

“Diverse Energy-Conserving Pathways in Microbes”

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Abstract:

All living organisms can be classified according to their energy sources into either phototrophs or chemotrophs. Microorganisms far exceed other organisms in their metabolic diversity. A third metabolic mechanism has been discovered since 2008 that thought to be exclusive to anaerobic microbial respiration. Gracilibacteria (BD1-5) is a unique bacterium that lacks all fundamental pathways to survive however still alive by the presence of a large number of proteins within its membrane. Electron Bifurcation is the third energy producing mechanism that used by several microbes to conserve energy. This mechanism is an example of energetic coupling that moves one electron “downhill”, to produce energy that is incentive to move the second electron “uphill” without opposition the law of thermodynamics. Acetobacterium woodii or the Intracellular syntrophy bacteria has the ability to complete the hydrogen cycle without the need of a syntrophy partner. Besides its ability to electrons bifurcation, it can be both a fermenter partner when cocultured with methanogen or hydrogen consuming when becomes a part of syntrophic interaction. Clostridioides difficile is highly adaptive bacteria and this is due to its highly adaptive metabolic pathways. Extracellular Electron Transfer is known for over a century and has a lot of application even though it's supposed to be unique to gram negative bacteria, Listeria monocytogenes breaks this believe by its ability to transform environmental iron from Fe^{3+} to Fe^{2+} via extracellular electron transfer. Understanding the several metabolic pathways within microbes can help us to improve our health as well as to facilitate our lives by using their metabolic diversity in useful applications.

Keywords: Electron bifurcation; Syntrophy; Energetic coupling; Extracellular electron transfer; Phototrophs; chemotroph

1. Background

Organisms keep their lives by collecting nutrients to harness energy, then expelling wastes or byproducts to their surrounding environments. Organisms can be categorized based on their energy sources into phototrophs if they utilize solar energy or chemotrophs if they use chemical molecules as their energy source (black 8thed, Burgin, et. al., 2011). No one can deny that oxidative phosphorylation is the dominant mechanism generating ATP in aerobes (Cahoon and Freitag, 2018, Russell, 2007). However microbes far exceed other organisms in their metabolic diversity (Burgin, et. al., 2011) in which they can obtain energy by three main ways, substrate level phosphorylation, and oxidative phosphorylation in addition to the lately discovered electron bifurcation mechanism (reddy, et. al., 2015, Hinderberger, et. al., 2008, Herrmann, et. al., 2008, Nealson and Popp 2005). A distinctive feature for microbe's metabolic diversity is the use of either organic or inorganic energy sources and with regard to little exception in eukaryotes, anaerobic respiration is an exclusive energy mechanism for prokaryotes. These unique features of microbes arose from the remarkable and diverse electron donors and electron acceptors that they have (Nealson and Popp, 2005).

Heterotrophic microorganisms can gain energy by respiring aerobically using oxygen as the final electron acceptor in the electron transport chain or they can adapt several mechanisms anaerobically either using many types of fermentation by substrate level phosphorylation or using final electron acceptors other than oxygen and/or electron bifurcation during anaerobic respiration (Fig. 1) (Cahoon and Freitag, 2018, black 8thed, Hinderberger, et. al., 2008, Herrmann, et. al., 2008).

This review highlights our current understanding of how far microbial bioenergetics diverse from other organisms, in addition this review represents the lately discovered pathways involved in energy utilization.

