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特发性肺纤维化的分子生物标记物研究进展

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摘　要

特发性肺纤维化(Idiopathic pulmonary fibrosis, IPF)是一种病因不明的间质性肺炎，其中位生存期2~4年。早期IPF一般是无症状的，常常导致诊断及治疗延迟。到目前为止，还没有很好的临床生物标记物可以准确地对IPF进行诊断、评估病情及预后。但是随着IPF研究的不断深入及大量样本的佐证，它们有可能成为有助于诊断、监测疾病进展和治疗效果的有用工具。本文对IPF相关的新的临床生物标志物进行综述，为提高临床诊治提供一定参考。

关键词

肺纤维化，特发性，生物标记物，进展

Advances in Molecular Biomarkers of Idiopathic Pulmonary Fibrosis

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Abstract

Idiopathic pulmonary fibrosis (IPF) is an interstitial pneumonia of unknown etiology, with a median survival of 2~4 years. Early IPF is usually asymptomatic and often results in delayed diagnosis and treatment. So far, there is no good clinical biomarker that can accurately diagnose, evaluate the condition and prognosis of IPF. However, with further research on IPF and the support of large numbers of samples, they may become useful tools for diagnosis, monitoring of disease progression and treatment effectiveness. In this paper, new clinical biomarkers related to IPF were reviewed to provide some reference for improving clinical diagnosis and treatment.

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Keywords

Pulmonary Fibrosis, Idiopathic, Biomarkers, Progress

1. 前言

特发性肺纤维化(Idiopathic pulmonary fibrosis, IPF)是一种病因不明的慢性、不可逆性发展的肺部疾病，以进行性加重的呼吸困难为主要表现，以不可逆的肺功能下降和寻常型间质性肺炎为主要特征[1]。由于各个地区数据收集方法和分类术语的差异，目前该疾病的流行病学调查结果差异较大，其发病情况每年每 10 万人中有 2 例至 60 例不等[2] [3]。IPF 一般预后较差，诊断后的中位生存时间为 2~4 年[4]。由于不同的临床表型，疾病的病程是可变的[5]。IPF 早期可能是无症状的，随着疾病进展逐渐出现刺激性咳嗽及进行性呼吸困难，就诊时肺部影像已呈现明显蜂窝肺表现，治疗难度大。目前指南推荐的 2 种抗纤维化药物为尼达尼布和吡非尼酮，可减缓疾病进展和改善预后[6]。随着对疾病认识的不断加深，生物标志物在疾病的发展、诊断及治疗评估中发挥着越来越重要的作用[7] [8]。但目前生物标志物仍然很难准确预测 IPF 的病程和对单个患者的治疗反应。这篇综述旨在对 IPF 相关的新近热点临床生物标志物进行综述，希望对临床有所帮助。

2. SFTPA2

肺表面活性物质相关蛋白 A2 (*SFTPA2/SP-A2*)是最先发现且在肺泡 II 型上皮细胞中表达含量最为丰富的蛋白之一。*SFTPA2* 由 n 端至 c 端依次为 4 个结构域：n 端区、胶原样区、茎区和 C 型凝集素糖识别域[9]。其中 C 型凝集素糖识别域突变可能导致异常蛋白前体的形成，此种异常蛋白在细胞内积聚，可引起内质网应激。如果内质网长期处于应激状态或者内质网应激严重的情况下，可以诱导未折叠蛋白(unfolded protein response, UPR)的激活。内质网应激和 UPR 的异常激活，导致肺泡上皮细胞(alveolar epithelial cell, AEC)损伤和修复能力丧失，造成 AEC 凋亡，进而导致肺纤维化的产生[10]。最近 Lv Liu 等[11]采用全外显子组测序来研究国内一 IPF 家族的候选基因，采用 Realtime-PCR 和 Western blotting 对鉴定的突变体进行体外功能研究。通过检测发现 IPF 患者存在 *SFTPA2* 基因位点 *p.N207Y* 突变，其功能研究进一步证实该基因点突变可影响 A549 细胞 *SFTPA2* 的分泌，诱导内质网应激和细胞凋亡，与肺纤维化形成有明显相关。由于 *SFTPA2* 水平可以在支气管肺泡灌洗液(bronchoalveolar lavage fluid, BALF)和血液中测量，它们可以在识别肺纤维化家族中的危险个体方面发挥作用。

