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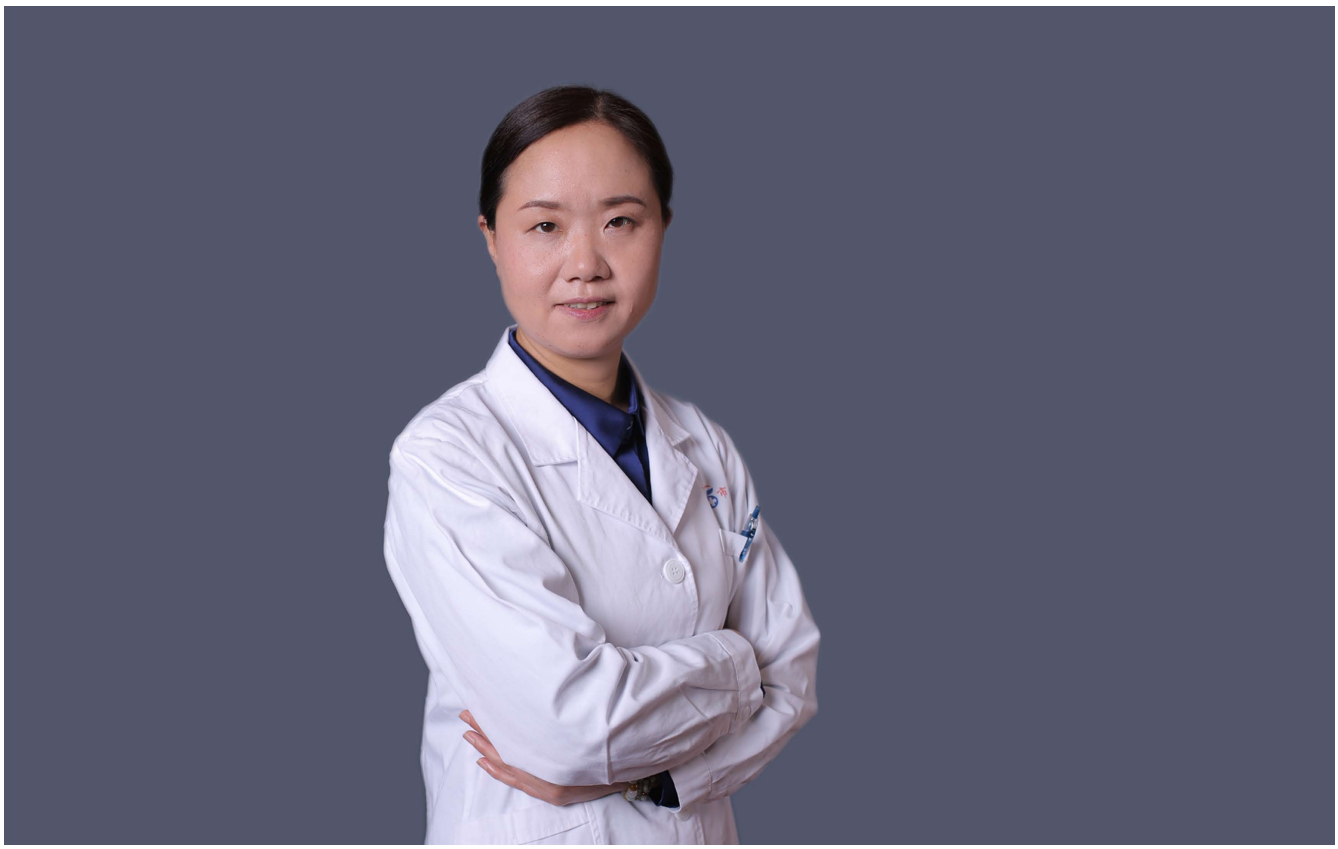

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述评 EDITORIAL

驱动蛋白家族在消化道肿瘤中的研究进展

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Role of kinesin superfamily in gastrointestinal cancer

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Abstract

Kinesins constitute a protein superfamily that belongs to motor proteins. Kinesins move along microtubules to exert their functions. They play a crucial role in intracellular transportation, mitosis, cell formation, and cell function. Kinesin are not only responsible for the transport of various membrane organelles, protein complexes, mRNA and so on to ensure the basic activity of cells, but also can regulate intracellular molecular signal pathways. Numerous studies have shown that kinesins are closely associated with the development of a variety of human diseases, especially the formation and development of gastrointestinal tumors. This article reviews the role of kinesins in gastrointestinal cancer.

