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VAULT COMPLEX – WHAT IT HOLDS IN STORE?

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ABSTRACT

The vault complex which is the largest ribonucleoprotein particle, can be found in the eukaryotes-ranging from protozoa to mammals (excepting budding yeast, *C. elegans*, *D. melanogaster* and *Arabidopsis*). Vaults are mainly localized in cytosol (very small fraction within nucleus). Consisting of two eight petalled equal halves, each vault can exist in open or closed conformation and is composed of three proteins (MVP, VPARP, TEP-1) and an RNA (vRNA), which may be evolutionary conserved. This review focusses on detailed structural and functional aspects of this vault constituents, concentrating mainly on their role in nucleocytoplasmic transport, cellular homeostasis and development and multidrug resistance during chemotherapy.

KEYWORDS: Vault, Major vault protein (MVP), Vault Poly ADP ribosyl polymerase (VPARP), Vault RNA (vRNA), Vaultosome, Vault nano-capsules.

Primordial organisms used to rely heavily on RNA rather than DNA for their metabolism and according to biochemical evolution such RNA containing particle persisted in modern organisms as molecular relics.[1][2] Some of the well-known ribonucleoprotein particles like ribosomes, Signal Recognition Particle (SRP), small nuclear RNA particles or snRNPs etc are critical for cellular metabolism.[3][4] Another such large ribonucleoprotein particle, the Vault complex was first identified in mid 1980s as clathrin-coated vesicles from rat liver.[5] [6] Vaults were named so as the particles closely resemble the vaulted ceiling of a cathedrals.[6] Similar complexes were identified in various eukaryotes including protozoa, molluscs, the slime mould *Dictyostelium discoideum*, echinoderms, fish, amphibians, birds and mammals[7][8] There are rare exceptions as well, so far such particles are not observed in

Saccharomyces cerevisiae[9], *Caenorhabditis elegans*, *Drosophila melanogaster* and the plant *Arabidopsis* sp.[6][8][10]

Vaults bear characteristics of both cytoskeletal and ribonuclear elements and being unusually large (almost three folds larger than eukaryotic ribosome and at least 10 folds larger than SNP and snRNP's), they are a class apart from other such ribonucleoprotein bodies.

Cellular localization

Vaults are mainly localized in the cytosol but a small fraction (~ 5%) can also be found within the nucleus of mammalian cells suggesting a role in the nucleocytoplasmic transport[11][12][13][14], most probably by interacting with cytoskeletal elements like actin stress fibre of rat fibroblasts[15] and differentiated PC 12 cells[16] or microtubules[17] in the cytosol. Almost 10,000-100,000 copies of vaults can be present per cell.[18] Moreover the structural resemblance of vault with the central plug of the octagonal Nuclear Pore Complex (NPC) that spans the nuclear membrane and provides a channel for nucleocytoplasmic transport indicates that vaults may function as shuttles between nucleus and cytoplasm[19][20][21], but these assumptions need confirmation from ongoing functional and genetic studies.[11]

Structure

The vault complex being 42-75 mm in size and having an approximate molecular mass of 13MDa[22] turns out to be the largest known ribonucleoprotein complex. Each vault complex separates into two symmetrical halves that can unfold into eight petalled flower-like structures, this is also confirmed by the presence of two centers of mass observed in the electron micrograph.[22] The plate like petals are joined to a central ring and may be split lengthwise into two or three roughly equal parts.[22] The petals are negatively charged on their outer part and they remain folded with their underside projected outward.

The vault structure must be important for its function as the flower-like structure is non-randomly symmetrical(Figure 1). folded with their underside projected outward. Vaults can also separate into two halves without unfolding, as seen in some vertebrate vaults which are negatively stained. Therefore the unfolding is thought to occur following one the two proposed models.

Two step process: Vaults separate into half vaults and then unfold.

One step process: The unfolding may be coupled with separation into half vaults.

By combining cryoelectron microscopy and three dimensional image reconstruction techniques scientists have revealed that at 22 Å resolution[23][24] vault particles are hollow barrel-like structure with tapered middle region and two cap like protrusions and has an 8-2-2 symmetry (Figure 2).Vertebrate vaults are ellipsoidal with two axes of symmetry: radial and bilateral. 'Broken vaults', produced by separation along the long axis produces two elliptical cones that look like half egg shells (Figure 3).