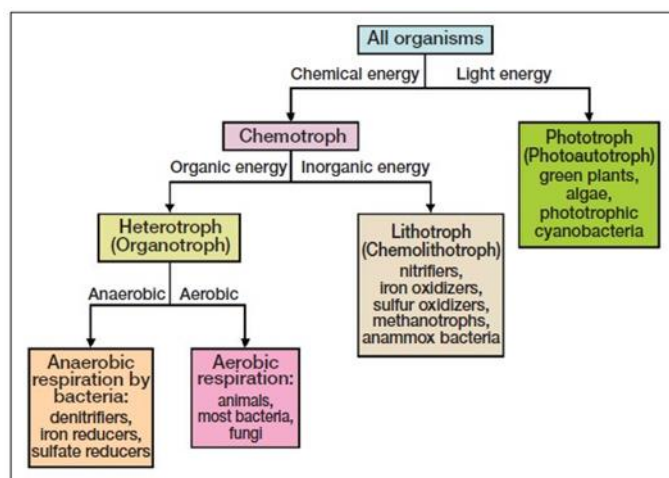


Figure 1 : Classification of Organisms Based on Energy Source

2. Several examples on energy pathways

2.1. Gracilibacteria (BD1-5)

All domain of life have to degrade glucose in order to provide ATP and several electron carriers in addition to other precursors for vital anabolism processes. This can be done using three main pathways the first and the common pathway is the Embden–Meyerhof–Parnas (EMP) pathway, second is the phosphoketolase pathway and the final is Entner–Doudoroff (ED) pathway. Whether the microbe live aerobically or anaerobically sugar should be dissimilated among one or more of these pathways (Chen, et. Al., 2016). Embden–Meyerhof–Parnas (EMP) pathway generally considered the standard pathway for glucose catabolism; it's simply defined as the breakdown of glucose to pyruvate. While thought to be originated from simple chemical that constitutes a prebiotic environment, its wide spread and used by many several organisms (Sánchez-Pascuala, et. Al., 2017).

(Sieber, et. al., 2019) with his/her team discovered unique bacteria with unique metabolic properties that break the rules mentioned above. Gracilibacteria (BD1-5) bacterium belongs to a large bacterial monophyletic group named the candidate phyla radiation (CPR) group. Gracilibacteria (BD1-5) bacteria with metagenomics experiments of Sieber team have shown lack of several fundamental mechanisms needed for their survival including the three main pathways of glycolysis. This make the team to ask two questions one of them is how these bacteria utilize their energy without any glycolysis pathways nor electron transport chain or even tri carboxylic acid cycle.

To answer this question, Sieber research results predicted several transporter types hypothetically to address the need of and acquire compounds from detritus or other cells. In addition to presumably multiple membrane-associated proteins and transmembrane domains that might have a transport function. Research team identified 80 transporter proteins, 122 transmembrane proteins with more than 3 transmembrane domains (Fig. 2). Based on these results this unusual metabolic bacteria are predicted to live in symbiotic or as scavenger relying on external nutrients resources such as amino acids, lipids, citrate malate and a few amount of sugars and other sources for building blocks to survive.