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Key Words: Kinesin; Molecular motor; Gastrointestinal cancer

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摘要

驱动蛋白是一类蛋白超家族, 属于分子马达的一种, 它沿着微管行动以行驶其功能. 它在胞内运输、有丝分裂、细胞形成、细胞功能等方面起着至关重要的作用. 驱动蛋白不仅负责运输各种膜细胞器、蛋白复合体、mRNA等以保证细胞的基本活性, 同时其自身也可对部分细胞内分子信号通路起调节作用. 大量研究表明, 驱动蛋白广泛地参与了机体多种疾病的发生发展过程, 尤其是消化道肿瘤的形成与发展, 本文将对近年来诸多关于驱动蛋白与消化道肿瘤疾病的研究进行综述.

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关键词: 驱动蛋白; 分子马达; 消化道肿瘤

核心提要: 大量研究证实驱动蛋白调控失衡与消化道肿瘤的发生和转移有关. 进一步深入研究消化道肿瘤细胞中各种驱动蛋白的具体作用机制, 可以为消化道肿瘤的靶向治疗提供理论支持, 从而为肿瘤的基因治疗提供一种新的选择, 改善肿瘤患者预后.

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0 引言

驱动蛋白家族(kinesin superfamilys, KIFs)是一类分子马达, 在细胞内负责沿着微管, 向其正极运送不同的分子货物, 是细胞内小泡、细胞器、蛋白复合物和RNA等货物转运的重要分子之一[1,2]. 1985年, Hirokawa等[3]首次通过高精度显微技术(快速冷冻深度 蚀刻)观察到在微管和细胞器之间有一些链接结构. 这些链接结构后来被证实可能是负责细胞内运输的分子马达蛋白, 包括驱动蛋白(kinesin)、动力蛋白(dynein)、肌球蛋白(myosin)等. 驱动蛋白与其他的分子马达一起, 在细胞水平发挥运输工具的作用, 以微管等细胞骨架为依托, 将不同的分子货物运送到指定的细胞内位置, 从而发挥其生物学作用[4].

驱动蛋白有3个结构域: 马达区、FHA结构域和PH结构域, 马达区在KIFs中高度保守[1], 可与ATP和微管结合水解提供能量, 缺失该结构域的驱动蛋白对货物的运输能力显著下降; FHA结构域的功能未知; PH结构域参与货物的运输, 且决定结合货物的特异性. KIFs及其参与的细胞内物质运输对维持细胞的基本功能起到极其重要的作用.

自1985年首次发现以来, KIFs已发现了14个亚家族的45个成员[1]分别为kinesin1到kinesin14B(表1)[5]. 驱动蛋白广泛地分布于各种组织细胞, 对于维持细胞的正常形态和功能发挥重要作用. 目前对驱动蛋白的功能已经有了很多认识, 证实KIFs与神经退行性变、糖尿病、肾病等的发生密切相关[6-8]. 此外, 大量研究表明, 驱动蛋白广泛地参与了多种肿瘤的发生发展, 其表达水平的变化和很多肿瘤的发生发展有直接关联[9-11]. 所有类型的肿瘤都有一个基本特征就是过度的细胞增殖, 后者源于细胞周期失控[9]. 异常的驱动蛋白表达可以通过染色体过度凝集、纺锤体形成异常、细胞分裂缺陷、形成后期桥或非整倍体及有丝分裂阻滞改变细胞内遗传物质的分布. 遗传物质的增加或减少都会引起子代细胞的众多功能异常, 最终可能渐进性地导致肿瘤发生.

消化道肿瘤是人类常见的恶性肿瘤, 共同点是起病隐匿, 病情发展迅速, 易转移, 恶性程度通常较高, 诊断时大多已处于进展期或晚期, 丧失了治疗的最佳时机. 目前临床上主要诊断方法是消化道内镜与影像学检查, 而对于CA19-9、CEA、AFP等肿瘤相关抗原, 由于其敏感性与特异性有限, 临床上只作为辅助诊断或筛查指标. 因此, 如若有一种同时具有高敏感性与高特异性的指标, 对于消化道肿瘤的诊断及预后有着重要的意义.