Composition

Mammalian vaults are composed of three proteins and one RNA. The protein components are: one Major Vault Protein (MVP) that constitute 75% of the mass[22], and two minor vault proteins : Telomerase associated Protein 1 (TEP1) – a 290 KD protein and Vault poly (ADP ribose) polymerase (VPARP) another 193 KD protein. The copy numbers of MVP is almost 96 while that of VPARP and TEP1 ranges between 2-8 per particle. There are at least 6 molecules of non-coding RNA (vRNA) in each particle, accounting for less than 5% of the particle mass. The minor vault proteins and the vRNAs are localized in the body and cap regions of the complex respectively.[24][25] A proposed stoichiometric metric model of vault contains 96 copies of MVP, 2 molecules of TEP1, 8 molecules of VPARP and 3 or more copies of VRNAs.[24]

i. MVP (Major vault protein)

Primary structure of each MVP protein contains a central region, flanked by 7 short, 55 amino acid repeated sequences in the amino terminal and a coiled coil domain at the carboxyl terminal.[26] MVPs interact through the amino terminal coiled coil domain during vault formation. Amino acid 26-401 in the repeat unit has the characteristic protein sequence that is highly conserved across eukaryotes. In the N terminal domain 2-3 calcium binding EF hands can be found which thought to mediate the interaction of MVPs with other proteins through calcium.[27] Solution NMR spectroscopy reveals the presence of three stranded anti parallel sheets in the wall of the central barrel.[28] It is proposed that the MVPs are aligned at the Vault cap region through the coiled coil C terminal domain.[28][29]

ii. Vault Poly ADP ribosyl polymerase (VPARP)

The vault p193 subunit with 193 KD molecular mass shares similar catalytic domain with the poly (ADP-ribose) polymerase (PARP).[30] It is known to ribosylate ADP of its own as well

as MVP and has no other substrates, thus it was renamed as vault PARP or VPARP. The PARP proteins share 29-60% overall similarity only in their PARP domain[31] and this indicates their different cellular function (Table 1). VPARP which is present within the nucleus is not associated with other vault components[30] and contains a BCRT(Breast Cancer Carboxy-Terminal) domain which assists PARP-1 in its interaction with base excision repair complex protein XRCC1.[32] This may indicates that like other PARP proteins the VPARP or even the entire vault may be involved in DNA damage repair.

iii. Telomerase Associated Protein 1

Another minor vault protein the p240 was previously identified to be associated with the telomerase complex and hence named Telomerase-associated protein 1 (TEP1).[25][33] The function of TEP1 within the telomerase complex is still not clear, but it was shown to interact with telomerase RNA (TR)[33] and vault RNAs (vRNAs).[25] As TERT and TR are the only two functionally important components of the telomerase, the TEP1 is thought to perform a structural role only[34][35], this is also supported by the analysis of a TEP1 deficient mouse model and also from the fact that the telomere length remains unaffected after TEP1 disruption.[36] In fact normal vault particles can also be found from the tissues of TEP1 knockout mice with only a decreased electron density at the ends of vault caps was revealed by cryoelectron microscopy.[37] The absence of TEP1 did not seem to affect the association of TR with the telomerase complex but the association of vRNA was severely disrupted suggesting the importance of TEP1 for stable association between the vRNA and the vault complex.[37]

iv. Vault RNA

As mentioned earlier the vRNA constituting less than 5% of the complex is thought to be a functional component as its disruption leaves the morphology of the vault complex unaltered.[5] [24] [36] The length of these short polymerase III transcripts is species-specific and ranges between of 86-141 bases. The copy number of vRNAs vary from species to species, for example: rats and mice have one 141 bases long vRNA[38][39], bullfrogs (*Rana catesbiana*) have 2 vRNAs of 89 and 94 bases length.[38] The presence of vRNA in sea urchin (*Strongylocentrotus purpuratus*) was confirmed[40] but its sequence is not yet been determined. The function of relatively long rodent vRNA is thought to be supplemented by multiple vRNAs in other species.[26] In humans there are related vRNAs: hvg1 (98 bases), hvg2 (88 bases), and hvg3 (88 bases). The respective genes are situated in a cluster on Chr.5

in triple repeats and are thought to arose by gene duplication.[41] Apart from these a fourth putative human vRNA – hvg 4 has been reported recently.[42] [43]

New concepts: Vaultosomes and Vault nanocapsules

1. Vaultosomes

In presence of potassium tellurite (K2TeO3) in the culture medium the MVP no longer concentrate near the nucleus in HeLa cytosol, instead large, irregularly shaped cytoplasmic aggregrates of MVP of about 7 µm diameter are found mostly at the cell margins where the cells come in contact with the substrate, suggesting a possible migration of the vault particles to the cell margin in response to tellurite treatment.[44] This temperature sensitive aggregation can occur within 15 min at as little as 5 µm tellurite concentrations. Moreover immunostaining with a polyclonal anti VPARP antibody reveals a large aggregation of VPARP at the cell periphery in presence of tellurite. This peripheral accumulation of MVP and VPARP is most likely to occur within intact vaults forming large vault aggregates referred to as Vaultosomes.

Basis of formation of vaultosome

Formation of vaultosomes by treating cells with ALLN (N-acetyl-Leu- Leu-Norleucinal), an inhibitor of neutral cysteine proteases suggests the accumulation of thiol-modified proteins in the vicinity of the vaultosomes indicating the involvement of vaults in the complex biochemical sensing and response to changes in the thiol:redox buffering system as selenium and tellurium compounds are known to be thiol reactive reagents which perturb the thiol:redox buffering system.[45] [46] Therefore vaults show marked responses to these toxic oxyanions.