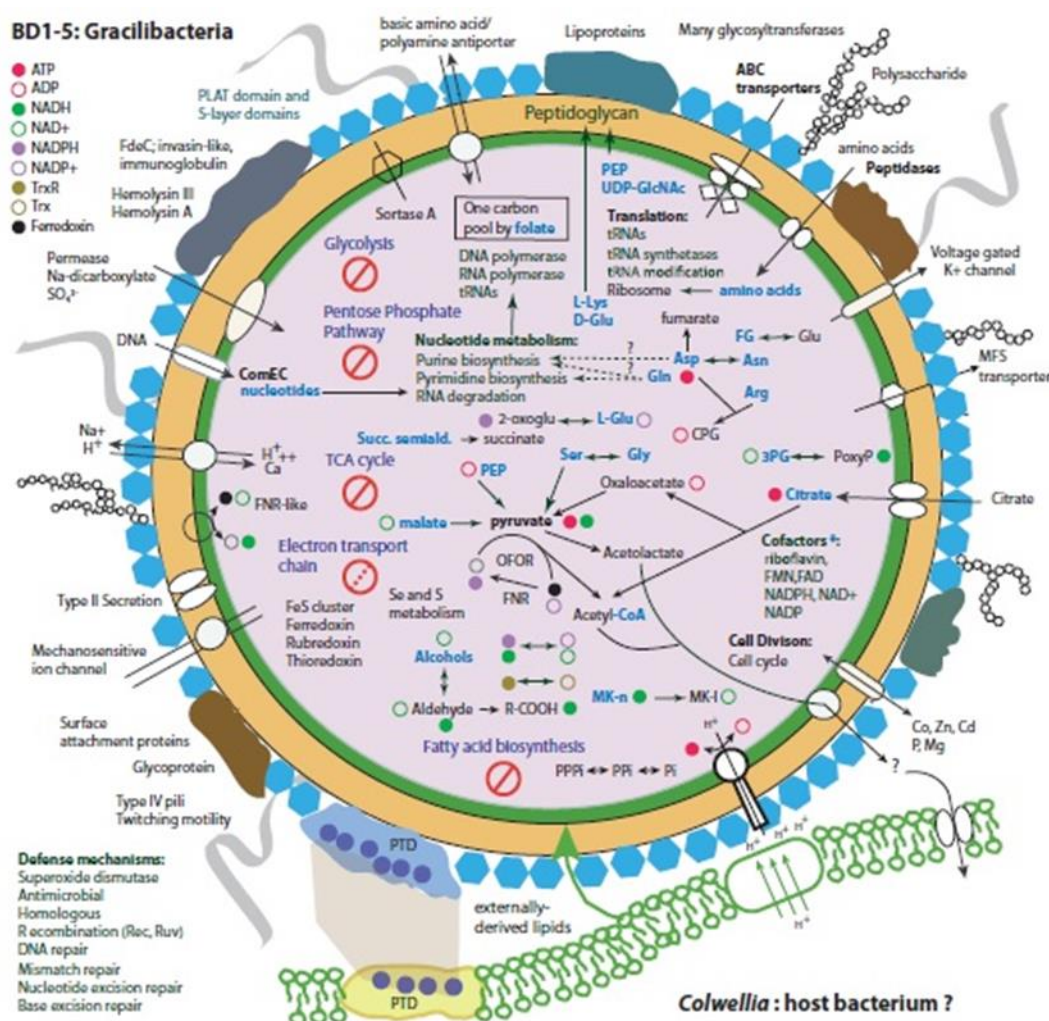


Figure 2: Gracilibacterium metabolism shows transporter proteins, transmembrane proteins and transmembrane domains.

2.2. Electron Bifurcation

In microbes, oxidative phosphorylation involves electrons transfer from a low potential electron donor to a more positive redox potential acceptor by redox reactions. Membrane-bound compounds catalyzed these reactions by using energy differences between acceptor and donor this makes an ion- gradient across that membrane, this ion-gradient converts electrical potential differences into chemical energy in the form of ATP (FraukeKracke, et. al., 2015, Anraku, 1988). However some organisms like fermenting bacteria, acetogenic bacteria and methanogenic archaea (Demmer, et. al., 2018) surprisingly tend to conserve energy by reducing a low potential acceptor comparably from high potential donor to be then the electron donor for other reaction. This novel mechanism was discovered since 2008 and called electron bifurcation (Hinderberger, et. al., 2008, Herrmann, et. al., 2008). Electron bifurcation in prokaryotes clarifies the adaptation of some microorganisms within anaerobic respiration. This process enables the microbe to drive thermodynamically unfavorable endergonic transfer of electrons during redox reactions by coupling to an exergonic redox reaction directly by soluble enzyme complex (Wiechmann, et. al., 2020, Muller, et. al., 2018, Buckel and Thauer, 2018, peters, et. al., 2018).

Electron bifurcation is an example of energetic coupling. Put EB simply, moves one electron “downhill”, and this energy is incentive to move the second electron “uphill” without opposition the law of thermodynamics. More precisely, it oxidizes a two-electron donor which has a medium-potential, using the two electrons one to reduce a high-potential acceptor while the other to reduce acceptor with a low potential (Fig. 3) (yuly, et. al., 2019).

