特约综述

纺锤体组装检验点

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摘要 在细胞分裂过程中, 纺锤体组装检验点(spindle assembly checkpoint, SAC)监控着染色体与纺锤体微管的结合以及有丝分裂中姐妹染色单体或减数分裂同源染色体间的张力, 从而保证染色体正确均等地分配到两个子细胞中。SAC 功能异常可能导致非整倍体产生, 后者与肿瘤的形成以及自发流产和先天出生缺陷等疾病有密切的关系。

关键词 纺锤体组装检验点; 非整倍体; 有丝分裂; 减数分裂; 肿瘤

在细胞分裂中, 染色体的正确分离需要细胞内的监控机制来保证, 其中, 纺锤体组装检验点(spindle assembly checkpoint, SAC)是保证染色体正确分离的重要机制之一, 它监控着纺锤体微管与着丝点之间的连接并且促使有丝分裂中姐妹染色单体或减数分裂中同源染色体间张力的形成。当所有的染色体与来自纺锤体两极的微管正确连接, 并排列在赤道板上时, SAC才能失活, 从而解除对细胞由分裂中期进入后期的抑制。有丝分裂中, 如果 SAC 功能异常, 则可能导致染色体错误分离, 进而促发肿瘤[1,2]。减数分裂中, 如果 SAC 功能异常, 则可能导致非整倍体配子的产生, 从而引起不育不孕、自发流产或先天出生缺陷[3-5]。本文从有丝分裂和减数分裂两方面, 对近年SAC的研究作简要综述, 以期阐明SAC异常与肿瘤发生和生殖相关疾病发生的可能关系。

1 有丝分裂SAC

1.1 SAC 蛋白组成

SAC 的概念是 1989 年由 Hartwell 和 Weinert 首次提出的[6], 而 SAC 蛋白则是 1991 年在出芽酵母中被首次发现的, 它包括 Mad 和 Bub 两个家族。Mad 家族成员有Mad1、Mad2和Mad3, Bub家族成员有Bub1、Bub2 和 Bub3 [7,8]。在真核生物中, 除上述 6 种蛋白质外, 近年还发现其它 SAC 蛋白, 如 CENP-E 等[9] (表 1) [1,2,10] 。当细胞分裂时, 这些蛋白质被有序地募集到着丝点上, 从而监控染色体在细胞赤道板上的排列、保证染色体的正确分离。

1.2 SAC 的机制

SAC 的主要功能是监控着丝点与纺锤体微管的正确连接以及保证张力的形成。细胞进入分裂时, Bub1 先定位于着丝点上, 并作为基础招募其它 SAC 蛋白如 Mad1、Mad2、BubR1、Bub3 和 Mps1 等至着丝点[2,11]。Mad1 被募集到着丝点上后, 细胞质中的 Mad2 也随后被募集到着丝点, 形成 Mad1-Mad2 二聚体; 与此同时, BubR1 与 Bub3 结合形成 BubR1- Bub3 二聚体也被募集到着丝点上。在 G_2/M 期, Mad2、BubR1、Bub3 和 Cdc20 形成 MCC (mitotic checkpoint complex) 四聚体与分裂后期促进复合体(anaphase promoting complex/cyclosome, APC/C)结合并抑制其活性(图 1) [12]。

Mad2 主要感应微管与着丝点之间的连接[13], 对于 SAC 的功能必不可少。在细胞中, Mad2 有两种构象, 即 O-Mad2 和 C-Mad2。没有与 Mad1 或 Cdc20 结合的 Mad2 为 O-Mad2, 而结合到 Mad1 或 Cdc20 上的 Mad2 则会转变为稳定的 C-Mad2 型构象。细胞质中存在着大量游离的O-Mad2, 以及与Mad1结合形成的 Mad1-C-Mad2 二聚体。P31^{comet} 能与 Mad1-C-Mad2 结合并使后者结合 O-Mad2 的活性受到抑制。Mad2 模板(Mad2 template)假说认为: 当着丝点未连接微管时, Mad1-C-Mad2先在着丝点上形成一个稳定的复合体, 并以此为模板来招募细胞中游离的 O-Mad2 形成 Mad1-C-Mad2-O-Mad2 三聚体。三聚体中的 O-Mad2 快速转变为C-Mad2并脱离三聚体与CDC20结合。着丝点上的C-Mad2与APC/C的激活因子Cdc20结合形