Probable function of vaultosomes

Large internal size of vaultosome is suggestive of their ability to house peripheral macromolecular complexes in response to tellurite treatment. Recent workers have shown that vaults are able to open and close transiently[47] creating possibilities to harbour complexes of organic telluroproteins[48], macromolecular complexes involved in the reduction of tellurite to elemental tellurium[49][50], or components of the thiol:redox system, these functions are yet to be determined.

2. Vault nanocapsule

Historical background of the Development

In 2003 Dr. Leonard Rome and his co-workers used an insect virus expression system to bioengineer the vault particle to contain two different metal binding sites for broad nano-systems application. Both the hexahistidine-tagged major vault protein (6-HIS-MVP) and the MVP with a cadmium binding peptide at the N-terminus produced proteins that assembled into vault-like particles in which both tags were localized to the central waist region by Cryo-EM reconstructions.

Cadmium tagged MVPs have increased stability compared to untagged or 6-HIS tagged particle as suggested by the better formation of cd-MVP vaults under the electron microscope.

As vault particle are known to open on deposition on a polylysine-coated surface[5], researchers are now trying to stimulate the interconversion of opened and closed conformations by probing vault conformation in solution using multiangle laser light scattering (MALLS) and spectrofluorimetry, to control the loading and release of entrapped materials. Recent workers are now trying to design particles aimed at encapsulating fluorescent probes, enzymatically active protein domains and chemically active small molecules.

Uses of Vault nanocapsule

Bioengineered vault nanocapsules are thought to have a wide variety of biological applications including drug delivery, biological sensors, enzyme delivery, controlled release, and nano-electrical machine (NEMS) applications. Vaults with binding sites for toxic metals can also be used in environmental and medical detoxification.

Use of engineered vault nanocapsules to act as potent adjuvants for the induction of combined cellular and humoral immune responses has already been established. There are evidences that immunization of OVA (Ovalbumin) encased in vault nanocapsules, was more effective at generating greater cellular immunity characterized by increased numbers of OVA responsive memory CD8+ and CD4+ T cells. Modification of the vault body, by addition of the “Z” domain has also been reported to alter the level of anti-OVA Ig subclass as shown by an increased IgG1:IgG2C ratio. These findings show that immune responses against OVA induced by vault nanoparticles differ compared to those induced by liposomes.[51]

Function of vaults

Detailed observation of individual components of the vault particles led to the development of a comprehensive structural model of these particles, but the functional aspect remained less elucidated. Following are some of the functions proposed by several workers.

1. Nucleocytoplasmic transport

Based on the subcellular localization and typical structure of the vault complex several researchers have proposed the role of vault particle in intracellular transport, particularly nucleocytoplasmic transport. The hypothesis of vaults being transported along cytoskeletal elements, (specially in microtubule) which would certainly enable vaults to shuttle cargo directionally to specific locations in the cell has emerged from the facts that these particles partially colocalize with cytoskeletal elements.[15] [16] [17] They are also found near secretory organelles in nerve growth factor treated PC12 neuron-like cells[16] and vaults are actively transported within axons between the soma and the nerve terminal.[52] Moreover, detection of vaults in close proximity to the nuclear pore complex in rat fibroblasts, also strengthen the above hypothesis. Chugani's observation[11] may reflect vaults docking at the nuclear pore in order to take up or give off cargo, but the nature of these cargos remained unclear.

2. Cellular homeostasis and development

Various researchers associated vaults with cellular homeostasis and development. So far three different MVP genes are discovered in *Dictyostelium*, which code for MvpA, MvpB and MvpC of Mr (Relative molecular mass) 94 000, 92 000 and 92 000, respectively.[53] [10] On disruption of two (MvpA and MvpB) of these three genes, growth stops under nutritional stress-this indicates the involvement of vault particles in fundamental processes such as proliferation and cell survival. However in mammals where only single genes code for the vault proteins, knockout mice with TEP1 and MVP disruptions[54] [36] [37] were healthy, fertile and showed no obvious abnormalities in spite of the absence of distinguishable vault particles in the MVP knockout.[54]

3. Vaults and multidrug resistance

A protein of Mr 110000 which was found to be overexpressed in a non-small-cell lung cancer cell line selected for doxorubicin resistance that did not express P-gp (permeability glycoprotein)[55], named initially as LRP (Lipoprotein receptor-related protein) and later identified by screening of expression library as the human MVP.[56] This finding suggested a role for vaults in drug resistance.

