analysis of a Subset of Plasma Membrane Raft Proteome Containing CXXC Metal Binding Motifs: Metal Binding Proteins

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ABSTRACT

In an attempt to identify the metal sensing proteins localized to mammalian plasma membrane, the authors screened a list of 300 raft associated proteins that are involved in cellular signaling mechanisms by searching the presence of metal thionin (CXXC) motifs. 50 proteins were found to possess CXXC motifs that could act as potential metal sensing proteins. The authors determined membrane topologies of the above CXXC motif containing proteins using TM-pred and analyzed the positions of their transmembrane (TM) domains using Bio-edit software. Based on the topology of CXXC domains, the authors classified all the raft-associated metal sensing proteins into six categories. They are (i) Exoplasmic tails with CXXC motif, (ii) Exoplasmic loops with CXXC motif, (iii) Cytosolic tails with CXXC motif, (iv) Cytosolic loop with CXXC motif, (v) TM domains with CXXC motifs, (vi) Proteins with multiple topologies of CXXC motif. The authors’ study will lead to understanding of the raft-mediated mechanism of heavy metal sensing and signaling in mammalian cells.

Keywords: Cytosolic Domain, Exoplasmic Domain, Heavy Metal, Motif, Plasma Membrane, Raft, Signal Transduction, TMD, Topology

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1. INTRODUCTION

Metal ions are essential cellular components that function as enzyme cofactors, building blocks of biomolecules (e.g. haemoglobin, chlorophyll pigments, iron-sulfur centers of proteins etc.), signaling components (e.g. Ca\(^{2+}\)) and maintenance of cellular ionic balance. However, metals such as lead (Pb\(^{2+}\)), mercury (Hg\(^{2+}\)), arsenic (As\(^{3+}\)), chromium (Cr\(^{3+}\)) and nickel (Ni\(^{2+}\)) etc. with density ≥ 5 g/cc are known as heavy metals and show cytotoxicity due to their high reducing power, non-biodegradability and accumulation inside the cells (Rainbow, 2007, pp. 576-82). Hence, cells must develop mechanisms to detect these harmful metals and detoxify them in order to survive the heavy metal stress in the medium.

Heavy metals are impermeable across plasma membrane (PM) due to the positive charge they carry. However, they can cross the PM through ion channels, ion-transporters or ionophores (Beier et al., 2015). Inside the cell, these heavy metals produce their toxic effect by binding to multiple cellular components such as proteins, enzymes, DNA and membrane lipids (Kim, Kim & Seo, 2015). As heavy metals possess much higher affinity for their substrates compared to naturally occurring metal ion cofactors (e.g. Ca\(^{2+}\), Mg\(^{2+}\) etc) they displace these cofactors from their substrates (e.g. enzymes and proteins). Heavy metals such as Hg\(^{2+}\) are known to form complexes with thiol (-SH) groups of proteins that leads to the damage of their iron-sulfur (FeS) centers resulting in loss of activity (Ranquet, Ollagnier-de-Choudens, Loiseau, Barras & Fontecave, 2007).

Most common heavy metals in industrial effluents include arsenic (As), cadmium (Cd), mercury (Hg), chromium (Cr), copper (Cu), lead (Pb), nickel (Ni), and zinc (Zn), all of which pose a cause risks for human health and the environment Jolly (Islam & Akbar, 2013). Investigation shows that oxidative deterioration of biological macromolecules is primarily mechanism of heavy metals toxicity resulting in oxidative damage of DNA, proteins and lipids (Imlay, Chin & Linn, 1888).

Mammalian PM is known to detect heavy metal ions and detoxify them by activating cellular detoxification machineries. PM of almost all cell types exhibit an inherent lateral heterogeneity in its lipid and protein components termed as rafts (Pike, 2003, pp. 655-67). Rafts are patches of PM with size varying from 15 nm to 50 nm that are molecular aggregations containing large amounts of glycolipid (GL), cholesterol (CH), sphingomyelin (SM), phospholipids (PLs) and associated proteins (Rao, Chung, Pike & Brown, 2005). Rafts in PM originate because of preferential association of SM, GL and CH with each other compared to their association with PLs. Biochemically; rafts are characterized by their resistance to mild detergents such as triton X-100, hence, also termed as detergent resistant membrane domains or DRM. These rafts possess low density that enables them to float in low density layer of a sucrose step gradient (light fraction) compared to non-raft portions of PM (Róg & Vattulainen, 2014).

Rafts containing specific association of lipids and proteins are known to act as platforms for inteintegration and modulators of cellular signals. Rafts achieve this incredible feat of modulating membrane protein activities by providing them with optimal combination of lipid and protein microenvironment. Many proteins such as G-protein coupled receptors (e.g. serotonin receptor) and phospholipid scramblases (PLSCRs) are activated when bound to cholesterol (Sahu, Saxena & Chattopadhyay, 2012). Similarly, entry of viruses (e.g. HIV) and bacteria into the cell, receptor mediated endocytosis and cell-cell interactions are mediated by PM rafts (Pike, 2003, pp. 655-67).

Structural and functional organization of rafts is altered in multiple pathological conditions such as malignancy. Chemicals that induce formation or dissociation of rafts can act as therapeutic molecules (e.g. plant saponins, triterpenes and flavinoids and synthetic molecules) (Reis-Sobreiro et al., 2013). However, the structure, organization and function of rafts in different cell types...
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