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Formation of molecular species of mitochondrial cardiolipin. 2. A mathematical model of pattern formation by phospholipid transacylation

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Summary

Formation of the unique molecular species of mitochondrial cardiolipin requires tafazzin, a transacylase that exchanges acyl groups between phospholipid molecular species without strict specificity for acyl groups, head groups, or carbon positions. However, it is not known whether phospholipid transacylations can cause the accumulation of specific fatty acids in cardiolipin. Here, a model is shown in linear algebra representation, in which acyl specificity emerges from the transacylation equilibrium of multiple molecular species, provided that different species have different free energies. The model defines the conditions and energy terms, under which transacylations may generate the characteristic composition of mitochondrial cardiolipin. It is concluded that acyl-specific cardiolipin patterns could arise from phospholipid transacylations in the tafazzin domain, even if tafazzin itself does not have substrate specificity.

Keywords

Cardiolipin; Fatty acids; Phospholipids; Tafazzin; Thermodynamics

1. Introduction

Mitochondrial cardiolipin (CL) shows a unique organization of molecular species, in which one or two types of fatty acids dominate and in which there is a high abundance of molecules with four identical acyl residues [1]. While the functional significance of this pattern has remained elusive, it has become clear that it is strictly dependent on the function of tafazzin because the acyl specificity of cardiolipin vanishes in human Barth syndrome and in several experimental models of tafazzin deficiency [2–5]. We have shown that tafazzin is a phospholipid-lysophospholipid transacylase that displays strong acyl specificity when assayed in mitochondrial membranes [6]. However, subsequent studies on the purified enzyme have shown that tafazzin exchanges acyl residues between multiple phospholipid species without strict specificity for acyl groups, head groups, or carbon positions [7]. Naturally, this raises questions about the mechanism, by which tafazzin generates acyl specificity. Here I propose an alternative model, in which acyl specificity emerges from the transacylation equilibrium

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rather than the substrate specificity of tafazzin. The model is based on the following assumptions:

- i. Tafazzin acts as an unrestricted facilitator of acyl exchange between various phospholipid species, including *sn*-1 and *sn*-2 positions. Although the catalytic rate may not be exactly identical for all acyl species, kinetic terms are neglected in the model.
- ii. Different molecular species make different free energy contributions due to specific interactions within mitochondrial membranes.
- iii. The effects of phospholipid *de novo* formation and phospholipid reacylation with acyl-CoA are negligible, i.e. the model applies only to membrane domains, in which the lipid composition is determined by the chemical equilibrium of the tafazzin reaction.

The model does not specify a mechanism of species selection, but rather uses a linear algebra approach to calculate equilibrium states, in which minimization of the composite free energy prevents randomization of acyl distribution.

2. Mathematical model

2.1. Transacylation space

To fully comprehend the consequences of acyl group exchanges between multiple phospholipid species, one has to find an appropriate mathematical representation of molecular compositions. In the case of 1,2-diacyl-phospholipids, square matrices provide a logical and expandable framework, by which compositions can be specified, mapped, and made accessible to computations. Thus, in this paper the molecular composition of a phospholipid that contains n types of fatty acids, is given by the $n \times n$ square matrix

$$M = \begin{pmatrix} m_{11} & \cdots & m_{1n} \\ \vdots & \ddots & \vdots \\ m_{n1} & \cdots & m_{nn} \end{pmatrix}, \quad (1)$$

in which the element m_{ij} defines the concentration of the molecular species with fatty acid i in 1-position and fatty acid j in 2-position. As a natural extension of this idea, fatty acid patterns are represented as vectors

$$v = \begin{pmatrix} v_1 \\ v_2 \\ \vdots \\ v_n \end{pmatrix}, \quad (2)$$

in which the elements v_i define the proportions of the individual fatty acids. As a matter of convenience, all elements will be treated as fractions, so that

$$\sum_i^n \sum_j^n m_{ij} = \sum_i^n v_i = 1. \quad (3)$$

With these definitions at hand, the relation between the composition of molecular species $\mathbf{M}$ and the composition of fatty acids $\mathbf{v}$, can be written as