Involvement of vaults in putative transport, drug handling and cellular distribution of fluorescent anthracyclines in vault-expressing resistant cell lines led to the hypothesis of vaults being involved in transport of drugs away from their subcellular targets by mediating the extrusion of drugs from the nucleus and/or the sequestration of drugs into exocytotic vesicles (see Figure 6 for an overview). Vaults are thought to operate in conjunction with ABC transporters present in various (intra) cellular membranes. Properties and localization of TEP1 and VPARP also indicates the involvements of vaults in the protection of the genome and imparting a drug resistance profile.

4. Vaults as analytical marker

The proposed connection of MVP with multidrug resistance has led several researchers to analyse its expression in human tumours focussing on whether MVP expression level can be used to predict clinical outcome after chemotherapy.

i) Acute myeloid leukemia (AML)

MVP is expressed in 26–91% of patients diagnosed for Acute myeloid leukemia (AML).[57][58] Correlation between MVP expression and other prognostic variables such as FAB (French–American–British) classification, older age, high white blood cell count or unfavorable karyotype is absent[57] [58] Based on data obtained so far, it can be said that MVP expression is observed in a considerable proportion of the patients, but concrete evidence regarding its prognostic significance is still lacking.

ii) Acute lymphoblastic leukemia (ALL)

Role of MVP in ALL is not well documented still now. Proportion of positive patients in childhood ALL ranges from 10% at diagnosis up to 68% at relapse[59] [60][61] In childhood ALL intracellular retention of daunorubicin is reduced with increase in MVP expression, rather than with P-gp or MRP expression which in fact is associated with a higher level of in vitro drug resistance, in general. These findings indicate an important role for MVP in the development of resistance to other diseases ALL. A group of scientists have shown greater occurrence of MVP expression at relapse (68%) than diagnosis (47%), suggesting that induction of MVP expression can occur during chemotherapy.[59] Like AML there is no significant correlation between other prognostic measures and MVP expression in case of ALL as well.

iii) Multiple myeloma (MM)

Studies concerning the prognostic significance of MVP using the immunocytochemistry have revealed MVP expression in 47–74% of Multiple myeloma patients who have not been under any treatment[62][63], but more researches are required to establish a role of MVP in MM.

iv) Solid tumors

Role of MVP in solid tumors is not well studied till date. Researches concerning the role of MVP in ovarian cancer indicate that in advanced ovarian cancer FIGO (International Federation of Gynecology and Obstetrics) stage III/IV and in localized cancer FIGO stage I/II, almost 77% of the patients express MVP at diagnosis i.e. a correlation was found between MVP expression and lack of response and/or shorter OS (overall survival) which was opposite in early-stage ovarian cancer.[64] [65] In colorectal tumors where the strongest expression of MVP is found, increase in expression from premalignant lesions such as colonic adenoma to aggressive colon carcinoma indicates that MVP may be associated with more aggressive disease.[66][67]

Table 1: Different PARPs and their functional aspects. Table adapted from Sejal Vyas et al (2014).[74]

PARP	Alternative names	Demonstrated activity*	Predicted activity	ADP-ribose-binding domains	Cancer-related functions	Cancers to target
PARP1	PARP and ARTD1	PAR[10]	PAR	ND	DNA repair[14], ERK and NF-κB signalling[118] and heat shock response[119]	Those that are homologous recombination-deficient and those with increased ERK and NF-κB signalling
PARP2	ARTD2	PAR[120]	PAR	ND	DNA repair[120]	Those that are homologous recombination-deficient
PARP3	ARTD3	MAR[121]	PAR	ND	DNA repair[122]	ND
PARP4	VPARP and ARTD4	MAR[61]	PAR	ND	ND	ND
PARP5A	TNKS1 and ARTD5	PAR[123]	PAR	ND	Telomere maintenance[124], WNT signalling[125], proteasome regulation[126], stress granule assembly[17] and cell division[127]	Solid tumours with increased WNT signalling that are telomerase-dependent and stress granule-positive
PARP5B	TNKS2 and ARTD6	PAR[128]	PAR	ND	Telomere maintenance[128] and WNT signalling[125]	Those with increased WNT signalling and that are telomerase-dependent
PARP6	ARTD17	ND	MAR[3]	ND	Negative regulator of proliferation[62] and potential tumour-suppressive functions	Unknown
PARP7	TIPARP and ARTD14	MAR[64]	MAR	WWE domain	ND	ND
PARP8	ARTD16	ND	MAR[3]	ND	ND	ND
PARP9	BAL1 and ARTD9	No automodification activity[113]	Inactive[3]	Two macro domains	Cell migration[60]	Metastatic cancers
PARP10	ARTD10	MAR[3]	MAR	ND	Inhibits MYC[88] and NF-κB[57] signalling and is pro-apoptotic[91]	Might have potential tumour-suppressive functions; therefore, increasing its expression in tumours might be useful
PARP11	ARTD11	ND	MAR[3]	WWE domain	ND	ND
PARP12	ARTD12	MAR[17]	MAR	WWE domain	Stress granule assembly[17]	Solid tumours that are stress granule-positive
PARP13	ZAP, ZC3HAV1 and ARTD13	No automodification activity[3]	Inactive[3]	WWE domain	Stress granule assembly[17] and miRNA–RISC regulation[17,56]	Solid tumours that are stress granule-positive
PARP14	BAL2 and ARTD8	MAR[3]	MAR	Three macro domains and a WWE domain	B cell survival[102], cell migration[52] and stress granule assembly[17]	Haematopoietic malignancies and metastatic cancers
PARP15	BAL3 and ARTD7	MAR[17]	MAR	Macro domain	Stress granule assembly[17]	Solid tumours that are stress granule-positive
PARP16	ARTD15	MAR[61,70]	MAR	ND	UPR[61]	UPR-dependent tumours

