RAFTING IN THE MEMBRANE. A LESSON LEARNT FROM LYMPHOPROLIFERATIVE DISORDERS

Švec A.

Department of Cellular Pathology, James Cook University Hospital, Middlesbrough, United Kingdom

Summary

Lipid rafts are chemically distinct compartments of the plasma membrane. Their integrity is a prerequisite for vital cellular functions particularly for signalling and trafficking. Their perturbation is associated with development of a broad spectrum of diseases. Lipid rafts are also important for therapeutic effects of some drugs. Moreover, some of the raft associated molecules are useful immunohistochemical markers in routine histopathology.
Key words: lipid rafts – malignant lymphoma – anti-lymphoma drugs

Souhrn

Na raftu a na membráně. Jedna zkušenost z biologie lymfoproliferativních onemocnění

Lipidové rafty jsou zvláštním kompartmentem cytoplazmatické membrány vyznačující se charakteristickým chemickým složením. Jejich integrita má zásadní význam pro životně důležité buněčné funkce, zejména signální procesy a membránový transport. Narušení lipidových raftů bylo prokázáno u řady onemocnění. Lipidové rafty jsou rovněž významné pro terapeutické účinky některých léků a určité molekuly zakotvené v lipidových raftech jsou navíc užitečnými diagnostickými markery v rutinní histopatologické praxi.

Klíčová slova: lipidové rafty – maligní lymfom – proti-lymfomové léky

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Why just the rafts?

Pathology used to provide clinical medicine with 'the base of diseases' and deliver diagnoses on the grounds of information obtained by direct visual observations of morphological changes. Except for other methods, it was the introduction of immunohistochemistry that added a new dimension to pathological observation both in practice and research. This method makes it possible to detect an array of molecules which would otherwise remain hidden in the 'red and blue mosaic' of the conventional histological sections. This progress imposed a considerable pressure on pathologists to embrace a significant bulk of new knowledge about microscopically elusive substances such as molecules, their functions, mutual relations as well as their cellular location.

The following text brings elementary information about plasma membrane microdomains called lipid rafts or glycosphingolipid-enriched microdomains, the home site of a number of molecules significant both in health and disease.

What are the rafts like?

A text-book scheme of the biological membrane as a phospholipid bi-layer with in-built proteins known as Singer&Nicolson's fluid mosaic model has become complicated by the discovery of marked chemical and structural heterogeneity of the membrane where molecules are engaged in preferential interactions, clustering into microdomains capable of lateral movements. Lipid rafts represent such microdomains with special physical-chemical properties and physiological roles. They show a higher degree of physical organisation called a liquid-ordered phase distinguishing them from the liquid disordered non-raft membrane (8, 25). In a figurative sense, they could be viewed as small solid islands 'rafting' in the membrane with some restrictions resulting from interactions with intracellular and extracellular molecules, but are they, really?

Although lipid rafts have become a hot topic only in the current millennium (39), the lipid raft story started unwinding as early as 1953 when George E. Palade, 1974 Nobel Prize winner, presented his observations of spherical vesicles in endothelial cells at the 11th annual meeting of the Electron Microscope Society of America (30). The vesicles were considered identical to 'pit-like' and 'cave-like vesicles' observed in microvilli of rat gall bladder epithelium by Yamada in 1955 who called them caveolae intracellulares (48). These are currently recognized as a special example of lipid rafts referred to simply as caveolae, generally described as flask-shaped invaginations of the plasma membrane 50–100 nm in size. Later, it was shown that caveolae are associated with a family of proteins known as caveolins; interestingly, with both -COOH and -NH_2 ends facing the cell interior and having no extracellular domains. The caveolins turned out to be critical for caveolae formation. Functionally, they act as adaptor proteins recruiting other signalling molecules to the caveolae (10).

Caveolae are present in nearly all cell types particularly in the endothelium and type 1 pneumocytes but typically missing in haematopoetic cells which do not express caveolins (10).

As a result, haematopoietic cell membranes comprise lipid rafts morphologically indistinguishable but highly sophisticated methods allowing tracking single molecules were used to visualise them (33, 37). Lipid rafts defined biochemically are plasma membrane compartments characterised by an increased proportion of sphingolipids with long saturated fatty

acid chains and the presence of interposed cholesterol molecules while the non-raft membrane is composed mainly of phospholipids with unsaturated fatty acids (8). This chemical composition is responsible for the liquid-ordered phase with decreased fluidity, resistance to certain detergents and increased buoyancy which allows separation of the rafts on sucrose gradient ultracentrifugation (29).

Lipid rafts further differ from the non-raft membrane by a lesser number of proteins with an important exception of a large group of proteins involved in signalling processes such as receptors, signalling effectors, e.g. Src-kinases or Ras proteins, and adaptor proteins, organizing multimolecular signalling complexes (50).

