**血小板线粒体具备作为一种新型的疾病生物标志物的潜力**

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**摘要：**

线粒体作为细胞功能的主要器官，在血小板中不仅为细胞提供能量，还参与调节血小板活化与凋亡，血栓形成等途径，与许多疾病的发生有关。血小板线粒体易于获得，其作为一种新型的生物标志物，应用于疾病的早期诊断，具有很大的应用前景。

**关键词**：血小板；线粒体；生物标志物；

**1，前言：**

线粒体（mitochondrion）是一种存在于大多数细胞中的直径在0.5到1.0微米左右的由两层膜包被的细胞器，是细胞制造能量的结构和进行有氧呼吸的主要场所。线粒体通过三羧酸 (TCA) 循环和氧化磷酸化 (OXPHOS)参与三磷酸腺苷 (ATP) 的产生为细胞正常生命活动（如增殖、分化和自噬）提供能量基础[1-4]。线粒体还可以通过产生活性氧（ROS）来调节细胞内信号传导，并通过释放细胞色素c启动细胞凋亡[5-6]。若线粒体功能在ROS的产生过程中受损，会导致疾病的发生与进展[7-8]。研究表明线粒体还与细胞其他生命活动有关，Ca2+稳态[9]、细胞凋亡调节[10]和 ER 应激反应机制[11]。线粒体功能障碍似乎也与衰老有关[12]，以及与神经退行性疾病（例如阿尔茨海默氏症)[13] 和帕金森病[14]有关。值得注意的是，线粒体在大脑、心脏和肝脏这些代谢活性组织中的作用众所周知。然而，线粒体在循环血细胞（如血小板）中的作用仍然难以捉摸[15,16]。

血小板是来源于骨髓巨核细胞的无核细胞，寿命为7-10天，与内皮密切接触，随时对内皮激活的突然变化或内皮下细胞外基质蛋白的暴露做出反应[17]。血小板主要有三层结构。最外层是由外膜单元膜等结构组成的，中间的一层是凝胶层，最里面的一层属于微器官层，会有线粒体、残核等结构。相比其它细胞，血小板有更大的ATP周转率，虽然它含有相对较少的线粒体。越来越多的证据表明，线粒体调节血小板活化，而不仅仅是提供ATP。 此外，线粒体在血小板凋

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亡方面也起着重要作用[18]。血小板线粒体不仅可以促进血小板介导的聚集，而且在非ATP介导的血栓信号传导和血小板凋亡中也是必不可少的[19-21]。血小板线粒体功能的改变具有不同病理的特异性，且易于提取，在系统干预后的多个时间点相对容易测量。因此，其具有用作疾病的生物标志物的很大潜力。

**2，血小板线粒体的功能**

**2.1 对血小板寿命的影响**

血小板生命周期主要是静息--活化--凋亡，线粒体在血小板的生命活动周期中起着重要作用。血小板处于静息状态时，血小板所需能量较少，线粒体功能不活跃。血小板处于活化状态时，需要大量的能量，线粒体在此时功能活跃，不断为血小板活化提供大量的氧化能。同时，线粒体提供大量的血小板活化的激动剂ROS，促进血小板的活化[22]。在血小板的凋亡过程中，线粒体也发挥着很大的作用[23]。在血小板功能状态发生变化时，血小板线粒体功能通常会发生改变，一般表现为线粒体膜电位和ATP的释放量的改变[24]。当血小板功能障碍时，线粒体开始启动凋亡机制，线粒体膜电位崩溃，打开线粒体通透性转换孔，细胞色素C从线粒体基质释放到胞浆，ROS的释放量增加。一旦进入胞浆，细胞色素c结合APAF-1(凋亡蛋白酶激活因子-1)启动一个信号级联，促进caspase-9自激活和随后激活caspase-3，它切割细胞骨架蛋白，以诱导凋亡细胞死亡的标志[25]。

血小板活化有两个途径，为胶原通路和TF通路。如果血管壁被破坏，胶原蛋白和TF暴露在血液中，血栓就开始形成。胶原蛋白促进血小板凝血和活化，TF启动凝血酶形成，激活血小板，使纤维蛋白原转化为纤维蛋白。活化的血小板产生血栓素，引起血小板强烈的聚集及释放反应，易形成微血管栓塞，进一步发展为血栓。故血小板在血栓形成中起着重要的作用。