ARTD, ADP-ribosyltransferase diphtheria-toxin-like; BAL, B aggressive lymphoma; MAR, mono(ADP-ribose); miRNA, microRNA; ND, not determined; NF-κB, nuclear factor-κB; PAR, poly(ADP-ribose); PARP, PAR polymerase; RISC, RNA-induced silencing complex; TNKS, tankyrase; UPR, unfolded protein response; WWE, Trp-Trp-Glu; ZAP, zinc finger antiviral protein; ZC3HAV1, zinc finger CCCH-type antiviral protein 1. *Catalytic activity is based on the ability of PARPs to automodify when incubated with NAD^+.

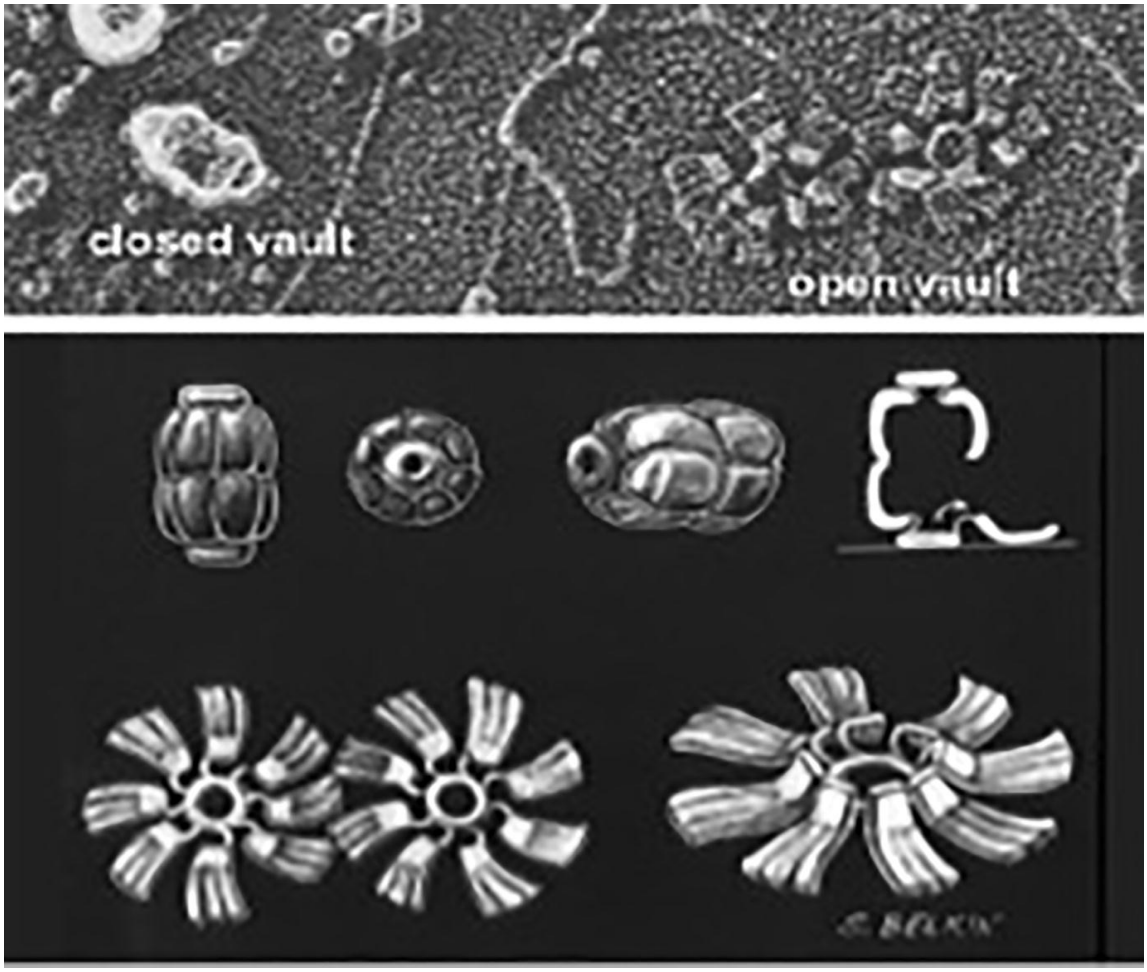

Figure 1: Electron microscopic photo and model of vaults (open and close). The cryoelectron micrograph above is taken by John Heuser (Wash U , St. Louis) and the model below is adapted from Kedersh et al (1991).[22]

