جامعة الملك سعود
King Saud University

Biochemistry437

Phospholipids of clinical significance

Biochemistry Team 437

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Color index:
Doctors slides
Doctor's notes
Extra information
Highlights

Respiratory block

EDITING FILE

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Objectives:

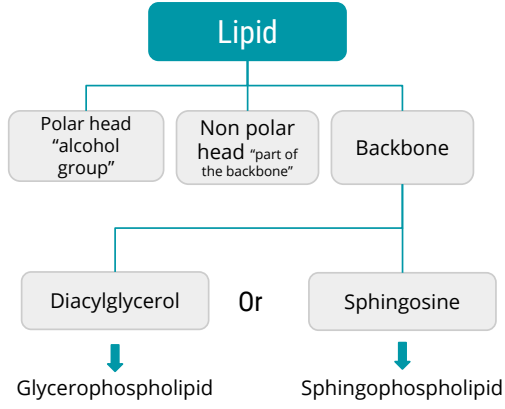
- identify the types and functions of phospholipids
- Discuss the physiological importance of phospholipids
- Understand the role of glycerphospholipids in lung surfactant and their clinical implications in respiratory distress syndrome (RDS)
- Identify the classes and physiological functions of phospholipase enzymes

OVERVIEW

- Types and functions of phospholipids
- Glycerophospholipids: Types, functions and role in lung surfactant, cell signaling and protein anchoring
- Respiratory distress syndrome (RDS)
- Sphingophospholipids
- Phospholipids in lipoprotein particles
- Phospholipases: Types and functions

PHOSPHOLIPIDS

- Phospholipids are **polar**[1], **ionic** compounds that contain an alcohol group attached either to (backbone):
  - Diacylglycerol* in this case we call it Glycerophospholipids
  - Sphingosine** in this case we call it Sphingophospholipids
- Major lipids of cell membranes Two classes:
  - Glycerophospholipids
  - Sphingophospholipids



Remember:

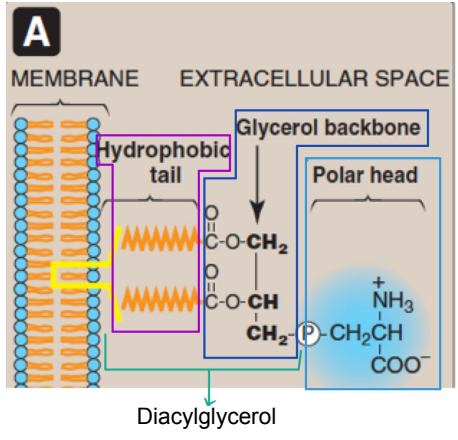
- Lipids are amphipathic molecules, meaning they have a hydrophilic end "polar group" and a hydrophobic end "non polar group".
- The have many functions including:
- Making o the lipid bilayer of the cell membrane, cell signaling, components of myelin sheath.

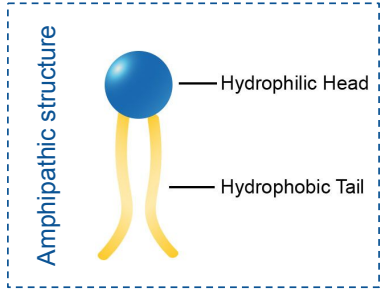
Tip:
Regarding structures, you don't have to know the shape, but it is important to know the names of the components in each structure. That has been said though, The pictures will help you identify the components, so please take a look at them