**2.2 在血栓形成中的作用**

血小板促进血栓形成主要分为三个阶段。第一阶段为黏附，当内皮受损时，血小板通过与具有特异性糖蛋白Ia/IIa表面受体的胶原直接结合而附着于内皮下组织。这种结合由ADP和凝血酶通过血小板表面的G蛋白偶联受体介导，并由从内皮和血小板中释放的血管性血友病因子（VWF）进一步加强。下一阶段被称为激活，血小板启动信号级联，包括磷酸肌醇3-激酶的激活和磷脂酶C的抑制，通过改变血小板形状以激活受体，并分泌化学信使来诱导激活和附着于其他血小板。第三阶段是是聚合。血小板通过受体桥相互连接而形成栓塞，血小板之间的这种相互作用随着表面糖蛋白IIb/IIIa表达的增加而增强，最终形成血栓[26]。

在血小板促进血栓形成过程中，线粒体是血小板的主要能量提供者[27,28]。因此，血小板线粒体受损或功能障碍，对血小板促进血栓过程会造成极大的影响。

同时，血小板线粒体本身也影响血栓形成，与线粒体的功能无关，通过促凝血小板的形成和线粒体ROS的形成来实现这一点[29,30]。

促凝血小板形成是由于血小板的强烈激活，胞浆Ca2+水平升高时发生的[31]。这些持续的高胞质钙水平导致线粒体储存越来越多的钙[32，33]。每当达到临界的线粒体钙阈值时，线粒体膜去极化，启动mPTP的开放[34，35]。mPTP的开放进一步增加了胞质Ca2þ，激活了超燃冲压酶TMEM16F[36]。同时，线粒体会去极化，消耗ATP并抑制鳍状蛋白酶[37]。这些过程最终导致带负电荷的磷脂酰丝氨酸从血小板脂质双层的内膜转移到外膜。凝血因子与血小板表面带负电荷的磷脂酰丝氨酸结合，并启动凝血酶的产生[36]。同样，在血小板活化过程中，线粒体会产生ROS[38]。线粒体ROS可以进一步激活血小板信号，产生激活扩增环，从而导致糖尿病和镰状细胞病的血栓并发症[39-41]。

1. **血小板线粒体作为疾病生物标志物的思考**

血小板是一种微创的、容易获得的线粒体来源，可以通过简单的静脉穿刺从外周血中获得。从实验动物和人类身上获取血小板相对容易。使用具有密度偏移的不连续蔗糖梯度从膜碎片中纯化线粒体，然后采用流式细胞术进行检测。线粒体在形态和功能上的变化容易观察。因此，它作为疾病的生物标志物具有检测方便、易于操作的优势。

**3.1 血小板线粒体在血液系统疾病中的变化**

血小板与血液系统疾病密切相关，而线粒体作为血小板内重要的细胞器，血小板活化、聚集、凋亡的过程中的起着重要作用，因此，血小板线粒体在许多血液系统疾病中也会发生形态功能上的改变。

据研究表明，在骨髓瘤和急性白血病中，血小板表现出结构[42]和功能[43]的改变，包括血小板聚集、化合物的释放和合成异常、激活标记物在其外膜中的暴露以及其他改变，这可能与这些患者通常出现的血栓和出血并发症有关。而在此过程中，血小板功能和结构的表现主要依赖于线粒体供能和线粒体释放活性物质介导。通过对急性白血病、多发性骨髓瘤或恶性淋巴瘤的患者血小板功能的研究，发现这些患者经历了化疗引起的血小板减少症。研究还发现了患者的血小板线粒体功能显著降低，膜电位低、耗氧量低但线粒体数量正常。此外，线粒体的损伤与活性氧的水平升高相吻合。[44]此外，在原发性血小板增多症和真性红细胞增多症中，表现出持续的血小板活化[45，46]。持续的血小板活化与血小板线粒体关系密切，也可以根据血小板线粒体的功能变化来判断血小板的功能改变，以及评估疾病并发血管栓塞的风险。因此，血小板线粒体作为一项良好的生物标志物，不仅便于获得，而且线粒体功能的改变具有不同病理的特异性，可以判断疾病的进展速度。