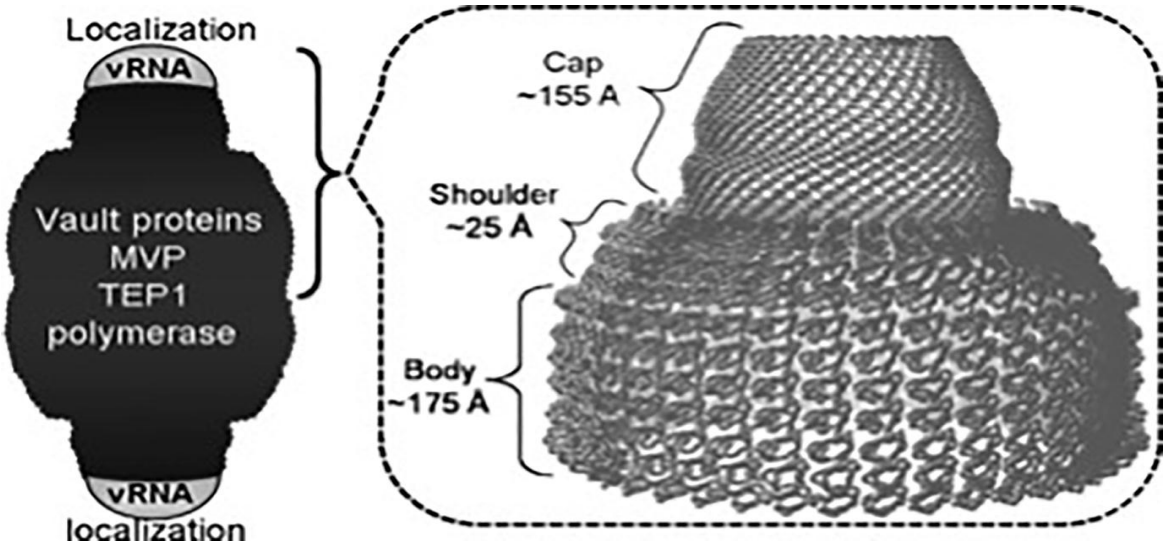

Figure 2: Vault particle component (Figure adapted from Gopinath SCB et al, 2010.[72]

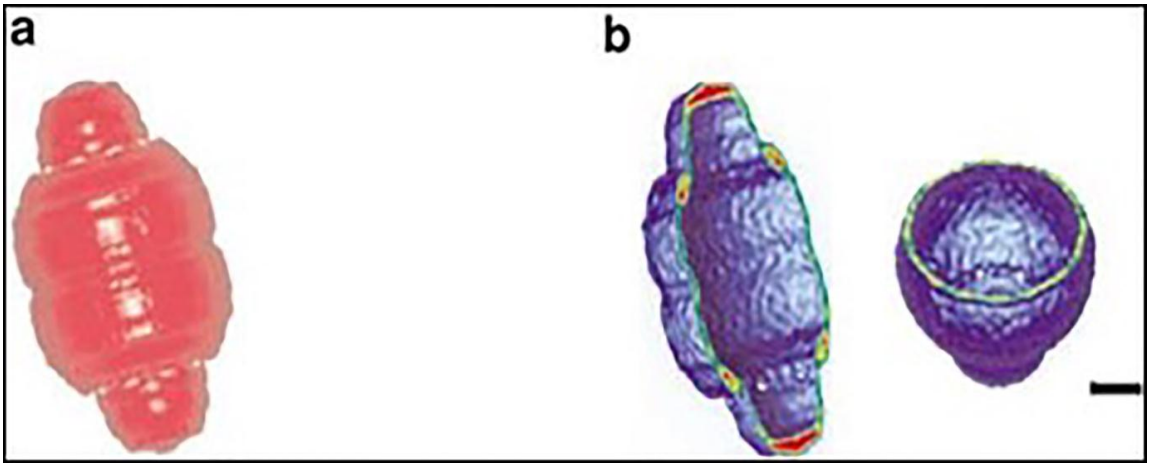

Figure 3: Reconstruction of the vault complex at a 22 Å resolution. (a) including two cropped views (b). Clearly visible is the symmetrical hollow barrel-shaped structure and two protruding caps. Figure reproduced from Kong et al. (2000).[24]