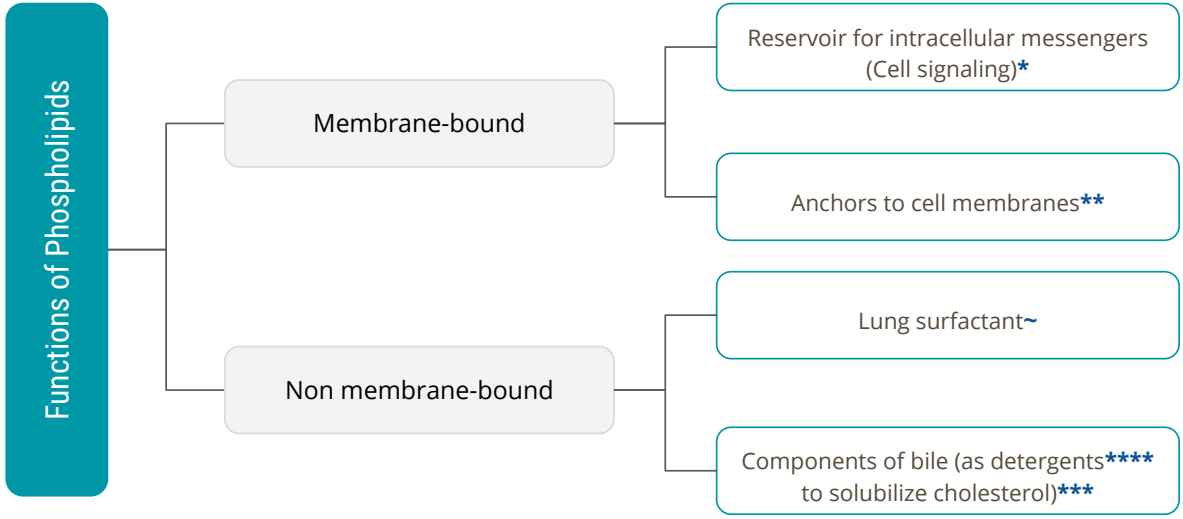
1- even though it is an amphipathic molecule, polar is written here because the polar head is responsible for all the interactions in the membrane
*is a glyceride consisting of two fatty acid chains covalently bonded to a glycerol molecule
**It's an amino alcohol with an unsaturated hydrocarbon chain (serine + palmitic acid)

Cont. PHOSPHOLIPIDS

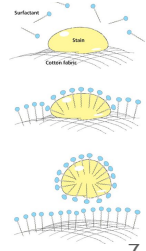
- Their hydrophobic (nonpolar) portion is **attached to the membrane**.
  "Considered Part of the membrane"
- Their hydrophilic (polar) portion extends outward **interacting with the aqueous environment.**



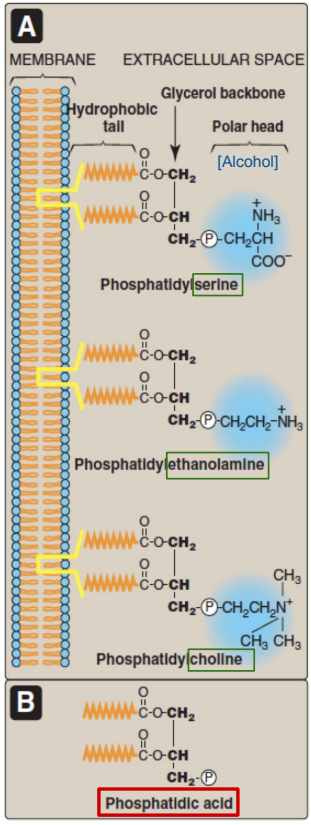




*E.g.: phosphatidylinositol "will be discussed later in this lecture".
**Attaching some proteins to the cell membrane to give it lateral mobility
~ a type of detergent, will be discussed in details.
**** bile is a fluid made in the liver and stored in the bile. It is released when we need to digest (solubilize) fat, meaning it works as a detergent.
What is a detergent? A molecule with a nonpolar end that attaches to the lipid, and a polar end that attaches to water. Because of this property, it can solubilize lipid in water."as Shown in the picture"
مثل مساحيق الغسيل عندما تقوم بتذويب البقع الدهنيه Team 435
***This property of detergents are used further in the body to solubilize (digest) cholesterol and to lower the surface tension.



GLYCEROPHOSPHOLIPIDS



- Also called phosphoglycerides.
- Contain glycerol.
- A major class of phospholipids.
- All contain phosphatidic acid (PA).
- PA is the simplest phospholipid.