**3.2 血小板线粒体甲基化与心血管疾病(CVD)**

血小板在心血管疾病中起着重要作用，如动脉粥样硬化机制和血栓形成中都有血小板的参与。血小板的异常与心血管疾病密切相关[47-50]。血小板通过调节黏附、聚集和激活过程，来介导血栓的形成，血小板线粒体在其中发挥着重要作用。线粒体基因组是血小板中唯一的遗传物质，其DNA（mtDNA）通过线粒体内部存在的机制甲基化[51-53]，来介导线粒体基因表达的控制[54]，进而控制血小板活化。在健康个体中观察到血小板mtDNA甲基化水平较低，而在CVD患者中则观察到线粒体DNA甲基化程度较高。此外，血小板mtDNA甲基化几乎无个体差异，但会因CVD状态的不同而出现显著差异。因此，血小板线粒体甲基化对CVD的早期诊断有重要意义。

**3.3 线粒体功能障碍与神经系统疾病**

许多神经系统疾病患者的血小板线粒体发生改变，包括AD（阿尔茨海默病）[55,56]、亨廷顿病[57]、精神分裂症[58]、偏头痛[59]和PD（帕金森病）[60,61]，主要表现为电子传输链功能上的改变[62-64]。在不同类型的神经系统疾病中，血小板线粒体功能改变也存在差异。如在帕金森病患者的血小板中观察到复合物I的活性降低，而精神分裂症患者通常表现出复合物I活性增加，AD患者血小板中复合物I增加，复合物IV和辅酶Q10浓度降低[65]。而且，AD早期会出现线粒体功能障碍、线粒体形态受损、线粒体断裂[66，67]、线粒体分裂活性增强[68]，线粒体含量减少[69，70]和线粒体的异常积聚[71]。这意味着血小板线粒体在不同的病理过程中发生的功能性变化具有特异性，功能失调的线粒体与神经元功能受损和相关的神经退行性疾病有关[72]。因此，其有可能作为神经系统疾病的生物标志物。

**3.4 血小板线粒体与癌症**

血小板通过与癌细胞的直接作用和血小板释放物介导的远程间接作用，在癌症进展中发挥着重要而多样的作用。血小板可以促进肿瘤细胞增殖和血管生成，并有助于建立转移灶[73]。而肿瘤细胞也可以通过与血管性血友病因子的结合来促进血小板活化和聚集。

癌症转移的速率与血管生成密切相关，肿瘤细胞的转移受到了紧密的血管壁屏障的阻碍[74]。但是原发性肿瘤的新血管系统通常由薄弱和易渗漏的内皮细胞连接，这促进了肿瘤细胞的跨内皮迁移[75-79]。而血小板含有血管生成因子和血管抑制因子，肿瘤细胞的转移可以触发向血管生成表型的转变[80，81]。肿瘤细胞可以通过与血管性血友病因子（vWF）结合来启动血小板聚集，从而释放血管内皮生长因子（VEGF），这是血管生成过程中的最强大的阳性调节因子之一[82]。也有实验证明原发性肿瘤细胞表达凝血酶以通过血小板促进转移。凝血酶通过完全激活血小板上的特异性膜受体，在体外增强肿瘤细胞诱导的血小板聚集（TCIPA）[83]。无论是肿瘤细胞促进血管生成过程，还是血小板促进肿瘤细胞的增殖和转移过程中，血小板线粒体都发挥着重要作用。在此过程中，血小板线粒体不仅仅提供了大量的能量，还提供大量的血小板活化的激动剂ROS，促进血小板的活化。所以血小板线粒体在肿瘤细胞的转移过程中发挥着重要作用，也可以根据血小板线粒体形态和功能的变化来帮助我们进行癌症是否转移的诊断。

1. **展望**

线粒体是细胞代谢的中枢，执行重要的调节功能。受损/功能失调的线粒体被认为是许多常见人类疾病的主要致病因素。目前线粒体功能的评估依赖于侵入性组织活检。而血小板作为外周血细胞，已经成为线粒体功能评估的理想候选者。与其他外周血细胞相比，血小板提供了同质的线粒体来源，限制了生物能量谱中细胞间的差异。且血小板不仅可以反映人类疾病中的系统和组织特异性生物能量特征，而且获得血小板的相对容易性、血小板数量丰富和高代谢表型都支持其作为线粒体功能生物标志物的候选。因此，循环血小板线粒体是一项理想的生物标志物，可以作为疾病早期诊断的生物标志物，可以有效提高疾病的诊断和预后。循环血小板线粒体作为一种新型的生物标志物可以诊断许多人类疾病，有效地监测疾病进展和评估治疗结果。

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