3. MUC5B

黏蛋白 5B (mucin-5 subtype B, MUC5B)是一种由终末气道黏液腺细胞所产生的黏蛋白。在 2011 年 Seibold 等[12]利用全基因组连锁扫描，发现 IPF 患者的 MUC5B 表达是无 IPF 患者的 14.1 倍，且与 MUC5B 表达增加相关等位基因为 rs35705950。该研究显示野生型等位基因纯合子的表达是未受影响受试者的 37.4 倍。亦有研究报道 MUC5B rs35705950 突变是迄今发现的最强的危险因子，占 IPF 发病风险因素的 30%~35% [13]。目前研究显示亚洲患者中的频率较低(突变组 7% vs 健康对照组 2%)，但其携带的风险似乎与欧洲人种风险相当[14]。国内研究[15] [16]同样显示 IPF 患者该基因的突变频率高于健康人群，表明

该变异与我国 IPF 发病明显相关。Rs35705950 基因点突变后可引起 MUC5B 异常合成增加，当干细胞再生修复受伤的细支气管和肺泡上皮时，过多的 MUC5B 蛋白可能通过干扰肺泡上皮细胞与细胞外基质的交互作用，导致肺泡上皮化失败，阻碍远端肺组织的正常修复，导致慢性纤维增生[17]。此外过多的 MUC5B 可能损害粘液纤毛功能，导致吸入物质(如空气污染物、香烟烟雾、微生物等)的过量滞留，并随着时间的推移，肺损伤的病灶可能引起瘢痕组织持续性纤维增生，导致肺纤维化逐渐进展[18]。目前 MUC5B 多态性与 IPF 预后及评估药物治疗效果关系仍未明确，仍需进一步研究探索。

4. SAP130

剪接体相关蛋白 130 (Spliceosome-associated protein 130, SAP130)亦可以称为 SF3b-3，是剪接因子 3b (splicing factor, SF3b)重要的组成部分之一，正常位于活细胞的细胞核中，当细胞死亡或受损时可以扩散并释放到细胞外环境中[19]。SF3b 是一种由包括 SAP49、SAP130、SAP145 等七种蛋白质组成分子量为 450 kDa 的蛋白质复合体[20]。SF3b 与 U2 核小核糖核蛋白复合物(U2 snRNP)结合，形成功能性的 17SU2 snRNP 聚合体，最终以 ATP 依赖的方式与内含子 pre-mRNA 分支点位点相互结合。因此 SF3b 在剪接体组装过程中，对于识别分支点和选择 3’剪接位点至关重要[21]。而 SAP130 是 SF3b 中唯一不能与前剪接体复合体中的 mRNA 前体交联的亚基，其在体内主要和 STAGA (SPT3-TAFII31-GCN5L-ACETYLASE，转录共激活物－组蛋白乙酰转移酶复合物)特异性结合。STAGA 在体内主要参与前 mRNA 的剪接，并和 DNA 损伤结合因子相互作用，实现染色质修饰、DNA 转录和转录偶联[22]。SAP130 则充当 STAGA 的功能转换器和整个剪接机制的转录调节器。

此外 SAP130 还可以与 Mincle (巨噬细胞诱导 C 型凝集素)受体特异性结合，在各种感染或非感染性炎症下触发促炎信号[23]。尤其在非感染性炎症方面，Gong 等[24]发现活动性 Crohn’s disease (CD)患者血清及结肠组织中 SAP130 水平显著升高，且与疾病严重程度显著相关。而 2020 年 Liu [25]第一次揭示 SAP130 在 IPF 患者全身和局部肺室中的临床意义。IPF 患者的血清 SAP130 水平明显高于对照组(824.2 ± 29.84 vs 413.8 ± 19.77 pg/mL, $P < 0.0001$)；通过对肺组织免疫组化发现，与对照组相比，SAP130 在正常肺泡组织中呈稀疏表达，而在 IPF 患者中 SAP130 弥漫性分布于肺泡上皮内壁间。在肺功能方面，IPF 患者 SAP130 水平与 DLCO、FEV1 呈负相关，说明 SAP130 水平越高，病情越严重。肺部影像同样有类似发现，病情稳定患者血清 SAP130 水平与 HRCT 纤维化程度呈正相关。但是该研究样本量较少，还需要更多前瞻性多中心研究和大量病例来验证。