1 驱动蛋白家族与肝癌

肝细胞癌(hepatocellular carcinoma, HCC)是全球第五大常见癌症, 也是导致癌症相关死亡的第二大常见病因[12]. KIFs的过度表达常常与HCC进展和预后显着相关, 表明KIF可能是HCC的预后和治疗性生物标志物. 很多驱动蛋白的过表达与细胞侵袭和迁移的生物标志物呈正相关如: KIF3B、KIF18A、KIF14、KIF4A、KIF20A、KIF23等[13-17]. 有研究证实与邻近的非肿瘤组织相比, HCC组织中KIF3B蛋白水平增加, 且KIF3B过表达与生存率差有关; 此外, 抑制KIF3B不仅减少癌细胞生长, 而且诱导细胞凋亡; KIF3B过表达涉及肝细胞癌的发病机制, 可能作为人类HCC的潜在治疗靶点[15]. Huang等[17]通过敲除KIF4A相关基因发现在细胞中通过消耗KIF4A可诱导G2/M期阻滞并抑制有丝分裂进程; 此外, 研究显示在细胞中消耗KIF4A可抑制HCC细胞中的Akt激酶活性来诱导细胞凋亡; 因此我们认为KIF4A过表达可能导致肝细胞失控的细胞周期进程和分裂, 这可能导致HCC的发生和发展. Lu等[18]的研究显示生存率和无复发生存率的Kaplan-Meier曲线表明高KIF20A表达与较差的存活结果相关, 原发性HCC组织的KIF20A表达显着高于正常肝组织. Liao等[19]研究表明癌组织中KIF18A蛋白水平高于癌旁组织; 在SMMC-7721和HepG2细胞中沉默KIF18A后, 细胞生长受到明显抑制并且迁移和侵袭能力显着降低, KIF18A可通过促进细胞周期信号通路以及Akt和MMP-7/MMP-9相关信号通路促进HCC细胞的增殖, 侵袭和转移, 并可作为HCC诊断和治疗的新靶点.

尽管多数KIF家族成员在HCC组织中呈高表达, 且与肿瘤细胞的增殖于侵袭呈显著相关, 但Zhang等[20]的研究显示KIF1B蛋白表达与静脉侵袭和肿瘤复发状态有关, 且KIF1B 表达下调的患者复发风险显著增加, 提示我们KIF1B是肝癌抑制基因, KIF1B mRNA水平可能是预后生物标志物. 但仍需进一步大规模的临床验证.

表 1 驱动蛋白超家族的分类

Kinesin	KIF家族
Kinesin1	KIF5A KIF5B KIF5C
Kinesin2	KIF3A KIF3B KIF3C KIF17
Kinesin3	KIF1A KIF1B KIF1C KIF13A KIF13B KIF14 KIF16A KIF16B
Kinesin4	KIF4A KIF4B KIF7 KIF21A KIF21B KIF27
Kinesin5	KIF11
Kinesin6	KIF20A KIF20B KIF23
Kinesin7	KIF10
Kinesin8	KIF18A KIF18B KIF19A KIF19B
Kinesin9	KIF6 KIF9
Kinesin10	KIF22
Kinesin11	KIF26A KIF26B
Kinesin12	KIF12 KIF15
Kinesin13	KIF2A KIF2B KIF2C KIF24
Kinesin14A	KIFC1
Kinesin14B	KIF25 KIFC2 KIFC3

2 驱动蛋白家族与胃癌

胃癌(gastric cancer, GC)是世界上癌症相关死亡的第二大原因[21]. GC的高侵袭性和快速转移导致其高死亡率[22]. 胃癌的转移是早期影响患者生存率及生存率的重要因素. KIF14和KIF18A、有丝分裂着丝粒相关驱动蛋白(mitotic centromere associated protein, MCAK)、KIF2A在胃癌组织中的表达水平显著高于癌旁组织[23-26]; KIF14 mRNA高表达者较低表达者恶性度更高, 发生复发转移的风险是低表达者的6.9倍. 然而, 驱动蛋白在肿瘤组织的抑制中同样也发挥着重要作用, 有研究检查了KIF4在胃癌样本中的表达谱, 并且产生了稳定表达GFP-KIF4融合蛋白(称为BGC-GFP-KIF4细胞, KIF4低表达与肿瘤分化差有显着相关性, KIF4在BGC细胞中的过表达抑制了体外细胞增殖, 以及它们在体内形成肿瘤的能力. 人类chromosinesin KIF4作为胃癌细胞增殖的抑制剂, 可能作为治疗人类胃癌的新型生物靶点[27]. 以上说明驱动蛋白可用作胃癌诊断可靠的非创伤性指标及新的治疗作用靶点.

3 驱动蛋白家族与食管癌

食管癌是全球第八大常见癌症, 在死亡率方面排名第六[28]. 这种癌症最常发生在非西方世界, 伊朗北部和中国北部的死亡率为1000/100-180万[29]. 尽管在手术和辅助放化疗方面取得了突破, 但患有ESCC的患者预后不佳. 因此, 早期诊断对其预后很重要. 驱动蛋白家族成员2C(KIF-2C)也称为MCAK, 定位于整个细胞周期的细胞质中, 尤其在中心体, 着丝粒以及有丝分裂期间的纺锤体中区[30-32], KIF-2C有助于正确形成纺锤体[33-36]微管对染色体的附着和染色体分离[31,32,37,38]. KIF-2C异常表达与异常有丝分裂, 染色体畸变和恶性转化有关[36,38,39]. 因此, KIF-2C表达的失调可能在癌症发展和进展中起作用. Duan等[40]对415个手术切除的原发性肿瘤组织和40个邻近的非癌组织进行了免疫组织化学分析, 研究发现较高的KIF-2C表达与较高的病理性肿瘤状态和较差的肿瘤分化显着增加的风险相关. 基于这些发现, KIF-2C在食管肿瘤组织中的表达有望作为男性患者的独立预后标志物. 对于KIF-2C高表达的男性患者, 与具有相同病理性肿瘤-淋巴结转移的患者相比, 预后更差. Imai等[41]对105例食管鳞癌(oesophageal squamous cell carcinoma, ESCC)患者的病理组织进行免疫组化分析, 结果显示105例ESCC病例中有61例(58)为KIF11阳性; 研究结果表明KIF11在ESCC和CRC的发病机制中起重要作用, 抑制KIF11可能对治疗抵抗性ESCC具有积极作用. 目前关于食管癌中驱动蛋白的研究相对较少, 有待进一步研究.