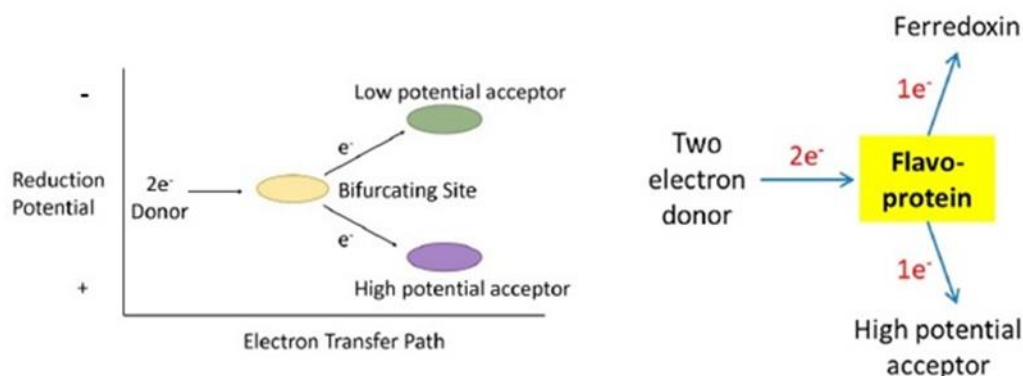


Figure 3: Illustration of electron transfer in electron bifurcation mechanism

For decades, electron bifurcation was unique to the quinone-based pathway (QBEB) that involves only in the complex III. However about a decade ago, flavin-based pathway was discovered (FBEB). FBEB is now comprehended to support anaerobic respiration through several reactions that involve the NADH oxidation and the reduction of flavodoxin or ferredoxin which coupled to exergonic reductions. Overall, FBEB and QBEB mechanisms seem analogous, because the redox properties of Quinones and flavins are similar (Fig. 4) (peters, et. al., 2018, Buckel and Thauer, 2018).

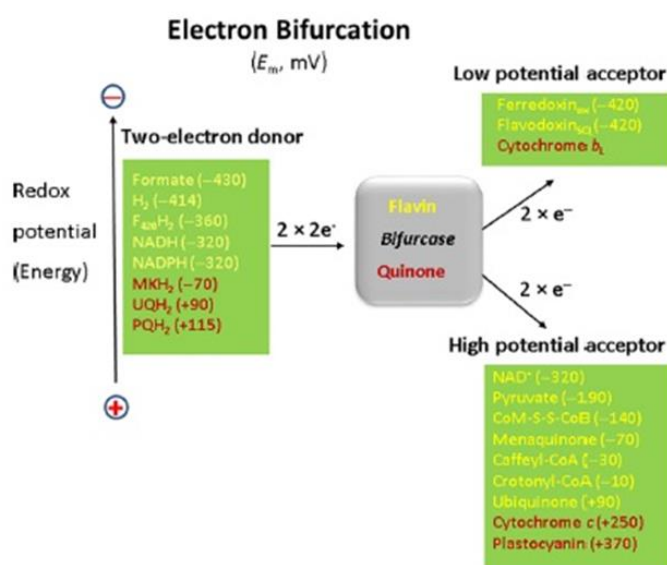


Figure 4 : Flavin (yellow) and quinone (red) bifurcation pathways

The first enzyme characterized in detail to be in bifurcation was from *Acidaminococcus fermentans* and *Clostridium kluyveri*. This enzyme is the flavoprotein (Etf)-butyryl coenzyme A (butyryl-CoA) dehydrogenase (Bcd) (Sucharitakul, et. al., 2020, Gonzalez-Garcia, et. al., 2017, Chowdhury, et. al., 2014). But by 2020 about eleven enzymes involve in EB have been discovered all of them follow the same concept of redox reaction coupling (kremp, et. al., 2020).