- Phosphatidic acid (PA) is the **simplest** phospholipid
- It consists of **diacylglycerol and a phosphate group.**
- As we change the **alcohol** group "polar head" we get different fatty acid

Phospholipids are derived from PA "phosphatidic acid" such as:

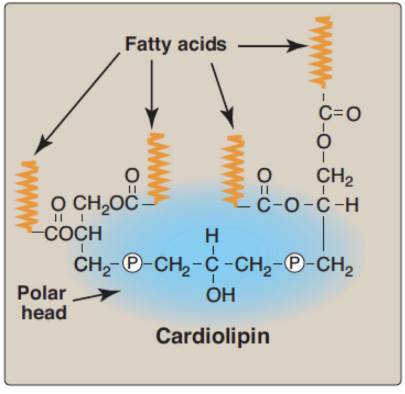
Alcohol+PA Serine + PA	Phosphatidylserine (PS)	*Cell signaling *Blood clotting
Ethanolamine + PA	Phosphatidylethanolamine (PE) **(cephalin)**	Play a role in membrane fusion
Choline + PA	Phosphatidylcholine (PC) **(lecithin)**	Lung surfactant
Inositol + PA	Phosphatidylinositol (PI)	Cell signaling
Glycerol + PA	Phosphatidylglycerol (PG)	Lung surfactant

Some examples

1- Cardiolipin

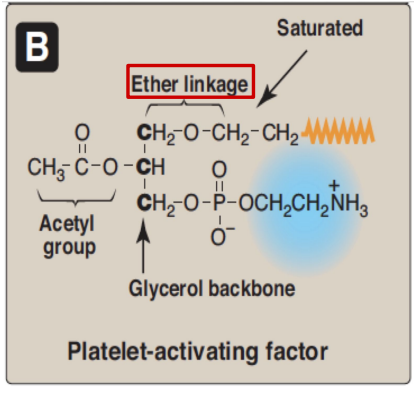
- Two molecules of PA joined to an additional molecule of glycerol through PO4 groups.
  [glycerol + 2 phosphatidic acid groups]
- In the inner mitochondrial membrane.
- Function: maintenance of respiratory complexes of electron transport chain.

It stabilizes the protein complex in the mitochondria and keep them together



2- Platelet activating factor (PAF)

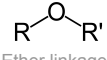
- Binds to cell surface receptors "of platelets or other cells"
- Triggers thrombotic and acute inflammatory reaction "which can cause tissue damage"
- It activates platelets to aggregate



*In Other phosphoglycerides, the fatty acids are attached to glycerol by Ester linkages, **while in PAF, it is bound by an Ether linkage**
** it also has an acetyl group at carbon 2

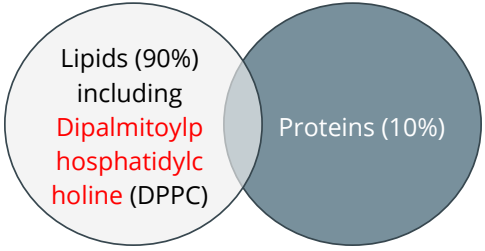
Extra:

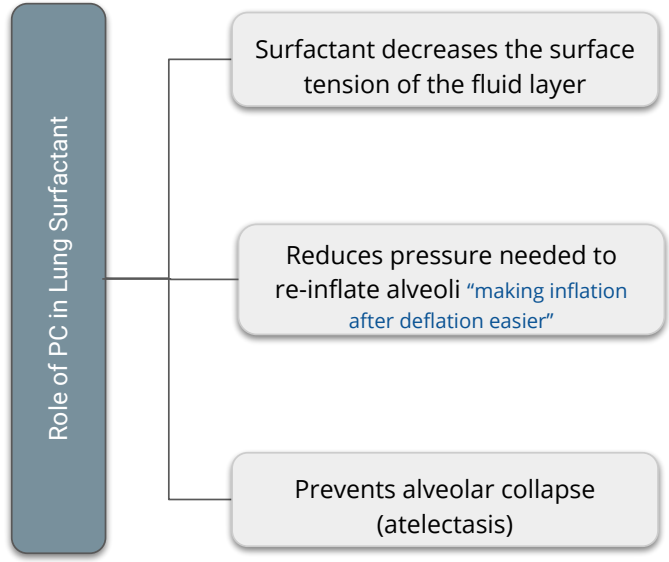

Ester linkage.


Ether linkage

Role of phosphatidylcholine (PC) in Lung Surfactant

- Alveolar cells of the lungs are lined by the extracellular fluid layer.
- Alveolar cells secrete *DPPC (a major lung surfactant).
- Lung surfactant is a complex mixture of:





- Surfactant is a detergent, has a hydrophilic and hydrophobic group.
- Water molecules have surface tension, they make a drop because they attach to similar molecules, they have big cohesive force.
- When surfactant is present it keeps water molecules separate from each other (its present between the water molecules) reducing surface tension and cohesiveness (coming together of water molecules), which makes it easier for alveoli to re-inflate.