4 驱动蛋白家族与结直肠癌

结直肠癌是一种常见的消化道癌症, 是肿瘤死亡的第三大原因[42-45]. 每年有超过一百万的新病人被诊断出来, 这种疾病在全球范围内是一个严重的经济和人口问题[46-48].

有研究发现KIF4A在CRC患者的肿瘤组织中表达上调, 并且KIF4A的下调在CRC细胞中可减少肿瘤细胞增殖, 说明KIF4A可能有促进肿瘤细胞增殖的功能[49]. Fan等[50]研究发现KIF2A mRNA和蛋白质产物均表现出CRC组织优先表达, 且高KIF2A表达与TNM分期和肿

瘤状态成显着正相关, 提示KIF2A可作为结直肠癌预后评估的重要指标. Wang等[51]研究表明KIF26B表达在原发性CRC组织中上调. 在免疫组织化学分析中, 直肠癌组织中高表达的KIF26B与其他恶性肿瘤特征如肿瘤大小, AJCC分期, 肿瘤深度, 分化组织学和淋巴结转移显着相关, 暗示KIF26B是恶性肿瘤的生物标志物. 在研究中, 还发现高KIF26B表达与Ki67表达正相关, Ki67是评估肿瘤细胞增殖的最常用标志物之一, 对某些类型的癌症具有预后价值[52-55], 表明KIF26B参与肿瘤细胞增殖. 另外利用PCR技术测定KIF26B和增殖相关基因(Ki67; cyclinD1)的表达显示在KIF26B敲低细胞中显着下调, 提示KIF26B作为CRC的潜在治疗靶标.

驱动蛋白家族在结直肠癌的侵袭转移中发挥重要作用. 研究发现KIF20B在CRC细胞中过表达并促进了由胶质瘤相关致癌基因1(Gli1)介导的上皮-间充质转变(EMT)过程以及CRC细胞迁移和侵袭[56]. MCAK是KIF-13家族的最佳特征成员, 并在有丝分裂期间的微管动力学中起重要作用, Ritter等[57]研究MCAK对于肿瘤细胞的迁移和侵袭非常重要, 其可能参与调节细胞骨架中的MT动力学. 干扰S19 zzx2磷酸化可阻碍肿瘤细胞的迁移和侵袭, 表明这种残基在细胞运动中起作用, 这种功能可能受Rac1-Aurora A-MCAK信号通路的调控. 结肠癌HCT116细胞通过敲低内源性MCAK显示出显著降低的侵袭能力, 表明MCAK的过度表达与结肠直肠癌患者中的淋巴侵袭和淋巴结转移相关. 因此结直肠癌组织中异常表达的驱动蛋白, 不仅可以作为诊断标志物, 还可以成为结直肠癌治疗新的治疗靶点.

5 结论

驱动蛋白与肿瘤之间的关系近些年来一直是研究的热点, 它在癌组织和正常组织中呈差异性表达, 可以作为多种肿瘤的诊断标志物. 目前可以肯定的是驱动蛋白的异常表达参与了肿瘤细胞的增殖、去分化、侵袭转移和抗凋亡等过程但具体分子机制的研究仍不十分明了, 如果能够明确驱动蛋白在肿瘤发生发展以及侵袭转移中所起的作用, 那么对于肿瘤的早期诊断治疗将十分有帮助. 目前关于驱动蛋白与肿瘤关系的报道, 也有不一致之处, 考虑可能与取材、实验方法以及肿瘤类型等多种因素有关. 因此, 驱动蛋白应用于消化系统肿瘤的诊断及靶向治疗还有很长一段路要走.