2.2.1. *Acetobacterium woodii*

In anoxic ecosystems, the interspecies hydrogen cycling is a common pathway in hydrogen cycle in which hydrogen diffuse outside fermenter bacterial cells by fermentation should be oxidized by an oxidizing microorganism like methanogenic archaea in order to survive. This is not the applicable rule by the intracellular syntrophy bacteria (*Acetobacterium woodii*). Intracellular syntrophy bacteria called by (Wiechmann, et. al., 2020) because of its ability to

complete the hydrogen cycle without the need of a syntrophy partner which usually used to avoid the thermodynamically unfavorable hydrogen formation that produced during fermentation.

Unlike methanogen archaeon *Methanosarcina barkeri* which has a cytoplasmic soluble hydrogenase and a membrane-bound hydrogenase located within the periplasm, *Acetobacterium woodii* lacks a membrane-bound enzyme hydrogenase. Hence, hydrogen oxidation does not follow Odom and Peck postulation (Odom, and Peck, 1984) and is not linked to energy conservation. Furthermore this unusual bacterium has the ability to play two roles either as a fermenter partner when cocultured with methanogen or as hydrogen consuming when becomes a part of syntrophic interaction. Determine which role to act depends on the surrounding environmental conditions (Wiechmann, et. al., 2020).

The modular metabolism in *Acetobacterium woodii* has three pathways, oxidative module and reductive or so called (the Wood-Ljungdahl) pathway in addition to a redox balance branch (Fig. 5).

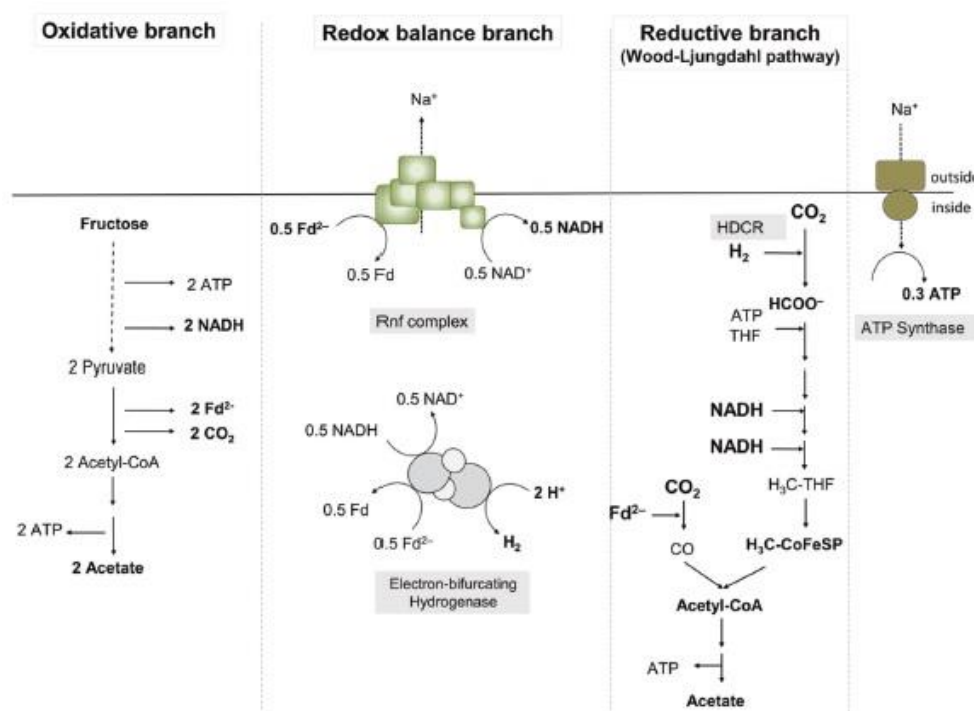


Figure 5: The three modules of *Acetobacterium woodii*

The soluble bifurcating enzyme that is one of the eleven types of the bifurcating enzymes (kremp, et. al., 2020) is localized within redox branch and function to ensure that electron carriers from the oxidative branch are fed in and converted to WLP specific carriers. This Enzyme couples the exergonic reaction of NAD reduction with the endergonic reaction allowing the ferredoxin (FD) of a low potential to be reduced (Wiechmann, et. al., 2020, Buckel and Thauer, 2018, peters, et. al., 2018, Gonzalez-Garcia, et. al., 2017) this enzyme has been recognized in other bacterial species including *Ruminococcus albus*, *Thermotoga maritime* and *Moorella thermoacetica* performing the same function (Gencic and Grahamea, 2020).