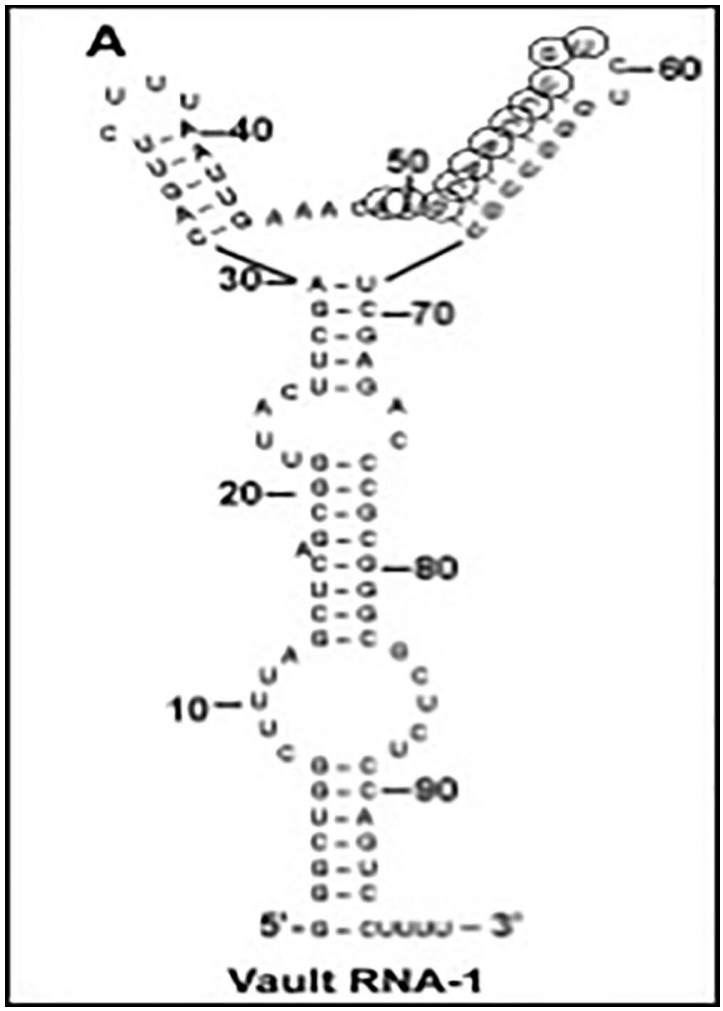

Figure 4: A, predicted secondary structure of vRNA-1 (RNA structure 3.71). Probable binding regions with mitoxantrone are indicated with circles. Figure adapted from Gopinath et al (2010).[72]

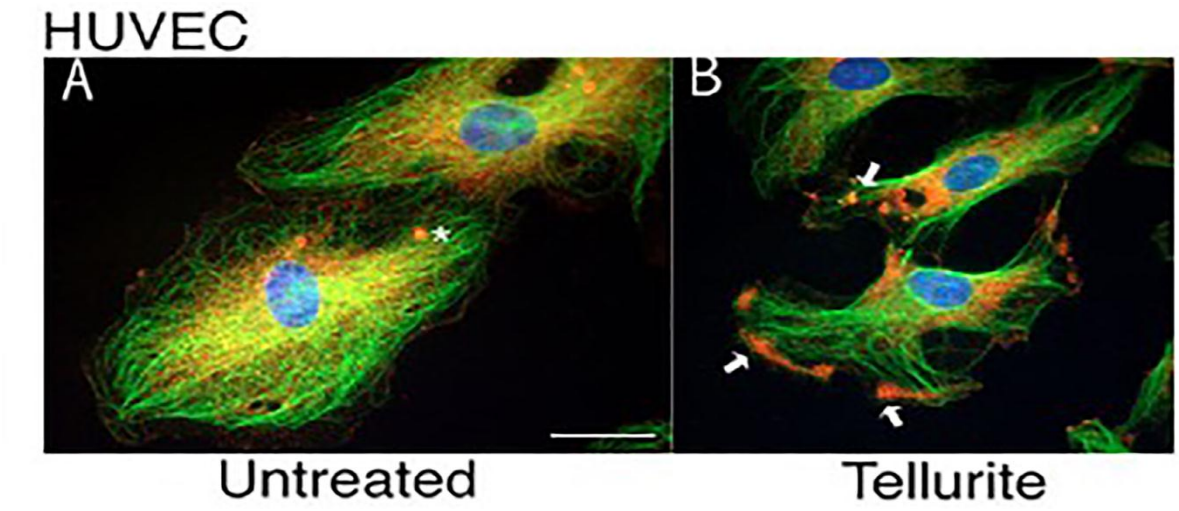

Figure 5: Vault aggregation in normal human vascular endothelial cells (HUVECs) and the HeLa cancer cell line. HUVECs were incubated at 37°C for 30•min in the presence (A) or absence (B) of 0.5•mmol•l–1 K2TeO3 and subsequently stained with antibodies against MVP Vault aggregation in normal human vascular endothelial cells (HUVECs) and the HeLa cancer cell line. HUVECs were incubated at 37°C for 30·min in the presence (A) or absence (B) of 0.5·mmol·l–1 K2TeO3 and subsequently stained with antibodies against MVP (red) and tubulin (green). MVP aggregates form at the cell periphery in HUVECs (arrows). Figure adapted from Suprenant et al (2007).[44]