6 参考文献

1 Miki H, Setou M, Kaneshiro K, Hirokawa N. All kinesin superfamily protein, KIF, genes in mouse and human. *Proc Natl Acad Sci* USA 2001; 98: 7004-7011 [PMID: 11416179 DOI: 10.1073/pnas.111145398]

2 Yu Y, Feng YM. The role of kinesin family proteins in tumorigenesis and progression: potential biomarkers and molecular targets for cancer therapy. *Cancer* 2010; 116: 5150-5160 [PMID: 20661912 DOI: 10.1002/cncr.25461]

3 Hirokawa N, Bloom GS, Vallee RB. Cytoskeletal architecture and immunocytochemical localization of microtubule-associated proteins in regions of axons associated with rapid axonal transport: the beta, beta'-iminodipropionitrile-intoxicated axon as a model system. *J Cell Biol* 1985; 101: 227-239 [PMID: 2409096]

4 Hirokawa N, Niwa S, Tanaka Y. Molecular motors in neurons: transport mechanisms and roles in brain function, development, and disease. *Neuron* 2010; 68: 610-638 [PMID: 21092854 DOI: 10.1016/j.neuron.2010.09.039]

5 Hirokawa N, Noda Y, Tanaka Y, Niwa S. Kinesin superfamily motor proteins and intracellular transport. *Nat Rev Mol Cell Biol* 2009; 10: 682-696 [PMID: 19773780 DOI: 10.1038/nrm2774]

6 Ari C, Borysov SI, Wu J, Padmanabhan J, Potter H. Alzheimer amyloid beta inhibition of Eg5/kinesin 5 reduces neurotrophin and/or transmitter receptor function. *Neurobiol Aging* 2014; 35: 1839-1849 [PMID: 24636920 DOI: 10.1016/j.neurobiolaging.2014.02.006]

7 Lockerbie RO, Eddé B, Prochiantz A. Cyclic AMP-dependent protein phosphorylation in isolated neuronal growth cones from developing rat forebrain. *J Neurochem* 1989; 52: 786-796 [PMID: 2537377 DOI: 10.1016/j.devcel.2014.08.028]

8 Duangtum N, Junking M, Sawasdee N, Cheunsuchon B, Limjindaporn T, Yenchitsomanus PT. Human kidney anion exchanger 1 interacts with kinesin family member 3B (KIF3B). *Biochem Biophys Res Commun* 2011; 413: 69-74 [PMID: 21871436 DOI: 10.1016/j.bbrc.2011.08.050]

9 Chandrasekaran G, Tátrai P, Gergely F. Hitting the brakes: targeting microtubule motors in cancer. *Br J Cancer* 2015; 113: 693-698 [PMID: 26180922 DOI: 10.1038/bjc.2015.264]

10 Chen S, Stout JR, Dharmaiah S, Yde S, Calvi BR, Walczak CE. Transient endoreplication down-regulates the kinesin-14 HSET and contributes to genomic instability. *Mol Biol Cell* 2016; 27: 2911-2923 [PMID: 27489338 DOI: 10.1091/mbc.E16-03-0159]

11 Kato T, Lee D, Wu L, Patel P, Young AJ, Wada H, Hu HP, Ujiie H, Kaji M, Kano S, Matsuge S, Domen H, Kaga K, Matsui Y, Kanno H, Hatanaka Y, Hatanaka KC, Matsuno Y, de Perrot M, Yasufuku K. Kinesin family members KIF11 and KIF23 as potential therapeutic targets in malignant pleural mesothelioma. *Int J Oncol* 2016; 49: 448-456 [PMID: 27279560 DOI: 10.3892/ijo.2016.3566]

12 Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; 65: 87-108 [PMID: 25651787 DOI: 10.3322/caac.21262]

13 Chen J, Li S, Zhou S, Cao S, Lou Y, Shen H, Yin J, Li G. Kinesin superfamily protein expression and its association with progression and prognosis in hepatocellular carcinoma. *J Cancer Res Ther* 2017; 13: 651-659 [PMID: 28901309 DOI: 10.4103/jcrt.JCRT_491_17]

14 Huang X, Liu F, Zhu C, Cai J, Wang H, Wang X, He S, Liu C, Yao L, Ding Z, Zhang Y, Zhang T. Suppression of KIF3B expression inhibits human hepatocellular carcinoma proliferation. *Dig Dis Sci* 2014; 59: 795-806 [PMID: 24368420 DOI: 10.1007/s10620-013-2969-2.]