5. CD163

CD163 是一种大小为 130 kDa 的 I 型跨膜蛋白，几乎只在单核/巨噬细胞上表达，是富含半胱氨酸的清道夫 B 族受体的成员[26]。该蛋白通常被认为是可作为 M2 型巨噬细胞特异性标志物[27]。CD163 可以识别血红蛋白/珠蛋白复合物，并与其结合在单核或巨噬细胞膜表面，体内细胞通过内吞的方式将结合体运送给内体和溶酶体，完成一系列的血红蛋白代谢[28]；另外 $CD163^+$巨噬细胞也参与炎症的消除、伤口愈合和血管生成的过程中[29]。CD163 不仅存在于细胞膜上，当机体发生感染性炎症、非感染性炎症或者肿瘤时，还可以从受刺激的巨噬细胞表面释放到血清中[30]。血清可溶性 CD163 水平已被报道与肝硬化和系统性硬化等疾病纤维化的严重程度相关[31] [32]。最近，有报道称血清单核细胞计数可以预测 IPF 的病情严重程度及预后[33]。而单核/巨噬细胞的细胞表型主要集中在 CD163 的表达上，因此越来越多的研究发现 $CD163^+$在鉴别 IPF、评估病情严重程度及预后有重要临床意义[34] [35]。但目前 CD163 与 IPF 疾病相关的具体机制尚不明确，可能是 $CD163^+$巨噬细胞对与 IPF 相关的组织损伤具有保护作用。Ye 等[36]报道 IPF 患者肺泡巨噬细胞血红素加氧酶-1 表达降低。而 CD163 是血红素结合珠蛋白复合物的清除

受体，可降低血红素加氧酶的毒性。

6. KL6

血清涎液化糖链抗原(Krebs von den Lungen-6, KL6)是在正常肺组织中，由 II 型肺泡细胞、呼吸性细支气管上皮细胞和支气管腺浆液细胞所分泌。其可反映肺泡损伤、II 型肺泡细胞再生和多种间质性肺疾病(Interstitial lung disease, ILD)的病情活动情况[37]。研究[38]发现 KL-6 在包括 IPF 在内的多种 ILD 患者的血清中均有升高。因此血清 KL-6 水平不能有效鉴别 IPF 与其他 ILD。但有研究[39]显示连续测量 KL-6 水平可以作为评估疾病进展和预后恶化的危险因素。此外对于 IPF 的急性加重期，血清 KL-6 值明显高于稳定期患者，较高 KL-6 水平是 AE-IPF 发病的预测因素[40]。最近的一项系统综述和 Meta 分析表明，IPF 中 KL-6 水平的增加是 AE 风险的一个预测指标，但似乎与死亡率无关[41]。除了血清 KL-6 外，支气管肺泡灌洗液(bronchoalveolar lavage fluid, BALF)中的 KL-6 水平检测应用越来越多，有研究报道 BALF 中的 KL-6 水平似乎是区分 IPF 与其他 ILD 的一个特异性标志物[42]。而 Bennet 等[43]研究证实，BALF 中 KL-6 水平不仅可鉴别 IPF 与其他 ILD，还可有效评估病情的严重程度。另外 KL-6 在抗纤维化治疗监测中的应用的研究也有了不错的数据。在一项研究中，吡非尼酮治疗的反应与血清 KL-6 的变化相关[44]；Bergantini 等[45]对使用尼达尼布治疗的 IPF 患者进行血清 KL-6 的动态监测，发现 KL-6 浓度与治疗后 6 个月及 12 个月患者的用力肺活量(forced vital capacity, FVC)和一氧化碳弥散量(carbon monoxide diffusing capacity, DLCO)有显著相关性。

7. 总结

目前随着对 IPF 研究的不断深入，越来越多的生物标志物将被发现，希望在不久的将来，这些生物标志物能尽快在大型临床试验中得到验证，以提高疾病诊断的准确性，评估治疗效果，让患者享受精准治疗及个体化治疗带来的益处。

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