The appealing concept of rafts as small islands floating in the plasma membrane has been challenged when fascinating raft dynamism emerged from a combination of the data obtained by experiments with plasma membranes, artificial membranes and computational modelling. The data suggest that rafts might not exist as preformed structures. By contrast, lipid rafts appear to be formed upon collision of spontaneously arising small cholesterol-containing domains which coalesce upon stabilisation by 'raftophilic' glycosylphosphatidylinositol-anchored proteins having a capacity to organize the rafts. The larger and more stable rafts are finally eliminated from the membrane by endocytosis once a critical size is achieved. The presumed lipid raft lifetime oscillates between milliseconds and a second and the size is measured in nanometres (13).

For the sake of balance it should be noted that there were certain reservations about the raft theory particularly due to obstacles in visualising such a dynamic structure of sub-microscopic size. Although these are now considered to have been overcome, some scepticism is still occasionally expressed (16, 21, 39).

What are the rafts good for?

In general, lipid rafts provide optimal micro-environment for molecular interactions sheltering the interacting molecules from undesired contacts with potential adverse consequences for the cell. They can transport larger signalling complexes within the membrane to a particular site of the membrane. Finally, lipid raft dynamism secures that the interactions are limited in time which is an important regulatory mechanism (50).

More specifically, the diverse functions of lipid rafts include nutrient absorption, cell-cell communication, cell signalling and endocytosis. Lipid rafts act as gateways for infectious agents exploited both by bacteria and viruses with the latter also undergoing the process of assembly and budding in the rafts (34, 49).

Last but not least, lipid rafts are important sites for drug-cell interactions as discussed later.

What about the raft pathology?

The multifaceted role of lipid rafts in cellular processes predestines them for involvement in a broad spectrum of diseases and indeed, their alterations have been identified in metabolic, neurodegenerative, infectious, autoimmune and neoplastic diseases (26). Even a concise insight into each category would be far beyond the scope of this article.

The following examples documenting involvement of lipid rafts in pathological processes are taken from the biology of malignant lymphomas.

Gene expression profiling revealed two types of small cell lymphoma/chronic lymphocytic leukaemia (SLL/CLL) and these types correlated with the different course of the disease. Briefly, the SLL/CLL type with a tendency for rapid progression is associated with germline, unmutated immunoglobulin genes while the type with an indolent course has mutated or re-arranged immunoglobulin genes (35). Later, several lines of evidence suggested that (auto)antigenic stimulation plays a crucial part in pathogenesis of the disease (9). Therefore the early signalling machinery must retain the capacity to transduce extracellular signals and it is the transduction of the signal where a difference between the two types has been recently disclosed. Recent results indicated that in the unmutated SLL/CLL type, B-cell receptor upon stimulation translocates to lipid rafts with subsequent activation of signalling pathways analogous to the situation in normal lymphocytes. By contrast, in the mutated SLL/CLL type with more favourable prognosis, B-cell receptor remains outside of the lipid rafts, detached from the down-stream signalling machinery resembling thus anergic B-cells not reacting to antigenic stimulation (2).

Diffuse large B-cell lymphoma (DLBCL) is notoriously known for its biologic heterogeneity. Gene expression profiling made it possible to identify clinically relevant types which cannot be recognized by conventional histological methods (1, 22, 36). These are a germinal centre DLBCL type with the gene expression profile similar to normal germinal centre cells and an activated DLBCL type with the gene expression profile similar to activated peripheral blood lymphocytes. The proposed surrogate algorithm to identify the types by immunohistochemistry is based on detection of CD10, BCL6, CD138, MUM1 (11,14). More recently, there have been identified additional proteins associated with the germinal centre cell phenotype and the germinal centre type DLBCL – HGAL, Jaw1 and PAG (28, 41, 44). While HGAL (human germinal center-associated lymphoma) protein now officially named germinal center expressed transcript 2 (GCET2) is a non-raft protein participating in cytokine signalling and Jaw1 is an endoplasmic reticulum-associated protein, PAG (phosphoprotein associated with glycosphingolipid microdomains) known also as Cbp (Csk-binding protein) is a raft-associated transmembrane adaptor protein playing a crucial role in negative regulation of Src-kinases and modification of the cytoskeleton (4, 6, 7, 17, 31). The capacity to identify germinal centre cells and their neoplastic counterparts make PAG/Cbp a potential candidate for a routine diagnostic marker (42, 45).