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Table 1 Components of spindle assembly checkpoint [1,2,10]

Core SAC proteins	Function
Mad1 (mitotic-arrest deficient-1)	Phosphorylated Mad1 facilitates recruitment of Mad2 to kinetochores unattached to microtubules or lack of tension between sister chromatids. Forms a complex with Cdc20, Mad2 and Mad3/BubR1 to inhibit APC/C activity
Mad2 (mitotic-arrest deficient-2)	To form the MCC with Bub3, Cdc20 and BubR1/Mad3 to inhibit the APC/C activity. Monitors attachment of microtubules to kinetochores
Mad3/BubR1 (mitotic-arrest deficient-3)	One component of the MCC, monitoring the tension between sister chromatids.
Bub1 (budding uninhibited by benzimidazole-1)	A protein kinase that phosphorylates Cdc20 and recruits other checkpoint proteins such as Mad2, BubR1 and CENP-E to kinetochores
Mps1 (multipolar spindle-1)	A protein kinase that phosphorylates Mad1, which is required for recruitment of other SAC proteins to kinetochores
Bub3 (budding uninhibited by benzimidazole-1)	Form a complex with Mad1, Mad2, Cdc20 and BubR1/Mad3 to inhibit the APC/C.
APC/C (anaphase promoting complex/cyclosome)	E3 ubiquitin ligase that targets mitotic regulators such as securin, cyclin B, shugoshin for proteolysis by 20S proteasomes when activated by Cdc20
CENP-E (centromeric protein E)	A kinesin family member; Binds to BubR1 to stimulate its kinase activity and is required for capture and stabilization of microtubules at kinetochores in prometaphase.
Cdc20 (cell division cycle-20)	An APC activator

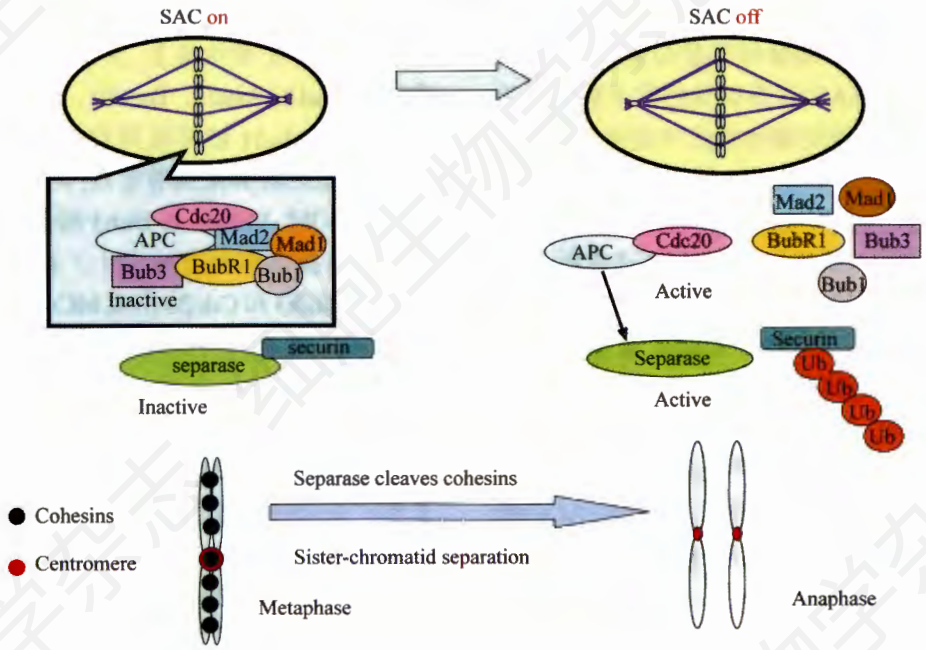

Fig.1 Spindle assembly checkpoint on and off (modified from reference [12])

成C-Mad2-Cdc20, 从而抑制APC/C的活性; 胞质中的O-Mad2也可与C-Mad2-Cdc20结合, 并转变为C-Mad2。通过这种级联放大作用, 在着丝点上形成大量的Mad2-Cdc20, 从而有效抑制APC/C的活性, 阻止细胞周期从中期进入后期。而胞质中的Mad1-C-Mad2因为结合了P31^{comet}蛋白而不能再募集O-Mad2, 因此只有在未连接微管的着丝点上可以产生这种级联放大作用[2,14]。