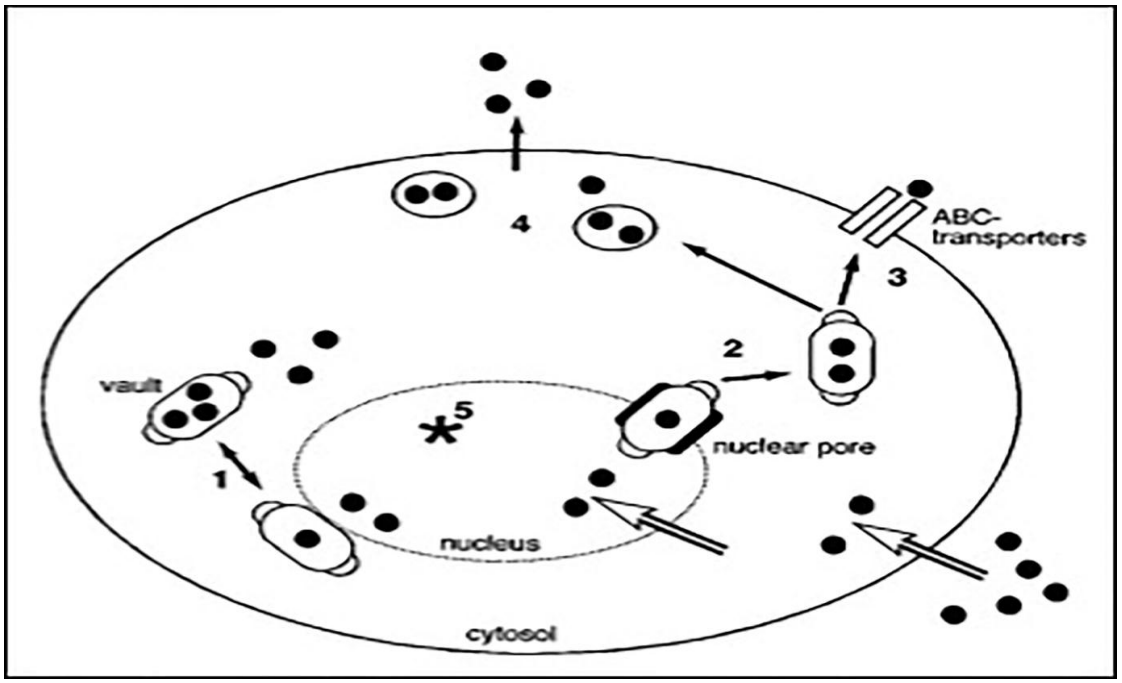

Figure 6: Schematic view of the hypothetical role of vaults in nucleocytoplasmatic and vesicular transport of drugs and/or metabolites. Vaults may be involved in the intracellular compart- mentalization and/or transport of biomolecules, particularly as it

concerns nucleocytoplasmice transport (1 and 2). Vaults may mediate multidrug resistance by transporting drugs away from their intracellular targets, for example, the nucleus (2) or by transporting them to efflux pumps (3) or exocytotic vesicles (4). Based on the characteristics of the minor vault proteins, vaults or vault components are possibly involved in the maintenance of genomic stability, indicated by an asterisk (5). Open arrows represent diffusion and black arrows represent active directional transport. Black dots indicate drugs and biomolecules. Figure adapted from Mossink Et al 2003.[6]

CONCLUSIONS/FUTURE PROSPECTS

In addition to the association of MVP/vaults with chemoresistance in primary tumors and various tumor cell lines, MVP is also identified as negative prognostic factor for response to chemotherapy and/or disease-free survival (DFS) and/or OS by several clinical studies. Till date few studies have attempted to answer the question whether vaults themselves play a direct role in drug resistance or whether they have to be merely considered as a marker of a drug resistance phenotype. In murine cells, the hypersensitivity for drugs is not associated with absence of vaults[68], whereas in colon carcinoma cells with MVP/vaults-overexpression, anthracyclines are cleared from the nucleus in an MVP- dependent fashion.[69][70]

Additional researches are required to determine the prognostic significance of vaults expression in different tumor samples. Matters like the ability of intact vaults to bind and transport drugs, association and copurification of vaults with exocytotic vesicles and also the subcellular localization and dynamics of vault complex requires further investigations. In fact the normal cellular function of vaults and its relation to the nonvault-associated pools of VPARP and TEP1 need to be studied further. New researches lead to determination of putative vault cargo, additional VPARP substrates, role of VPARP in the nucleus and the determination of the conditions that induce VPARP activity. It was recently published that both VPARP and vRNA are also partially associated with the telomerase complex[71], since then possible crosstalk and cooperation between vaults and the telomerase complex has provoked mush interest.

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