2.2.2. *Clostridioides difficile*

C. difficile is a gram positive pathogen that cause food poisoning and cause several death cases after antibiotic treatment. This bacterium is highly adaptive because of its highly adaptive metabolism (Neumann-Schaal, et. al., 2019). Because substrate level phosphorylation yields less ATP this versatile pathogen recovers more ATP by a reverse ATPase reaction. Moreover this smart pathogen couples the fermentation of an amino acid at the Rnf complex by EB to membrane potential generating processes. *C. difficile* also use incomplete Krebs cycle to prevent unnecessary NADH production, which needs to be re-oxidized by cost-intensive energetic reactions. Hence this organism produces one instead of three NADH.

Furthermore pyruvate formate-lyase produces formate and acetyl-CoA which then transformed into protons by formate dehydrogenase and to hydrogen by a hydrogenase (Neumann-Schaal, et. al., 2019).

2.3. Extracellular Electron Transfer (EET)

Not all microbes use oxygen as the final electron acceptor in the electron transport chain also not all microbes can use fermentation as the only way of respiration in the absence of oxygen (Cahoon and Freitag, 2018, Glasser, et. al., 2017, Shi, et. al., 2016). Some microbes which habitat environments that lack energy sources for fermentation while still rich in minerals can use final electron acceptor other than oxygen such as iron (iii) or oxide (Fe_2O_3). *Geobacter metallireducens* and *Shewanella oneidensis* for example use this way in respiration but because these mineral cannot transport to the interior of bacterial cells, electrons from the oxidation of NADH transfer from the interior of the cell into its exterior use a quinone in the lipid membrane and also a series of proteins that contain heme as a bath for electron transfer (Fig. 5) (Cahoon and Freitag, 2018, Shi, et. al., 2016). This mechanism that enable electrons to beyond cell wall and allow bacteria to interact with their environment called extracellular electron transfer (EET). (EET) is known for over a century (Potter, 1911). Opening the door for a lot of application such as bioremediation, waste and waste water treatment as well as the production of electricity (Krackeetal, et. al., 2015).

2.3.1. *Listeria monocytogenes*

EET was thought to be unique to gram negative bacteria and this is because of its structure that contain two lipid membrane and periplasmic space the parts where EET proteins are located. However light et. al., 2018 reported gram positive bacteria that produce current when placed in an electrochemical chamber. *L. monocytogenes* is a gram positive bacteria in which neither respiration nor minerals is crucial for its survival but its ability to convert the extracellular iron from Fe^{3+} to Fe^{2+} is an evidence on its EET ability. So how these occur? Light et al., in their study show that Ndh2, EetB, EetA and PplA proteins are key components of EET process. And the initial steps of electron-transfer during EET in this gram positive bacteria resemble those already specialists in mineral-respiring. By contrast to *Geobacter metallireducens* and *Shewanella oneidensis*, in *L. monocytogenes*, a single protein that contains two flavins called PplA is suffices to extracellular electrons transfer to the cell's exterior electron acceptors (Fig. 6).

Light and colleagues reveal EET activity in diverse subset of gram positive bacteria most notably those found in human guts such as *Lactobacillus* bacteria an interesting foundation that may be helpful in the future (light, et. al., 2018, Cahoon and Freitag, 2018).