Bub1和BubR1主要感受姐妹染色单体上着丝点间的张力[13], 促使与纺锤体微管错误连接的姐妹染色单体上的着丝点分别与来自纺锤体两极的微管连接, 从而保证分裂后期染色体能正确分配到子代细胞中。

当着丝点和纺锤体微管正确连接并在姐妹染色单体间产生合适张力后, 着丝点上的Mad1-C-Mad2二聚体, 被动力蛋白(dynein)沿微管运向纺锤体的两极[15,16]。Mad1-C-Mad2移离着丝点后, 即导致Cdc20从C-Mad2-Cdc20复合体上释放出来。游离的Cdc20与APC/C结合使后者活化[2]。活化的APC/C通过泛素化介导的蛋白质降解途径使securin降解, 从而释放出separase。游离的separase可降解连接姐妹染色单体着丝粒的cohesin蛋白1 (sister chromatid cohesion protein 1, SCC1), 从而使姐妹染色单体分开; 同

时, 活化的APC/C通过泛素化介导的蛋白质降解途径使细胞周期蛋白B1降解, 从而让细胞分裂从中期进入后期[2,10]。

2 有丝分裂SAC异常与肿瘤

大量的研究表明, 乳腺癌、前列腺癌、肺癌和淋巴癌等多为非整倍体[17]。而非整倍体的形成源于染色体的错误分离[18], SAC是保证染色体正确分离的重要机制[2,10]。在有丝分裂中, SAC功能异常和非整倍体的形成及肿瘤发生存在着密切的联系[1,2]。SAC基因发生突变, 可能会影响SAC功能, 从而导致非整倍体乃至肿瘤的发生[19]。自Cahill等[20]首次在19个非整倍体直肠癌细胞系中发现4个细胞系存在*bub1*或*bubR1*突变之后, 相继有学者报道在人类肿瘤和肿瘤细胞系存在SAC基因的突变。如Nomoto等[21]在肺癌等细胞系中发现*mad1*突变增加, Gemma等[22]发现原发肺癌以及人类肺癌细胞系中*bub1*基因突变率明显升高。Ohshima等[23]在10个ATLL (adult T-cell leukemia/lymphoma)病例中发现, 患者细胞全为非整倍体, 而且其中4例存在*bub1*或*bubR1*突变, 1例为*bubR1*单碱基纯合突变, 1例为*bubR1*单碱基杂合突变; 另外两例分别为*bubR1*碱基缺失突变和*bub1*单碱基杂合突变。Tsukasaki等[24]在44个肿瘤细胞系以及133原发肿瘤中发现, 3个肿瘤细胞系及5个原发肿瘤中存在*mad1*基因错义突变。

需要指出的是, 在肿瘤中, SAC基因的突变率很低[25], 而较为常见的是SAC基因表达异常, 尤其是SAC表达不足。如Han等[26]在66例浸润性乳腺导管癌病人中, 发现44例患者无Mad1表达, 而在其余22例中, Mad1表达也明显降低。在鼻咽癌和卵巢癌细胞系中也发现Mad2表达减少, 而且这些细胞系多为非整倍体[16,27,28]。Dai等[29]发现*bubR1*$^{+/-}$杂合小鼠经azoxymethane (AOM)处理后, 非整倍体细胞率和肺癌及肠腺癌的发病率较野生型显著升高。

显然, SAC蛋白低表达可导致染色体分离异常而形成非整倍体, 从而促进肿瘤发生。但新近越来越多的研究表明, SAC蛋白高表达在一些肿瘤中更为明显。如Grabsch等[30]在胃癌组织中发现84%的Bub1、68%的BubR1和79%的Bub3都发生了高表达, 其中非整倍体细胞率则高达81.4%。Yuan等[31]在乳腺癌及其细胞系中均发现SAC蛋白Mad1、Mad2、Bub1、BubR1、Bub3和Mps1发生了高表达, 其中Mps1表达增加了520倍, Mad2表达增加了11倍。Pinto等[32,33]在非整倍体肾癌中也相继发现Mad2、Bub1和BubR1存在高表达, 并且认为这些基因的高表达可能导致了染色体异常和肾癌发生。Sotillo等[34]发现Mad2过表达的小鼠, 非整倍体发生率高, 其中50%在75周因患肝癌、肺癌或淋巴癌等癌症而死亡。另外, Hernando等[35]研究发现抑癌基因与SAC蛋白的表达密切相关, 如在*Rb*突变肿瘤中, E2F表达增加, 进而促进Mad2蛋白过表达和非整倍体细胞的产生。

