

# 腫瘤與癌症



了确诊率。繼而改善了早期癌症的治愈率。

## 前言

腫瘤或癌症依然是人類所面臨的最嚴重的健康負擔之一。2014 年 6 月发布的《2013 年北京市卫生与人群健康状况报告》表明，2012 年，北京市恶性肿瘤新发病例 40307 例，比上年增长了 3.22%。这意味着 2012 年北京市平均每天有 110 人被确诊为癌症。而 10 年前，这一数字约为平均每天 63 人，相当于十年增长了将近一倍。目前，先进的检测手段大大提高

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## The cancer glycocalyx mechanically primes integrin-mediated growth and survival

by MATTHEW J. PASZEK

Malignancy is associated with altered expression of glycans and glycoproteins that contribute to the cellular glycocalyx. We constructed a glycoprotein expression signature, which revealed that metastatic tumours up-regulate expression of bulky glycoproteins. A computational model predicted that these glycoproteins would influence transmembrane receptor spatial organization and function. We tested this prediction by investigating whether bulky glycoproteins in the glycocalyx promote a tumour phenotype in human cells by increasing integrin adhesion and signalling. Our data revealed that a bulky glycocalyx facilitates integrin clustering by funneling active integrins into adhesions and altering integrin state by applying tension to matrix-bound integrins, independent of actomyosin contractility. Expression of large tumour-associated glycoproteins in non-transformed mammary cells promoted focal adhesion assembly and facilitated integrin-dependent growth factor signalling to support cell growth and survival. Clinical studies revealed that large glycoproteins are abundantly

expressed on circulating tumour cells from patients with advanced disease. Thus, a bulky glycocalyx is a feature of tumour cells that could foster metastasis by mechanically enhancing cell-surface receptor function.[1]

## Cancer: Sugar-coated cell signalling

by ANDREW J. EWALD AND MIKALA EGEHLAD

Cell membranes are covered with sugar-conjugated proteins. New findings suggest that the physical properties of this coating, which is more pronounced in cancer cells, regulate cell survival during tumour spread.[2]

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### 肿瘤细胞的保护层

细胞糖萼 (覆盖细胞表面的一个糖蛋白/多糖层) 的组成通过组织分化和疾病等过程随细胞性质的变化而变化。Valerie Weaver 及同事试图弄清癌细胞中糖萼组成的变化是否会影响癌症表现型。他们发现，大块糖萼是转移性癌细胞的一个特征，是由大型糖蛋白的生成而产生的。大块糖萼会以物理方式将被称为“整联蛋白”或“粘合素”的糖蛋白粘附分子束缚住，后者反过来又会促进一个有利于细胞生

存和增殖的信号传导体系。临床研究显示，大型糖蛋白在来自侵袭性乳腺癌患者的循环肿瘤细胞上大量表达。这些发现表明，糖萼及其分子组分是以使跨膜受体信号传导正常化为

目的的治疗干预的有吸引力的目标。[1, 2]

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*An interesting caption to this drab picture...*

## 利用 R-环来促进癌症

by VAIBHAV BHATIA

Genome instability is central to ageing, cancer and other diseases. It is not only proteins involved in DNA replication or the DNA damage response (DDR) that are important for maintaining genome integrity: from yeast to higher eukaryotes, mutations in genes involved in pre-mRNA splicing and in the biogenesis and export of messenger ribonucleoprotein (mRNP) also induce DNA damage and genome instability. This instability is frequently mediated by R-loops formed by DNA-RNA hybrids and a displaced single-stranded DNA. Here we show that the human TREX-2 complex, which is involved in mRNP biogenesis and export, prevents genome instability as determined by the accumulation of  $\gamma$ -H2AX (Ser-139 phosphorylated histone H2AX) and 53BP1 foci and single-cell electrophoresis in cells depleted of the TREX-2 subunits PCID2, GANP and DSS1. We show that the BRCA2 repair factor, which binds to DSS1, also associates with PCID2 in the cell. The use of an enhanced green fluorescent protein-tagged hybrid-binding domain of RNase H1 and the S9.6 antibody did not detect R-loops in TREX-2-depleted cells, but did detect the accumulation of R-loops in BRCA2-depleted cells. The results indicate that R-loops are frequently formed in cells

and that BRCA2 is required for their processing. This link between BRCA2 and RNA-mediated genome instability indicates that R-loops may be a chief source of replication stress and cancer-associated instability.[3]