Respiratory distress syndrome (RDS)

- **When the lung surfactant isn't present the alveoli will collapse which will lead to RDS.**
- **In preterm infants due to:** deficiency of lung surfactant.
- **A major cause of:** neonatal death.
- **Treatment:** "when premature delivery is expected" Glucocorticoids to mother to promote lung maturation.[1]
- **In adults due to:** damaged alveoli by infection or trauma.[2]

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How to measure if the lung is having respiratory distress syndrome or not?
By measuring the ratio between Sphingomyelin and Lecithin, if the ratio is 2 or more that means the person is healthy, if less that means the person is having respiratory distress syndrome.

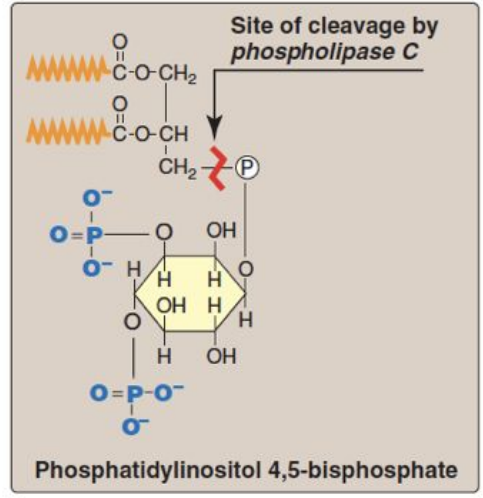
[1] It is actually a preventive method, if there's any complication in the mother or the baby leading to earlier delivery " baby is expected to be delivered before surfactant had a chance to be synthesized " we give the mother glucocorticoids (by injection) which activates specific enzymes leading to earlier production of lung surfactants. After birth,the treatment is giving the early born child an intratracheal lung surfactants (either natural or synthetic).

[2] Can also happen to heavier chronic smokers because smoking causes inflammation which leads to accumulation of water in lungs.

Role of PI in cell signaling

- Plays important role in intracellular signaling
- PI is a part of Calcium -phosphatidylinositol system

- PI is present in the cell membrane
- Phospholipase C cleaves PIP2(phosphatidylinositol 4,5-bisphosphate) to give Diacylglycerol(DAG) and inositol triphosphate (IP3)



Binding

- Hormone or neurotransmitter binds to G protein coupled receptor
- The receptor consists of 3 subunits, alpha,beta and gamma

Receptor interaction

- Receptor will interact with G protein which will lead to replacing **GDP** with **GTP**

Dissociation

- Alpha subunit dissociates from Beta and Gamma subunits, and activates phospholipase C

Breaking down

- Phospholipase C cleaves PIP2 to DAG and IP3
- DAG stays in the membrane while IP3 will bind to the endoplasmic reticulum

Calcium release

- Endoplasmic reticulum will release calcium when IP3 binds to it

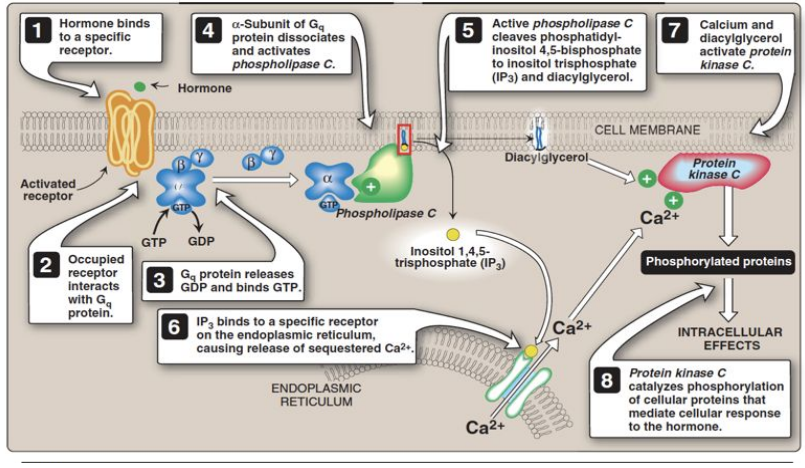
Kinase C activation

- Calcium and DAG activates protein kinase C

Responding to action

- Protein Kinase C catalyze protein phosphorylation. These protein will give the response of the hormone or neurotransmitter

Please don't skip the picture



Role of inositol trisphosphate and diacylglycerol in intracellular signaling.