15 Sun X, Jin Z, Song X, Wang J, Li Y, Qian X, zhang Y, Yin Y. Evaluation of KIF23 variant 1 expression and relevance as a novel prognostic factor in patients with hepatocellular carcinoma. *BMC Cancer* 2015; 15: 961 [PMID: 26674738 DOI: 10.1186/s12885-015-1987-1]

16 Huang Y, Wang H, Lian Y, Wu X, Zhou L, Wang J, Deng M, Huang Y. Upregulation of kinesin family member 4A

enhanced cell proliferation via activation of Akt signaling and predicted a poor prognosis in hepatocellular carcinoma. *Cell Death Dis* 2018; 9: 141 [PMID: 29396392 DOI: 10.1038/s41419-017-0114-4]
17 Xu H, Choe C, Shin SH, Park SW, Kim HS, Jung SH, Yim SH, Kim TM, Chung YJ. Silencing of KIF14 interferes with cell cycle progression and cytokinesis by blocking the p27(Kip1) ubiquitination pathway in hepatocellular carcinoma. *Exp Mol Med* 2014; 46: e97 [PMID: 24854087 DOI: 10.1038/emm.2014.23]
18 Lu M, Huang X, Chen Y, Fu Y, Xu C, Xiang W, Li C, Zhang S, Yu C. Aberrant KIF20A expression might independently predict poor overall survival and recurrence-free survival of hepatocellular carcinoma. *IUBMB Life* 2018; 70: 328-335 [PMID: 29500859 DOI: 10.1002/iub.1726]
19 Liao W, Huang G, Liao Y, Yang J, Chen Q, Xiao S, Jin J, He S, Wang C. High KIF18A expression correlates with unfavorable prognosis in primary hepatocellular carcinoma. *Oncotarget* 2014; **5**: 10271-10279 [PMID: 25431949 DOI: 10.18632/oncotarget.2082]
20 Yang SZ, Wang JT, Yu WW, Liu Q, Wu YF, Chen SG. Downregulation of KIF1B mRNA in hepatocellular carcinoma tissues correlates with poor prognosis. *World J Gastroenterol* 2015; 21: 8418-8424 [PMID: 26217094 DOI: 10.3748/wjg.v21.i27.8418]
21 Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005; 55: 74-108 [PMID: 15761078]
22 Wang Z, Chen JQ. Imaging in assessing hepatic and peritoneal metastases of gastric cancer: a systematic review. *BMC Gastroenterol* 2011; 11: 19 [PMID: 21385469 DOI: 10.1186/1471-230X-11-19]
23 Tong H, Wang J, Chen H, Wang Z, Fan H, Ni Z. Transcriptomic analysis of gene expression profiles of stomach carcinoma reveal abnormal expression of mitotic components. *Life Sci* 2017; 170: 41-49 [PMID: 27923621 DOI: 10.1016/j.lfs.2016.12.001]
24 Wang L, Yang S, Sun R, Lu M, Wu Y, Li Y. Expression of KIF18A in gastric cancer and its association with prognosis. *Zhonghua Wei Chang Wai Ke Za Zhi* 2016; 19: 585-589 [PMID: 27215532]
25 Gao J, Sai N, Wang C, Sheng X, Shao Q, Zhou C, Shi Y, Sun S, Qu X, Zhu C. Overexpression of chromokinesin KIF4 inhibits proliferation of human gastric carcinoma cells both in vitro and in vivo. *Tumour Biol* 2011; 32: 53-61 [PMID: 20711700 DOI: 10.1007/s13277-010-0090-0]
26 Nakamura Y, Tanaka F, Haraguchi N, Mimori K, Matsumoto T, Inoue H, Yanaga K, Mori M. Clinicopathological and biological significance of mitotic centromere-associated kinesin overexpression in human gastric cancer. *Br J Cancer* 2007; 97: 543-549 [PMID: 17653072 DOI: 10.1038/sj.bjc.6603905]
27 Zhang S, Huang F, Wang Y, Song Q, Yang X, Wu H. KIF2A Overexpression and Its Association with Clinicopathologic Characteristics and Poor Prognoses in Patients with Gastric Cancer. *Dis Markers* 2016; 2016: 7484516 [PMID: 27773961 DOI: 10.1155/2016/7484516]
28 Dawsey SP, Tonui S, Parker RK, Fitzwater JW, Dawsey SM, White RE, Abnet CC. Esophageal cancer in young people: a case series of 109 cases and review of the literature. *PLoS One* 2010; 5: e14080 [PMID: 21124934 DOI: 10.1371/journal.pone.0014080]
29 Rafiemanesh H, Maleki F, Mohammadian-Hafshejani A, Salemi M, Salehiniya H. The Trend in Histological Changes and the Incidence of Esophagus Cancer in Iran (2003-2008). *Int J Prev Med* 2016; 7: 31 [PMID: 26955461 DOI: 10.4103/2008-7802.175990]