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R-环 (自然出现的三链核酸结构, 由一个 RNA-DNA 杂合体和被取代的单链 DNA 组成) 是基因组不稳定性的潜在诱导因素之一。这项研究显示, TREX-2 (在“信使核糖核蛋白” (mRNP) 的生物生成和输出中所涉及的一种复合物) 通过与乳腺癌易感基因因子 BRCA2 相互作用来处理 R-环。不含 BRCA2 的人细胞会积累高水平的 R-环。在肿瘤抑制因子与 R-环之间的这一出乎意料的相互作用表明, R-环也许是造成复制应激和肿瘤发生的一个主要原因。

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**Notch-Dependent Repression of miR-155 in the Bone Marrow Niche Regulates Hematopoiesis in an NF- $\kappa$ B-Dependent Manner**

by WANG LIN

The microRNA miR-155 has been implicated in regulating inflammatory responses and tumorigenesis, but its precise role in linking inflammation and cancer has remained elusive. Here, we identify a connection between miR-155 and Notch signaling in this context. Loss of Notch signaling in the bone marrow (BM) niche alters hematopoietic homeostasis and leads to lethal myeloproliferative-like disease. Mechanistically, Notch signaling represses miR-155 expression by promoting binding of RBPJ to the miR-155 promoter. Loss of Notch/RBPJ signaling upregulates miR-155 in BM endothelial cells, leading to miR-155-mediated targeting of the nuclear factor  $\kappa$ B (NF- $\kappa$ B) inhibitor  $\kappa$ B-Ras1, NF- $\kappa$ B activation, and increased proinflammatory cytokine production. Deletion of miR-155 in the stroma of RBPJ(-/-) mice prevented the development of myeloproliferative-like disease and cytokine induction. Analysis of BM from patients carrying myeloproliferative neoplasia also revealed elevated expression of miR-155. Thus, the Notch/miR-155/ $\kappa$ B-Ras1/NF- $\kappa$ B axis regulates the inflammatory state of the BM niche and affects the development of myeloproliferative disorders.[4]



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由印第安纳大学儿科副教授 *Nadia Carlesso* 博士领衔的研究团队发现，类似一串倒下的多米诺骨牌一样，骨髓中的一连串分子事件会产生高水平的炎症反应，该反应会扰乱正常的血液形成，从而可能会导致白血病。这项研究的成果 7 月 3 日发表在 *Cell Stem Cell* 杂志上。该研究指出了一条可能的治疗血液病的新策略，进一步阐明了炎症和癌症之间的关系。骨髓中包含造血过程产生的白血球和红血球，而骨髓同时也为造血细胞提供了支持系统（被称作造血微环境）。最新的研究提示了造血微环境在一系列潜在致命疾病（被称作骨髓增

生性疾病）的进程中起到的重要作用。实际上，多年来人们已经知道炎症和癌症之间的联系。例如，已知骨髓中的高水平炎症和骨髓增生性疾病的发展相关，而骨髓增生性疾病会因为产生过多的髓细胞（这些细胞正常情况下用来抵御感染）导致严重的疾病。这些疾病给患者带来心脏病发作和中风的危险，并常发展为急性白血病和骨髓衰竭。而目前这些研究缺乏基因模型，特别是对于血液相关的恶性肿瘤，尚没有有效的疗法治疗大部分骨髓增生性疾病。

此次研究针对在血细胞产生的过程中起到重要作用的 *Notch* 分子发生异常而导致表达水平降低的现象，研究人员使用基因修饰的小鼠发现，造血微环境中如果缺失 *Notch* 会引发一连串分子事件，结果产生一连串的炎症因子。研究人员阻断了这个生化级联反应链中的一个分子的活动后，小鼠上的骨髓增生性疾病发生了逆转。此外，人类骨髓增生性疾病患者体内该分子的水平也有明显提高。这些发现提示，针对这个免疫反应过程中的不同关键点来开发药物可能是个有潜力的治疗骨髓增生性疾病的策略。*Carlesso* 表示此次研究的另一关键发现是，引起炎症反应的分子链并不直接发生在骨髓造血细胞中，而是存在于构成骨髓微环境的细胞中，特别是在内皮细胞中。

这项工作提示人们不仅需要靶向肿瘤细胞，还应当靶向环绕肿瘤细胞的炎症微环境中的细胞。研究人员相信该策略会在阻止骨髓增生性疾病的进展和急性白血病转移中展现疗效。*Carlesso* 博士还指出 *Notch* 分子大多被称为原癌基因，因此过去的研究往往都是靶向 *Notch* 基因治疗。该研究提示医生们需要意识到降低 *Notch* 功能水平能够抑制血液病发展进程。

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