$$\frac{1}{2}(\mathbf{M} + \mathbf{M}^T)\mathbf{u} = \mathbf{v}, \quad (4)$$

where $\mathbf{M}^T$ is the transposon of matrix $\mathbf{M}$ and $\mathbf{u}$ is an n -dimensional vector, all elements of which

equal one,
$$\mathbf{u} = \begin{pmatrix} 1 \\ \vdots \\ 1 \end{pmatrix}.$$

Equation (4) merely shows in compact notation, how one would ordinarily calculate the fatty acid pattern from the composition of molecular species. However, this equation acquires special significance in the context of transacylations, such as the tafazzin reaction, because it specifies the complete set of molecular compositions $\mathbf{M}$ that can be derived from a given fatty acid composition $\mathbf{v}$, provided that all possible combinations of acyl exchange may occur. In that sense, the equation defines the operational boundaries of the tafazzin reaction. If one thinks of molecular compositions as points in n^2 dimensional space, equation (4) maps out the subspace of all possible molecular compositions associated with a particular fatty acid pattern. This subspace is herein referred to as the “transacylation space”.

2.2. Free energy map

The transacylation space can be regarded as a continuous field of configurations, all of which are molecular compositions that satisfy equation (4). Since we are merely dealing with configurational changes in the fatty acid distribution, there is an associated field of entropies. That is, in the present framework, the concentrations of molecular species can be treated as probabilities, i.e. m_{ij} is the probability that a randomly selected phospholipid molecule has fatty acid i in 1-position and fatty acid j in 2-position. Consequently, the associated entropy can be calculated from the concentrations of molecular species by

$$S = -kN \sum_i \sum_j (m_{ij} \log m_{ij}), \quad (5)$$

where k is Boltzmann's constant, N is the number of molecules, and $\log$ stands for the natural logarithm. The molecular composition with the highest entropy is the one created by random fatty acid distribution, for which probability theory holds that each element of the compositional matrix has to satisfy the equation

$$m_{ij} = v_i v_j. \quad (6)$$

Therefore, any non-random molecular composition $\mathbf{M}$ ($\mathbf{M} = [m_{ij}]$) requires an input of free energy equivalent to

$$\Delta G = TkN \sum_i \sum_j (m_{ij} \log m_{ij} - v_i v_j \log v_i v_j), \quad (7)$$

where T is the temperature. Equation (7) produces an energy map of the transacylation space as it assigns a ΔG value to each molecular composition in reference to the state of random acyl distribution. In that context, the notion of distance exists within the transacylation space, which is an objective measure of the difference between compositions. Using basic algebraic rules [8], the difference between two molecular compositions M_A and M_B is given by

$$\text{Difference} = \sqrt{\text{Tr}[(M_A - M_B)^T(M_A - M_B)]} = \sqrt{\sum_i \sum_j (a_{ij} - b_{ij})^2}, \quad (8)$$

where a_{ij} and b_{ij} are the elements of M_A and M_B respectively.

3. Results

In the following, the concept of transacylation space will be examined for two cases, namely transacylations between molecular species of a single phospholipid and transacylations between two different phospholipids. Then, insight gained from these analyses will be applied to the remodeling of CL in mitochondria.

3.1. Transacylations between molecular species of a single phospholipid

Let us imagine a single 1,2-diacyl-phospholipid with two fatty acids, X and Y. Obviously, four molecular species can be formed and the molecular composition M and the fatty acid composition v can be written as

$$M = \begin{pmatrix} m_{XX} & m_{XY} \\ m_{YX} & m_{YY} \end{pmatrix}; \quad v = \begin{pmatrix} v_X \\ v_Y \end{pmatrix}. \quad (9)$$