30 Wordeman L, Mitchison TJ. Identification and partial characterization of mitotic centromere-associated kinesin, a kinesin-related protein that associates with centromeres during mitosis. *J Cell Biol* 1995; 128: 95-104 [PMID: 7822426]
31 Walczak CE, Mitchison TJ, Desai A. XKCM1: a Xenopus kinesin-related protein that regulates microtubule dynamics during mitotic spindle assembly. *Cell* 1996; 84: 37-47 [PMID: 8548824]
32 Maney T, Hunter AW, Wagenbach M, Wordeman L. Mitotic centromere-associated kinesin is important for anaphase chromosome segregation. *J Cell Biol* 1998; 142: 787-801 [PMID: 9700166]
33 Stout JR, Rizk RS, Kline SL, Walczak CE. Deciphering protein function during mitosis in PtK cells using RNAi. *BMC Cell Biol* 2006; 7: 26 [PMID: 16796742 DOI: 10.1186/1471-2121-7-26]
34 Holmfeldt P, Stenmark S, Gullberg M. Differential functional interplay of TOGp/XMAP215 and the KinI kinesin MCAK during interphase and mitosis. *EMBO J* 2004; 23: 627-637 [PMID: 14749730 DOI: 10.1038/sj.emboj.7600076]
35 Ganem NJ, Compton DA. The KinI kinesin Kif2a is required for bipolar spindle assembly through a functional relationship with MCAK. *J Cell Biol* 2004; 166: 473-478 [PMID: 15302853 DOI: 10.1083/jcb.200404012]
36 Cassimeris L, Morabito J. TOGp, the human homolog of XMAP215/Dis1, is required for centrosome integrity, spindle pole organization, and bipolar spindle assembly. *Mol Biol Cell* 2004; 15: 1580-1590 [PMID: 14718566 DOI: 10.1091/mbc.e03-07-0544]
37 Andrews PD, Ovechkina Y, Morrice N, Wagenbach M, Duncan K, Wordeman L, Swedlow JR. Aurora B regulates MCAK at the mitotic centromere. *Dev Cell* 2004; 6: 253-268 [PMID: 14960279]
38 Kline-Smith SL, Khodjakov A, Hergert P, Walczak CE. Depletion of centromeric MCAK leads to chromosome congression and segregation defects due to improper kinetochore attachments. *Mol Biol Cell* 2004; 15: 1146-1159 [PMID: 14699064 DOI: 10.1091/mbc.e03-08-0581]
39 Gnjatic S, Cao Y, Reichelt U, Yekebas EF, Nölker C, Marx AH, Erbersdobler A, Nishikawa H, Hildebrandt Y, Bartels K, Horn C, Stahl T, Gout I, Filonenko V, Ling KL, Cerundolo V, Luetkens T, Ritter G, Friedrichs K, Leuwer R, Hegewisch-Becker S, Izbicki JR, Bokemeyer C, Old LJ, Atanackovic D. NY-CO-58/KIF2C is overexpressed in a variety of solid tumors and induces frequent T cell responses in patients with colorectal cancer. *Int J Cancer* 2010; 127: 381-393 [PMID: 19937794 DOI: 10.1002/ijc.25058]
40 Duan H, Zhang X, Wang FX, Cai MY, Ma GW, Yang H, Fu JH, Tan ZH, Fu XY, Ma QL, Wang XY, Lin P. KIF-2C expression is correlated with poor prognosis of operable esophageal squamous cell carcinoma male patients. *Oncotarget* 2016; 7: 80493-80507 [PMID: 27563815 DOI: 10.18632/oncotarget.11492]
41 Imai T, Oue N, Sentani K, Sakamoto N, Uraoka N, Egi H, Hinoi T, Ohdan H, Yoshida K, Yasui W. KIF11 Is Required for Spheroid Formation by Oesophageal and Colorectal Cancer Cells. *Anticancer Res* 2017; 37: 47-55 [PMID: 28011472 DOI: 10.21873/anticanres.11287]
42 Li P, Xue WJ, Feng Y, Mao QS. MicroRNA-205 functions as a tumor suppressor in colorectal cancer by targeting cAMP responsive element binding protein 1 (CREB1). *Am J Transl Res* 2015; 7: 2053-2059 [PMID: 26692949]
43 Yu X, Li Z, Yu J, Chan MT, Wu WK. MicroRNAs predict and modulate responses to chemotherapy in colorectal cancer. *Cell Prolif* 2015; 48: 503-510 [PMID: 26202377 DOI: 10.1111/cpr.12202]
44 Zhang Y, Zheng L, Huang J, Gao F, Lin X, He L, Li D, Li Z, Ding Y, Chen L. MiR-124 Radiosensitizes human colorectal