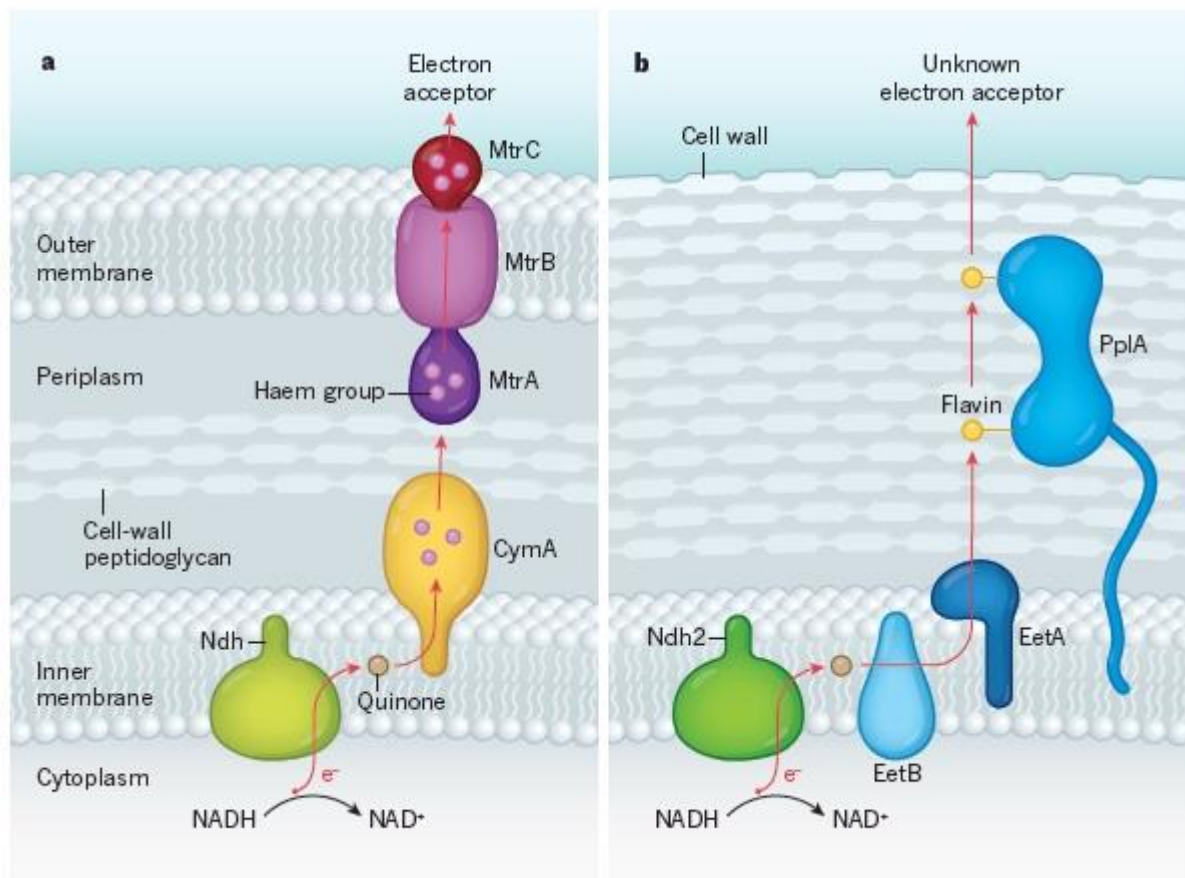


Figure 6: differ between (a) gram negative and (b) gram positive EET membrane proteins