If the two fatty acids exchange freely between all molecular species and if there is no preference for either carbon position, the molecular composition will be

$$M_0 = \begin{pmatrix} v_X^2 & v_X v_Y \\ v_X v_Y & v_Y^2 \end{pmatrix}, \quad (10)$$

reflecting random fatty acid distribution. However, if external forces favor for instance molecular species with two identical fatty acids, the concentration of these species will increase at the expense of heterogeneous species, shifting the molecular composition towards

$$M_m = \begin{pmatrix} v_X & 0 \\ 0 & v_Y \end{pmatrix}. \quad (11)$$

M_0 and M_m represent opposing states, the former having the highest entropy and the latter having the lowest free energy. Therefore, the actual molecular composition is likely to be found in between and can be expressed as a scaled sum of M_0 and M_m

$$M = (1 - \gamma)M_0 + \gamma M_m. \quad (12)$$

In equation (12), γ is the degree of remodeling ($0 \leq \gamma \leq 1$), which defines the status of the transacylation system and which depends on the magnitude of the thermodynamic driving force, i.e. the interaction energies that cause species selection. Assuming that the two fatty acids are present in equal proportion ($v_X = v_Y = 0.5$), the interaction energy can be calculated from γ by substituting into equation (7):

$$\frac{\Delta G}{\text{TkN}} = \frac{1}{2} \left[(1+\gamma) \log \frac{1+\gamma}{4} + (1-\gamma) \log \frac{1-\gamma}{4} \right] + \log 4. \quad (13)$$

A plot of equation (13) shows that remodeling becomes more costly from the energetic point of view as the transacylation system moves further away from the point of randomness (Fig. 1). Complete remodeling, i.e. conversion of the molecular composition from M_0 to M_m , can be achieved in this specific example at the expense of 427 cal/mol.

While the present model does not specify the driving forces of remodeling, several mechanisms exist in biological membranes, which may potentially select molecular species. First, the presence of membrane domains may favor certain molecular species; second, the formation of membrane curvature may impose constraints on lipid packing, which may favor one type of species over another; and third, membrane proteins may selectively interact with certain molecular species. These membrane properties, alone or combined, could select the optimal species composition if a transacylation mechanism is available. These properties also determine the values of the empirical remodeling parameters α , β , γ and ϕ (see below).

3.2. Transacylations between two phospholipids

Let us now turn to transacylations between two different phospholipids, A and B. Again, we are considering only two types of fatty acids, X and Y, so the molecular compositions can be written as

$$M_A = \begin{pmatrix} a_{XX} & a_{XY} \\ a_{YX} & a_{YY} \end{pmatrix} \text{ and } M_B = \begin{pmatrix} b_{XX} & b_{XY} \\ b_{YX} & b_{YY} \end{pmatrix}. \quad (14)$$

If fatty acids distribute randomly, the molecular compositions of A and B must equal M_0 , as defined by equation (11), except that v_X and v_Y are now the total concentrations of X and Y in the A–B reaction system. As in the previous example, randomness prevails in the absence of thermodynamic forces to organize the molecular species, i.e. if $\Delta G = 0$.

Next, let us assume that fatty acid X accumulates in phospholipid A because X lowers the free energy of molecular species of A (but not of B). To work this fact into the model, the empiric factor ϕ ($1 \leq \phi < \infty$) is introduced, by which the probability of a given molecular species of A increases in relation to another molecular species of A if the former contains one more residue of X. As a result, the molecular composition of A is transformed by the factor matrix

$$\Phi = \begin{pmatrix} \phi^2 & \phi^1 \\ \phi^1 & \phi^0 \end{pmatrix}, \quad (15)$$

which assigns a multiplier to each molecular species depending on how many residues of X it contains. Φ is a function that acts on the random composition M_0 and transforms it into the remodeled composition by forming the Hadamard product $\Phi \circ M_0$ [9]. After proper normalization, the molecular composition of phospholipid A becomes

$$M_A = \frac{1}{\langle \Phi | M_0 \rangle} (\Phi \circ M_0), \quad (16)$$

where $\langle \Phi | M_0 \rangle$ is the inner product of Φ and M_0 . Finally, the molecular composition of phospholipid B can be calculated from M_A by the rule of mass conservation:

$$\begin{aligned} b_{xx} &= \left[2v_x - (M_A + M_A^T) \begin{pmatrix} 0.5 \\ 0 \end{pmatrix} \right]^2 \\ b_{xy} &= b_{yx} = \left[2v_x - (M_A + M_A^T) \begin{pmatrix} 0.5 \\ 0 \end{pmatrix} \right] \left[2v_y - (M_A + M_A^T) \begin{pmatrix} 0 \\ 0.5 \end{pmatrix} \right] \\ b_{yy} &= \left[2v_y - (M_A + M_A^T) \begin{pmatrix} 0 \\ 0.5 \end{pmatrix} \right]^2 \end{aligned} \quad (17)$$

In the above example, acyl specificity is generated by asymmetric transacylation of fatty acids between two phospholipids. Their molecular compositions are determined by the function Φ , which has two effects, (i) it increases the proportion of X in phospholipid A at the expense of phospholipid B, and (ii) it re-distributes the molecular species of phospholipid A in favor of XX. However, other types of pattern formation may exist and they can be put into the model using a similar approach. For instance, if fatty acid X were to prefer the 1-position in phospholipid A, but the 2-position in phospholipid B, the functions

$$\Phi_A = \begin{pmatrix} 1 & 1+\alpha \\ 1-\alpha & 1 \end{pmatrix} \text{ and } \Phi_B = \begin{pmatrix} 1 & 1-\beta \\ 1+\beta & 1 \end{pmatrix} \quad (18)$$

could be substituted into equation (16) to yield M_A and M_B . In that case, positional specificity would result as a function of the empiric variables α and β ($0 \leq \alpha, \beta \leq 1$).

3.3. Remodeling of CL

The analysis of CL remodeling requires an expansion of the compositional matrix in order to account for the fact that CL carries two diacylglycerol moieties. Thus, the molecular composition of CL with n types of fatty acids can be represented as matrix of matrices

$$M = \begin{pmatrix} M_{11} & \cdots & M_{1n} \\ \vdots & \ddots & \vdots \\ M_{n1} & \cdots & M_{nn} \end{pmatrix} = [M_{pq}], \quad (19)$$

in which each element M_{pq} is defined as

$$M_{pq} = \begin{pmatrix} m_{p1q1} & \cdots & m_{p1qn} \\ \vdots & \ddots & \vdots \\ m_{pnq1} & \cdots & m_{pnqn} \end{pmatrix} = [m_{piqj}]. \quad (20)$$

Here, the variable m_{piqj} is the concentration of the molecular species with fatty acid p in 1-position of the 1'-glycerol, fatty acid q in 1-position of the 3'-glycerol, fatty acid i in 2-position of the 1'-glycerol, and fatty acid j in 2-position of the 3'-glycerol. For random fatty acid distribution, we find

$$m_{piqj} = v_i v_j v_p v_q. \quad (21)$$

As in the preceding examples, we will only consider two categories of fatty acids. Category L are fatty acids that accumulate in CL and category X are fatty acids that do not. The letter L was chosen for the former category because L is often linoleic acid. However, L can also be palmitoleic acid [6], palmitic acid [10], docosahexaenoic acid [11], or it may encompass two kinds of fatty acids, such as palmitoleic and linoleic acid [1], depending on species and tissue type. Accordingly, the molecular composition of CL is given by

$$M = \begin{pmatrix} m_{LLLL} & m_{LL LX} & m_{LL XL} & m_{LL XX} \\ m_{LX LL} & m_{LX LX} & m_{LX XL} & m_{LX XX} \\ m_{XL LL} & m_{XL LX} & m_{XL XL} & m_{XL XX} \\ m_{XX LL} & m_{XX LX} & m_{XX XL} & m_{XX XX} \end{pmatrix}. \quad (22)$$