综上所述, SAC、非整倍体和肿瘤之间存在着密切联系, SAC蛋白表达及功能正常对于维持细胞的染色体稳定性和抑制肿瘤的的发生都是不可或缺的[36]。SAC蛋白的低表达和高表达都可能导致非整倍体乃至肿瘤的形成。

3 减数分裂纺锤体组装检验点

精母细胞中存在SAC早已被公认[37], 而卵母细胞中存在SAC直到近年才被确认[38]。Brunet等[39]发现, 在小鼠卵母细胞中, 纺锤体微管的改变会导致Bub1一直聚集在着丝点上, 并保持磷酸化状态, 从而阻止MPF (M-phase promoting factor)失活和染色体分离; Yin等[40]发现Bub1缺失会引起卵母细胞染色体的错误分离, 这些研究均表明卵母细胞中同样存在着SAC。进一步的研究发现, SAC关键蛋白, 如Mad和Bub家族成员等在减数分裂和有丝分裂中均相同[36,41]。

减数分裂由两次细胞分裂组成, 即减数分裂I和II。在减数分裂I, 同源染色体以成对的形式排列在细胞赤道板上, 并且分别连接着来自纺锤体两极的微管, 即每条染色体的两个姐妹染色单体上的着丝点都与来自同一极的纺锤体微管相连, 从而借助同源染色体间交叉(chiasmata)和cohesins的作用, 在同源染色体间而非姐妹染色单体间形成张力(图2)。如果同源染色体的着丝点没有正确连接到微管上并在同源染色体间形成合适张力, 则会激活SAC, 使细胞停滞于前中期。除此之外的SAC机制, 在减数分裂I与有丝分裂之间并无明显差别。在减数分裂II, 染色体在赤道板上的排列及与纺锤体微管的连接、SAC激活等均与有丝分裂相同(图3) [42]。

在减数分裂中, 姐妹染色单体臂间和着丝粒间的cohesins的解离途径不同。在减数分裂I, Plk1激酶磷酸化姐妹染色单体臂间的减数分裂特异的cohesin组分Rec8, 磷酸化后的Rec8能被separase降解, 从而使具有交叉的同源染色体分开[43]; 而着丝粒处的cohesins由于受到shugoshin以及蛋白磷酸酶2A (PP2A)的作用, 依然处于非磷酸化状态, 而不能被separase降解[44,45] (图2)。在减数分裂II, 着丝粒处的

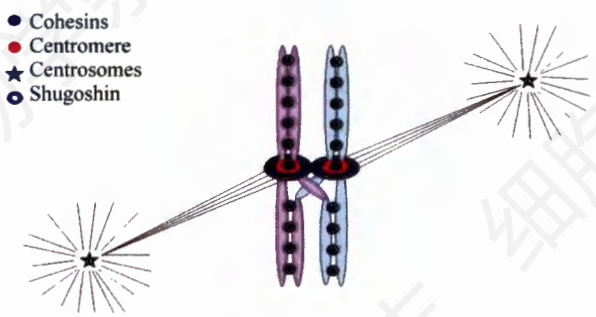

Fig.2 Attachment of sister chromatid kinetochores to spindle microtubles at prometaphase in meiosis I, with sister chromatid kinetochores of each chromosome pair co-connecting to one spindle pole

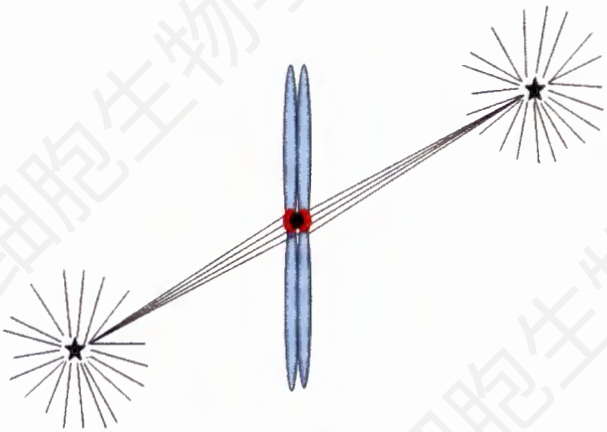

Fig.3 Attachment of sister chromatid kinetochores to spindle microtubles at prometaphase in meiosis II, with sister chromatid kinetochores of each chromosome pair co-connecting to different spindle poles

shugoshin 和 PP2A 发生移位, 使得 cohesins 能被磷酸化并被 separase 降解[46,47] (图 3)。Bub1 对 shugoshin 与着丝粒的结合起着重要作用, 在酵母中, Bub1 的 N 端与 shugoshin1 连接, 而 C 端的激酶结构域与 shugoshin2 共同作用促进减数分裂I姐妹染色单体上的着丝点与来自纺锤体同一极的微管连接[48]。