Furthermore, a complex of PAG/Cbp, Src-kinase Lyn and STAT3 (signal transducers and activators of transcription 3) prevents lymphoma cell lines from apoptosis. This was considered significant for tumour-tailored drug design along with differences in the raft arrangement in B-cell non-Hodgkin malignant lymphoma, ALK+ T-cell lymphoma and Hodgkin lymphoma cell lines, with the preferential location of PAG/Cbp in the non-raft plasma membrane in the latter two (43).

Lipid rafts are important not only for internalisation and budding of viruses in infectious diseases but also for viral oncogenesis. Epstein-Barr virus (EBV) is a crucial oncogenic factor in endemic Burkitt's lymphoma, EBV-positive Hodgkin lymphoma (HL) and in immunodeficiency-related lymphoproliferative disorders (18).

The HL neoplastic cell, Hodgkin-Reed-Sternberg cell (HRS), is a transformed pre-apoptotic germinal centre cell which typically lacks B-cell receptor. In normal germinal centres this is a forbidden phenotype attracting a death penalty by apoptosis (12, 20, 24). However, this fate unfavourable for the cell can be selfishly reversed by EBV infection, unfortunately, with all the sinister connotations for the organism (3).

HRS cells are associated with latency type 2 EBV infection characterised by production of proteins EBNA1 (Epstein-Barr nuclear antigen-1) and LMP1 and LMP2 (latency membrane proteins 1 and 2) with the latter two being anchored in the lipid rafts (15, 32). LMP1 acts as a source of signals normally transmitted by CD40 receptor, a member of the tumour necrosis factor family, which is a potent activator of NFκB (nuclear factor kappa B) pathway while LMP2 generates signals substituting survival signals normally mediated by the B-cell receptor (23, 47). When anchored in the lipid rafts, LMP1 and LMP2 exploit the associated signalling hardware to

set in motion signalling pathways whose combinatorial effects allow HRS cells to survive and proliferate (5).

The following examples demonstrate the importance of lipid rafts for a mechanism of anti-cancer drugs. Some of the effects of Rituxan (Rituximab), the most widely used anti-CD20 antibody for treatment of malignant lymphomas and some autoimmune diseases, depend on the integrity of lipid rafts (19). The cross-linked CD20 moves to lipid rafts where it forms a channel for influx of extracellular calcium which initiates apoptosis via activation of caspase 3. This effect disappeared in cells treated by cholesterol-depleting drugs affecting the lipid rafts. Moreover, an earlier study indicated that the raft associated protein PAG/Cbp is necessary for Rituximab to impose its anti-tumour effect as well (38). Another study demonstrated that alemtuzumab, a monoclonal antibody against the raft-associated antigen CD52, requires unperturbed rafts to kill leukaemic cells (27). Furthermore, a class of drugs known as alkylphopholipids are internalised via lipid rafts-organized endocytosis but only if the rafts are intact (46). On the other hand, lipid rafts in Burkitt's lymphoma cell lines can rescue neoplastic cells from death by sequestration of Apaf-1 (apoptotic protease-activating factor-1), a molecule necessary for etoposide (chemotherapeutic drug activating up-stream regulators of caspase 3) to elicit apoptosis (40). These examples show that lipid rafts play a pivotal role in cell-drug interactions and indicate that lipid rafts and their associated proteins have a potential to become targets for anti-cancer drugs.

Lipid rafts? Yes, they deserve it!

In summary, recent research suggests that lipid rafts exist in a form of highly dynamic, unstable plasma membrane microdomains characterised by an increased proportion of sphingolipids, cholesterol and a significant number of signalling proteins. They participate in diverse cellular processes which turns them into a privileged plasma membrane compartment with a crucial influence on the fate of cells in both health and disease. Better understanding lipid rafts and their role in cell biology has provided a deeper insight into pathogenesis of neoplastic and non-neoplastic diseases and this may be significant for diagnostic procedures and development of new therapeutic strategies. Finally, all the data suggest that lipid rafts are worthy of pathologists' attention.

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Alexandr Švec, MD, Ph.D.
Department of Cellular Pathology
James Cook University Hospital
Marton Rd
Middlesbrough
TS4 3BW
Velká Británie
Telefon: +44-01642 850850
E-mail: alexandr.svec@stees.nhs.uk

HISTORKY ZE ŽIVOTA HEŘMANA ŠIKLA

V dávných dobách, ještě za vládního rady profesora Hlavy, se do ústavu patologie dostavil dosti zanedbaně oblečený muž a nabízel k prodeji svou kostru. Moc zájmu nebylo, nevypadal zrovna důvěryhodně, až se ho asistent MUDr. Heřman Šikl zeptal: „A proč ji chcete vůbec prodat? Na co ty peníze potřebujete?“ „Chtěl bych odjet do Argentiny.“ – Z koupě sešlo.

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