We now let CL interact by transacylation with other mitochondrial phospholipids, specifically with PC and PE. If v_L is the concentration of L and v_X is the concentration of X in the entire transacylation system ($v_L + v_X = 1$), random fatty acid distribution ($\Delta G=0$) will generate the CL composition

$$M_0 = \begin{pmatrix} v_L^4 & v_L^3 v_X & v_L^2 v_X^2 & v_L v_X^3 \\ v_L^3 v_X & v_L^2 v_X^2 & v_L v_X^3 & v_X^4 \\ v_L^2 v_X^2 & v_L v_X^3 & v_L^2 v_X^2 & v_L v_X^3 \\ v_L v_X^3 & v_L^2 v_X^2 & v_L v_X^3 & v_X^4 \end{pmatrix}. \quad (23)$$

However, if the presence of L in CL confers a reduction in free energy, L will accumulate in CL and consequently X will accumulate in PC/PE. As a result, the CL composition will shift from M_0 to

$$M = \frac{1}{\langle \Phi | M_0 \rangle} (\Phi \circ M_0) \quad (24)$$

(see section 3.2.), where Φ is a factor matrix that is now defined as

$$\Phi = \begin{pmatrix} \phi^4 & \phi^3 & \phi^3 & \phi^2 \\ \phi^3 & \phi^2 & \phi^2 & \phi^1 \\ \phi^3 & \phi^2 & \phi^2 & \phi^1 \\ \phi^2 & \phi^1 & \phi^1 & \phi^0 \end{pmatrix}. \quad (25)$$

With the conservation rule $v_X = 1 - v_L$, the molecular composition of CL becomes

$$M = \frac{1}{\text{Trace}(\Phi^T M_0)} \begin{pmatrix} \phi^4 v_L^4 & \phi^3(v_L^3 - v_L^4) & \phi^3(v_L^3 - v_L^4) & \phi^2 v_L^2(1 - v_L)^2 \\ \phi^3(v_L^3 - v_L^4) & \phi^2 v_L^2(1 - v_L)^2 & \phi^2 v_L^2(1 - v_L)^2 & \phi v_L(1 - v_L)^3 \\ \phi^3(v_L^3 - v_L^4) & \phi^2 v_L^2(1 - v_L)^2 & \phi^2 v_L^2(1 - v_L)^2 & \phi v_L(1 - v_L)^3 \\ \phi^2 v_L^2(1 - v_L)^2 & \phi v_L(1 - v_L)^3 & \phi v_L(1 - v_L)^3 & (1 - v_L)^4 \end{pmatrix}. \quad (26)$$

In equation (26), the composition of CL is dependent only on v_L (concentration of L in the mitochondrial transacylation compartment) and ϕ (remodeling factor). A quick check reveals that CL has random acyl distribution for $\phi = 1$, but it will contain only a single molecular species (L₄-CL) for $\phi = \infty$:

$$M = M_0 \text{ if } \phi = 1$$

$$\lim_{\phi \rightarrow \infty} M = \begin{pmatrix} 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \quad (27)$$

This is consistent with the fact that L₄-CL is the ultimate product of the remodeling reaction, and with the notion that $\phi = 1$ represents the absence of remodeling, whereas $\phi = \infty$ represents maximal remodeling. The concentration of L₄-CL shows sigmoidal dependence on both v_L and ϕ (Fig. 2).

Although the formation of L₄-CL and other L-containing CL's decreases the total energy, they can only accumulate to a point where the decrease in energy balances the decrease in entropy. This balance of energy and entropy determines the empiric factor ϕ , which according to this model is a characteristic function of the membrane and can vary between different types of mitochondria.

3.4. Application of the model

The model was used to calculate the composition of CL of two different cell types, in which characteristic yet distinct profiles are present. The examples include liver mitochondria, where CL contains predominantly linoleic acid, and insect cell mitochondria, where CL contains predominantly palmitoleic acid [6,13]. For both examples, detailed analyses of the molecular species of CL are available [7,12]. First, the value of v_L was determined from the abundance of L (linoleic acid or palmitoleic acid) in total mitochondrial phospholipids. Then, the ϕ value with the best fit to the experimental data was determined and it was shown that the calculated pattern agrees well with the measured CL composition (Fig. 3).