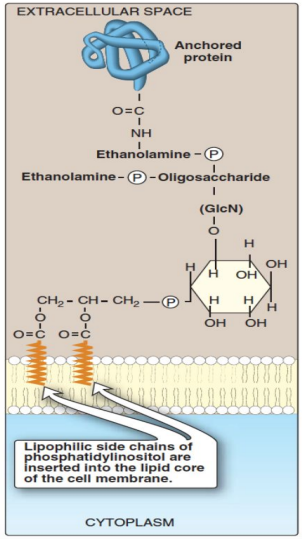
Role of PI in Membrane Protein Anchoring

Anchoring of proteins to membranes through **carbohydrate-PI bridge** "sometimes called glucose PI bridge"

- **Examples:**

1. **Alkaline phosphatase** (on the surface of small intestine)
2. **Acetylcholinesterase** (on postsynaptic membrane of neurons)

- Anchoring proteins can be cleaved by **phospholipase C enzyme**



SphingoPhospholipids

A long-chain fatty acid attached to sphingosine

Example:

- Sphingomyelin:
  - An important component of myelin that protects and insulates nerve fibers
    - Also increases transmission velocity in the nerve
  - the only significant sphingophospholipid in humans
  - Backbone of sphingosine

Components:
[Ceramide + phosphorylcholine]
*ceramide= sphingosine +2 fatty acid chains
*sphingosine= palmitic acid + serine
*phosphoryl choline= Choline + phosphate

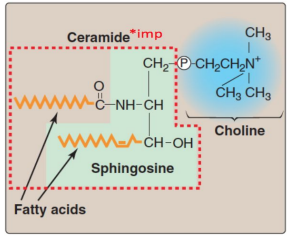


Figure 17.4
Structure of sphingomyelin, showing sphingosine (in green box) and ceramide components (in dashed box).

Phospholipids in Lipoprotein Particles

- The outer core of lipoprotein particles is hydrophilic
- Contains phospholipids and free cholesterol
- Allows transport of core lipids (hydrophobic) in aqueous plasma (hydrophilic)
- Has many types including HDL and LDL

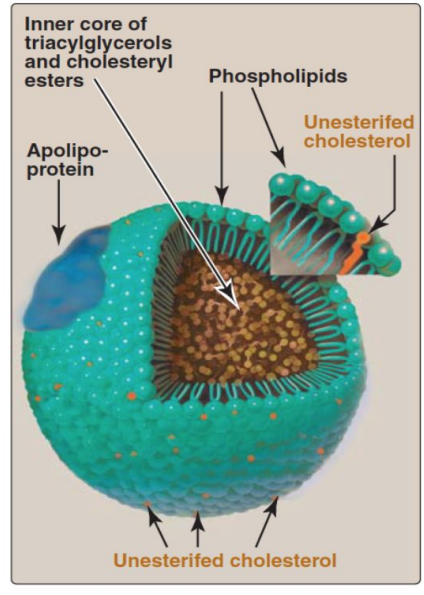


Figure 18.14
Structure of a typical lipoprotein particle.

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Lipoproteins are composed of:

- lipid core (containing **triacylglycerol and cholesteryl esters**)
- surrounded by a shell of amphipathic **apolipoproteins, phospholipid, and unesterified (free) cholesterol**.
- They main function is to keep lipids **soluble** as they **transport** them between tissues.

Extra explanation:
Since lipids cannot dissolve in water/ plasma, we need something to help us transport them in the blood to the tissues, so we need to assemble them in away that will allow them to be Water soluble. This assembly is called lipoprotein.
The transported lipid will be inside a shell of amphipathic molecules.
The hydrophilic part of the shell will interact with water "making the entire molecule lipid soluble" and the inside will contain the lipid.