总之, 在哺乳动物卵母细胞中, SAC 无论在减数分裂 I 还是减数分裂 II, 对于保证染色体的正确分离都是必需的。但需要指出的是, 尽管有时SAC蛋白表达及功能正常, 却仍然无法有效地防止染色体的异常分离, 如在联会复合体组分 *scp3* 敲除的小鼠中, 非整倍体的次级卵母细胞发生率明显增加; 这可能由于 *scp3*$^{-/-}$形成的单价体上的姐妹染色单体着丝点分别与纺锤体两极的微管连接, 从而蒙骗了 SAC 的监控, 而导致姐妹染色单体在减数分裂I发生了提前分离并最终形成非整倍体卵子[49,50]。

4 减数分裂SAC异常

近年大量的研究表明, 减数分裂 SAC 活性异常可能导致染色体错误分离、细胞周期紊乱等[51]。在 Mad2 RNAi 的小鼠初级卵母细胞中, 细胞周期蛋白 B 和 securin 发生提前降解, 并导致非整倍体发生率升高[52]; 在 *mad2*$^{+/-}$ 小鼠的卵母细胞中, 次级卵母细胞的非整倍体发生率也有所升高, 并会引起雌鼠生育力下降[53]。在 BubR1 表达不足小鼠中, 生殖细胞非整倍体发生率明显升高, 且小鼠不育[54]。与 Mad2、BubR1 表达下调类似, 向小鼠卵母细胞注射 Bub1 抗体也会导致分裂后期提前发生[55]。此外, SAC 蛋白过表达也会导致减数分裂染色体分离异常, Niault等[53]发现, Mad2 过表达的小鼠卵母细胞同样会发生减数分裂I染色体错误分离, 而产生非整倍体次级卵母细胞。上述结果表明, Mad2、BubR1 和 Bub1 等在生殖细胞中也是保证染色体正确分离的关键蛋白, 其含量的改变会导致 SAC 功能异常[56]。

众所周知, 在女性中, 非整倍体配子发生率随年龄增长会明显升高[3,57,58]。尽管非整倍体的发生率随年龄增长而升高可能有多种原因, 如姐妹染色单体间 cohesins 的提前解离[59,60], 但新近的研究发现, 这也可能与SAC蛋白表达量的下降有关。如Steuerwald等[61]发现在年老女性的卵母细胞中, Mad2 的 mRNA 含量降低; Baker 等[62]和 Hamatani 等[63]分别在小鼠卵母细胞中发现, BubR1 和 Bub1 的表达也会随年龄增加而有所下降。而这些蛋白质表达下降就可能引起 SAC 活性降低[56]。因此, 在年老的女性中, SAC 功能减弱就无法保证染色体的正确分离, 而导致非整倍体的发生率升高。

5 展 望

自发现以来, 纺锤体组装检验点一直是细胞生物学和遗传学研究的热点, 但其分子机制至今未完全明了。如细胞质中的 O-Mad2 是如何与 C-Mad2 作用并促使前者发生构象改变并与 Cdc20 结合目前仍不清楚[2]。SAC 异常与非整倍体、肿瘤和出生缺陷的发生密切相关, 了解SAC的机制对于有效防止先天出生缺陷, 以及非整倍体肿瘤的预防、诊断和治疗具有重要作用。

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Spindle Assembly Checkpoint

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Abstract The spindle assembly checkpoint monitors attachment of microtubles to chromosomes, and the proper tension between sister chromatids during mitosis or homologous chromosomes during meiosis, to ensure equal distribution of chromosomes into daughter cells. Dysfunction in the spindle assembly checkpoint could lead to the generation of aneuploidy, which is closely related to diseases such as cancer, spontaneous abortions or birth with defects.

Key words spindle assembly checkpoint; aneuploidy; mitosis; meiosis; cancer

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