The free energy requirement of remodeling was also estimated. For this purpose, the molar ratio of CL:PE:PC was assumed to be 1:4:5 [13], and the difference in free energy between random and remodeled fatty acid distribution was calculated either from the configurational

entropy by applying equation (7) to the entire ensemble of mitochondrial phospholipids, or from the mixing entropy of the exchanged fractions of L and X. Using either method, the estimated remodeling energies were about 120 to 150 cal per mol mitochondrial phospholipid for both mouse liver and insect cells. This equates to interaction energies of 1.2–1.5 kcal per mol CL, assuming CL interactions are the sole source of energy for the remodeling reaction.

4. Discussion

The present paper examines the consequences of a universal transacylation equilibrium between phospholipids. While global non-specific acyl exchange is generally expected to generate random acyl distribution, it is equally plausible that acyl-specific patterns may arise if differences in free energy exist between individual molecular species. A mathematical function was proposed, which converts the random composition M_0 into the remodeled composition $\Phi(M_0)$ in good agreement with measured CL patterns. Acyl specificity is created as a matter of self-organization, owing to specific interactions of individual molecular species within the membrane. The required interaction energies are low because they only have to overcome the entropy effect of non-random acyl distribution. One may speculate about the forces that bring about acyl group remodeling (see section 3.1.); however, it is certainly possible that the highly organized, protein-rich cristae membrane, imposes sufficient constraints to produce small energy differences between phospholipid molecular species. For instance, respiratory supercomplexes [14] and other organized membrane domains [15,16], some of which depend on CL for stability [17–19], may favor CL species with homogeneous acyl groups.

It remains puzzling why different mitochondria accumulate different fatty acid species in CL. According to the present model, this phenomenon could be caused by differences in membrane structure (affecting Φ) or by differences in fatty acid patterns (affecting M_0). Of course, other enzymes besides tafazzin may be involved in CL remodeling, such as acyl-CoA dependent acyltransferases, and they may modify the composition of CL as well. The overall remodeling process is certainly more complex than portrayed in this mathematical model. Different remodeling reactions may dominate in different compartments. In fact, it is likely that the transacylation equilibrium does not extend over the entire membrane but is confined to local domains, in which tafazzin is present. From the thermodynamic point of view, such domains would be highly flexible because they could easily transform their lipid composition in response to membrane alterations, such as changes in protein composition, membrane curvature, and so forth. In that sense, tafazzin may assist in assembly, folding, and dynamic reorganization of mitochondrial membranes.

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Abbreviations

Acyl species are abbreviated X:Y

where X specifies the number of carbon atoms and Y specifies the number of double bonds

CL

cardiolipin

PC

phosphatidylcholine

PE

phosphatidylethanolamine

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Fig. 1.

Free energy requirement of remodeling. The graph shows the dependence of $\Delta G/TkN$ on the degree of remodeling according to equation (13). The transacylation system consists of a single phospholipid with two fatty acids, which are present in equal proportions. Complete remodeling of this phospholipid from a composition of random fatty acid distribution to a composition in which all species have two identical fatty acids, requires 427 cal/mol.

Fig. 2. Dependence of the proportion of L₄-CL (m_{LLLL}) on ϕ (remodeling factor) and v_L (concentration of L in the transacylation compartment). The graph was calculated by equation (26).

Fig. 3.

Composition of CL in mitochondria from mouse liver and Sf9 insect cells. L represents linoleic acid (mouse liver) or palmitoleic acid (insect cells). X represents all other fatty acids. The upper bar graphs show the composition at random fatty acid distribution and the lower bar graphs show the remodeled composition. Black columns represent calculated patterns and red columns represent measured patterns [7,12]. Patterns were calculated by equation (26), assuming $v_L=0.20$ and $\phi=18$ for mouse liver, and assuming $v_L=0.33$ and $\phi=20$ for insect cells. The concentration of L in the transacylation compartment (v_L) was estimated from the fatty acid pattern of total mitochondrial phospholipids [6,13].