436
بحمد الله تم دخول الـLipid
للاسلام حيث غيرت اسمها الى ليبو بروتين وليست العباءة المكونة من الفوسفوليبيد والكوليسترول لكي تمشي بدون جذب انتباه اقرانها المشابهين لها (الهيدروفوبيك)
شكر للولوة الشيحة *

PHOSPHOLIPASES

What are phospholipase?
enzymes that hydrolyzes phospholipids into fatty acids and other lipophilic substances. (إنزيمات تحلل الليبيد)
There are four major classes, termed A, B, C and D, each class has its own subtypes, they are distinguished by the type of reaction which they catalyze

1- Present in:

all tissues including pancreatic juice

2-degradation:

- **Phospholipids are degraded by**: phospholipase enzymes
- **Glycerophospholipids are degraded by**: Phospholipase A1, A2, C, D
- **Sphingophospholipids are degraded by:** Sphingomyelinase [present in the lysosomes, mostly liver lysosomes]

3- functions of phospholipase:

- Digestion of phospholipids by pancreatic juice
- Important for remodeling of phospholipids

[remodeling: breaking down a phospholipid to make another type of phospholipids]

- Production of second messengers
- Pathogenic bacteria produce phospholipases to dissolve cell membranes and spread infection

Types of phospholipase:

1- Phospholipase C:
- found in the liver lysosomes and some bacteria.
- Membrane bound.
- Activated by the PIP2 system and plays a role in producing second messengers [IP3 and DAG]

2- phospholipase D
- found in plant and human tissues.
- Related to Alzheimer's.
- Cleaves the phospholipid to give us inositol and phosphatidic acid.

3-phospholipase A1
- present in mammalian tissue.
- Cleaves The fatty acid chain on the first carbon.

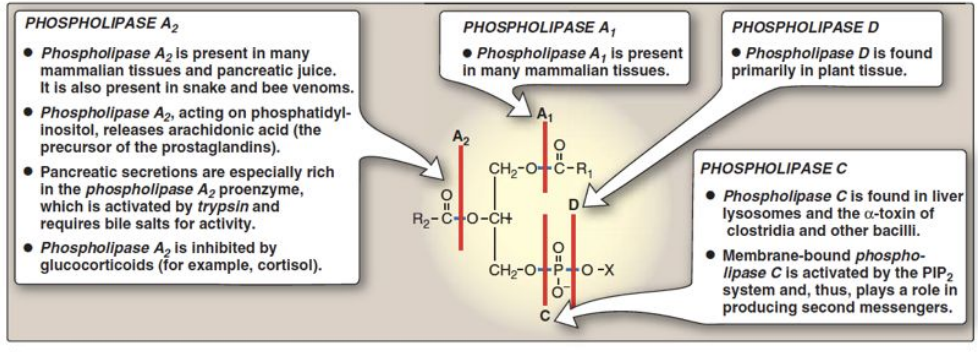

Figure 17.11
Degradation of glycerophospholipids by *phospholipases*.

4-Phospholipase A2
- Present in mammalian tissue
- Present in the pancreatic juice
- Releases arachidonic acid
- Activated by trypsin
- Inhibited by glucocorticoids

Take home messages

- Phospholipids are complex lipids that perform important physiological functions in the body
- Membrane-bound phospholipids are involved in cell signaling, protein anchoring and myelin protective functions
- Non Membrane-bound phospholipids function as lung surfactant and as detergent in the bile
- Phospholipases are enzymes that degrade phospholipases
- They are important for remodeling of phospholipids

Summary

There functions are Degrades phospholipids ,Remodeling phospholipids ,Produce second messengers and Bacteria produces phospholipase to dissolve cell membranes and spread infection

They have a hydrophobic tail and hydrophilic head.

Phospholipids

They are membrane bound or non membrane bound.

On the cell membrane are two types
1- Glycerophospholipids.
2 Sphingophospholipids.

MCQs:

1. Which of the following is not correct about glycerophospholipids

A It's a major class of phospholipids
B Contain glycerol
C contain phosphatidic acid
D Its a important component of myelin sheath

2. Which of the following is a type of phospholipase

A phospholipase A4
B phospholipase A2
C phospholipase B1
D phospholipase B4

3. One of phospholipase functions is digestions

T or F

4. Long surfactant is contain 90% of proteins

T or F

5. Phospholipids it's an ionic compounds that contains an alcohol group attached either to sphingosine or Triacylglycerol

T or F

1) D
2) B
3) T
4) F
5) F

Team leaders

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- شهد الجبرين
- لينا الرحمة
- منيرة المسعد
- ليلى الصّباغ
- العنود المنصور
- أرجوانة العقيل
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