上海科技大学在 Cell 杂志发表癌症相关新成果

ShanghaiTech University Has Published the New Results Related to Cancer in Cell

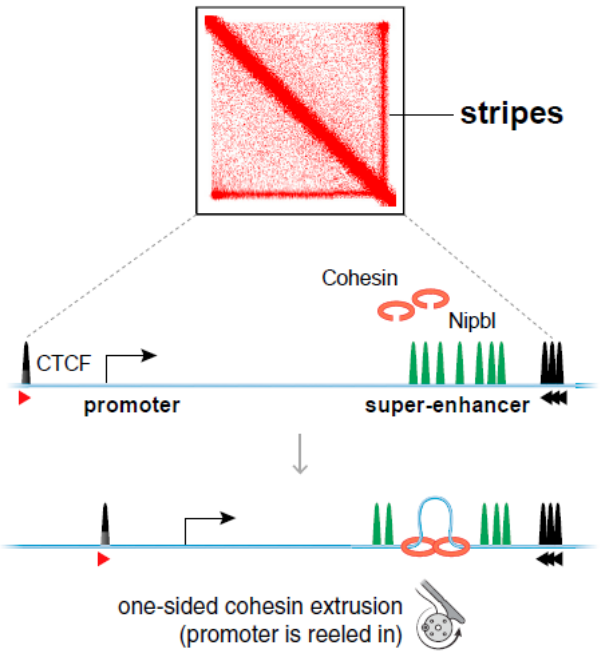
Erez Lieberman Aiden

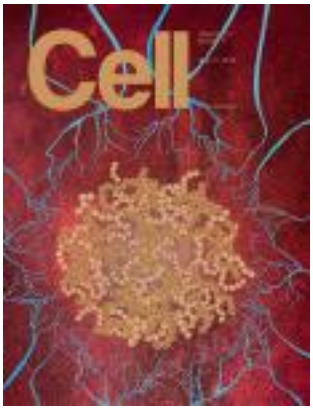
【Cell 系列】2018 年 5 月 17 日，发表在 Cell 杂志上题为“The Energetics and Physiological Impact of Cohesin Extrusion”的论文中，上海科技大学 Erez Lieberman Aiden 等人发表了与癌症相关的研究成果。

黏连蛋白挤压（Cohesin extrusion）被认为在建立哺乳动物基因组结构中起着核心作用。然而，这类挤压先前一直没有在体内被观察到过，因此，它的功能影响和能量学一直是未知的。在这项研究中，利用 ultra-deep Hi-C（High-throughput chromosome conformation capture，一种高通量染色质构象捕获技术），科学家们证实，环状域（loop domains）是通过一个需要黏连蛋白 ATPases 的过程形成的。然而，一旦形成，环和隔间（loops and compartments）能够在没有能量输入的情况下被维持数小时。值得注意的是，在没有 ATP 的情况下，研究人员观察到了数百个独立于 CTCF 的环（CTCF-independent loops，连接着调节 DNA）的出现。

研究中，Erez Lieberman Aiden 等还鉴定出了结构“条纹”（architectural “stripes”）。Stripes 通常将超级增强子（super-enhancers）拴在同源启动子上。在 B 细胞中，Stripes 会促进 Igh 转录和重组。Stripe 锚点（Stripe anchors）还是拓扑异构酶介导的病变（topoisomerase-mediated lesions，可促进染色体易位和癌症）的主要热点（hotspots）。而在浆细胞瘤中，stripes 能够解除对 Igh 易位癌基因（Igh-translocated oncogenes）的控制。

总结来说，作者们认为，高等生物已经选择了黏连蛋白挤压来增强转录和重组，这对肿瘤的发展有一定的意义。





The Energetics and Physiological Impact of Cohesin Extrusion
黏连蛋白挤压的的能量学和生理影响

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Cohesin extrusion is thought to play a central role in establishing the architecture of mammalian genomes. However, extrusion has not been visualized in vivo, and thus, its functional impact and energetics are unknown. Using ultra-deep Hi-C, we show that loop domains form by a process that requires cohesin ATPases. Once formed, however, loops and compartments are maintained for hours without energy input. Strikingly, without ATP, we observe the emergence of hundreds of CTCF-independent loops that link regulatory DNA. We also identify architectural “stripes,” where a loop anchor interacts with entire domains at high frequency. Stripes often tether super-enhancers to cognate promoters, and in B cells, they facilitate Igh transcription and recombination. Stripe anchors represent major hotspots for topoisomerase-mediated lesions, which promote chromosomal translocations and cancer. In plasmacytomas, stripes can deregulate Igh-translocated oncogenes. We propose that higher organisms have coopted cohesin extrusion to enhance transcription and recombination, with implications for tumor development.