cancer cells by targeting PRRX1. *PLoS One* 2014; 9: e93917 [PMID: 24705396 DOI: 10.1371/journal.pone.0093917]
45 Bachmayr-Heyda A, Reiner AT, Auer K, Sukhbaatar N, Aust S, Bachleitner-Hofmann T, Mesteri I, Grunt TW, Zeillinger R, Pils D. Correlation of circular RNA abundance with proliferation--exemplified with colorectal and ovarian cancer, idiopathic lung fibrosis, and normal human tissues. *Sci Rep* 2015; 5: 8057 [PMID: 25624062 DOI: 10.1038/srep08057]
46 Perilli L, Vicentini C, Agostini M, Pizzini S, Pizzi M, D'Angelo E, Bortoluzzi S, Mandruzzato S, Mammano E, Rugge M, Nitti D, Scarpa A, Fassan M, Zanovello P. Circulating miR-182 is a biomarker of colorectal adenocarcinoma progression. *Oncotarget* 2014; 5: 6611-6619 [PMID: 25115394 DOI: 10.18632/oncotarget.2245]
47 Zhang C, Liu J, Wang X, Wu R, Lin M, Laddha SV, Yang Q, Chan CS, Feng Z. MicroRNA-339-5p inhibits colorectal tumorigenesis through regulation of the MDM2/p53 signaling. *Oncotarget* 2014; 5: 9106-9117 [PMID: 25193859 DOI: 10.18632/oncotarget.2379]
48 Svoboda M, Slyskova J, Schneiderova M, Makovicky P, Bielik L, Levy M, Lipska L, Hemmelova B, Kala Z, Protivankova M, Vycital O, Liska V, Schwarzova L, Vodickova L, Vodicka P. HOTAIR long non-coding RNA is a negative prognostic factor not only in primary tumors, but also in the blood of colorectal cancer patients. *Carcinogenesis* 2014; 35: 1510-1515 [PMID: 24583926 DOI: 10.1093/carcin/bgu055]
49 Matsumoto Y, Saito M, Saito K, Kanke Y, Watanabe Y, Onozawa H, Hayase S, Sakamoto W, Ishigame T, Momma T, Kumamoto K, Ohki S, Takenoshita S. Enhanced expression of KIF4A in colorectal cancer is associated with lymph node metastasis. *Oncol Lett* 2018; 15: 2188-2194 [PMID: 29434924 DOI: 10.3892/ol.2017.7555]
50 Fan X, Wang X, Zhu H, Wang W, Zhang S, Wang Z. KIF2A overexpression and its association with clinicopathologic characteristics and unfavorable prognosis in colorectal cancer. *Tumour Biol* 2015; 36: 8895-8902 [PMID: 26070867 DOI: 10.1007/s13277-015-3603-z]
51 Wang J, Cui F, Wang X, Xue Y, Chen J, Yu Y, Lu H, Zhang M, Tang H, Peng Z. Elevated kinesin family member 26B is a prognostic biomarker and a potential therapeutic target for colorectal cancer. *J Exp Clin Cancer Res* 2015; 34: 13 [PMID: 25652119 DOI: 10.1186/s13046-015-0129-6]
52 Yerushalmi R, Woods R, Ravdin PM, Hayes MM, Gelmon KA. Ki67 in breast cancer: prognostic and predictive potential. *Lancet Oncol* 2010; 11: 174-183 [PMID: 20152769 DOI: 10.1016/S1470-2045(09)70262-1]
53 Allegra CJ, Paik S, Colangelo LH, Parr AL, Kirsch I, Kim G, Klein P, Johnston PG, Wolmark N, Wieand HS. Prognostic value of thymidylate synthase, Ki-67, and p53 in patients with Dukes' B and C colon cancer: a National Cancer Institute-National Surgical Adjuvant Breast and Bowel Project collaborative study. *J Clin Oncol* 2003; 21: 241-250 [PMID: 12525515 DOI: 10.1200/JCO.2003.05.044]
54 Brown DC, Gatter KC. Ki67 protein: the immaculate deception? *Histopathology* 2002; 40: 2-11 [PMID: 11903593 DOI: 10.1046/j.1365-2559.2002.01343.x.]
55 Amini A, Masoumi-Moghaddam S, Ehteda A, Morris DL. Bromelain and N-acetylcysteine inhibit proliferation and survival of gastrointestinal cancer cells in vitro: significance of combination therapy. *J Exp Clin Cancer Res* 2014; 33: 92 [PMID: 25425315 DOI: 10.1186/s13046-014-0092-7]
56 Lin WF, Lin XL, Fu SW, Yang L, Tang CT, Gao YJ, Chen HY, Ge ZZ. Pseudopod-associated protein KIF20B promotes Gli1-induced epithelial-mesenchymal transition modulated by pseudopodial actin dynamic in human colorectal cancer. *Mol Carcinog* 2018; 57: 911-925 [PMID: 29573464 DOI: 10.1002/mc.22812]
57 Ritter A, Sanhaji M, Friemel A, Roth S, Rolle U, Louwen F, Yuan J. Functional analysis of phosphorylation of the mitotic centromere-associated kinesin by Aurora B kinase in human tumor cells. *Cell Cycle* 2015; 14: 3755-3767 [PMID: 26148251 DOI: 10.1080/15384101.2015.1068481]

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