3. Conclusion

Microorganisms are everywhere, they adapt several mechanisms in order to survive. The reason behind their adaptation resides in their diverse metabolic pathways they have. Microbes can live aerobically or anaerobically. Furthermore they can utilize their energy from organic or inorganic substrates and this depends on which environment they are located. Microbes far exceed other organisms in metabolism pathways in which they have three energetic pathways, first the substrate level phosphorylation that could be followed by one or more of several types of fermentations and second the oxidative phosphorylation either aerobically using oxygen as final electron acceptor or anaerobically using other molecules than oxygen as the final electron acceptor. The third mechanism is the lately discovered electron bifurcation that enables a lot of microbes which live anaerobically to yield more ATP than that would during fermentation as in the case of *Acetobacterium woodii* which also has the ability to complete hydrogen cycle without the need of external syntrophy a unique feature which can have several future applications. One microbe shows lack in fundamental metabolic pathways and even though it finds a way to survive this *Gracilibacteria* (BD1-5) bacteria shows unusual number of membranous proteins to get their nutrient from the exterior of the cell by these proteins. On the other hand other microbes can use several pathways and mechanisms of metabolism and the target is to get more ATP for several anabolic pathways some of which could be harmful to us as in the case of *Clostridioides difficile* pathogen. While other microbes could use extracellular electron mechanisms in their metabolism pathways, a mechanism which can be beneficial to us and usable in several applications such as bioremediation, and microbial fuel cells as well as in waste and wastewater treatments and other applications.

Discover and understanding metabolic pathways of microorganisms enable us to avoid their pathogenicity by creating a way to stop their lives or infection while on the other side knowing these mechanisms could open the door for several future beneficial applications.

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"مسارات متنوعة لحفظ الطاقة في الميكروبات"

الملخص:

يمكن تصنيف جميع الكائنات الحية وفقاً لمصادر طاقتها الى كائنات تعتمد على التغذية الضوئية أو كائنات تعتمد على التغذية الكيميائية. الكائنات الدقيقة تتجاوز بكثير الكائنات الحية الأخرى في تنوعها الأيضي. تم اكتشاف آلية التمثيل الغذائي الثالثة منذ عام 2008 والتي يعتقد أنها تحدث بالاجمال في التنفس الميكروبي اللاهوائي. تعد بكتيريا *Gracilibacteria* (BD1-5) بكتيريا فريدة تقتصر إلى جميع المسارات الأساسية للبقاء على قيد الحياة، ومع ذلك لا تزال على قيد الحياة بسبب وجود عدد كبير من البروتينات داخل غشائها. تشعب الإلكترون هو آلية إنتاج الطاقة الثالثة التي تستخدمها العديد من الميكروبات للحفاظ على الطاقة وبالتالي على بقاءها. هذه الآلية هي مثال على الاقتران النشط الذي يحرك إلكترونًا واحدًا "إلى أسفل"، لإنتاج طاقة تحفز على تحريك الإلكترون الثاني "صعودًا" دون معارضة قانون الديناميكا الحرارية. تمتلك *Acetobacterium woodii* أو البكتيريا التخليقية داخل الخلايا القدرة على إكمال دورة الهيدروجين دون الحاجة إلى شريك تخليقي. إلى جانب قدرتها على القيام بالتشعب الإلكتروني، هذه البكتيريا يمكن أن تكون شريكًا في التخمر عندما تزرع بالميثانوجين أو الهيدروجين عندما تصبح جزءًا من التفاعل التخليقي. *Clostridioides difficile* هي بكتيريا شديدة التكيف وهذا بسبب امتلاكها لمسارات أيضية مختلفة. يُعرف نقل الإلكترون خارج الخلية منذ أكثر من قرن وله الكثير من التطبيقات على الرغم من أنه من المفترض أن يكون حصريًا للبكتيريا سالبة الجرام، إلا أن *Listeria monocytogenes* كسرت هذا الاعتقاد من خلال قدرتها على تحويل الحديد البيئي من Fe^{3+} إلى Fe^{2+} عبر نقل الإلكترون خارج الخلية البكتيرية موجبة الغرام. يمكن أن يساعدنا فهم مسارات التمثيل الغذائي المتعددة داخل الميكروبات على تحسين صحتنا عن طريق فهمها في الميكروبات المسببة للأمراض وكذلك تسهيل حياتنا باستخدام تنوعها الأيضي في العديد من التطبيقات المفيدة للإنسان مستقبلاً.