New Method Developed to Study MeCP2 Function in Humans

研究人类 MeCP2 蛋白功能的新方法

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We wanted to share with the RSRT community a little about a new method we're using to gain a better understanding of how the MECP2 protein functions. Our expectation is that this research, which is funded by RSRT and the NIH, will help guide approaches to therapeutics that will hopefully change the lives of all who struggle with Rett Syndrome. We hope our words here reflect our enthusiasm for the work we do, and the gratitude we have to RSRT and all its supporters.
我们想和 RSRT 社区分享一些有关我们正在使用的一种能用来更多的理解 MeCP2 蛋白质功能的新方法的信息。我们期望这项由 RSRT 和 NIH 资助的研究能够引导与助力于一些有希望的治疗方法的研发，从而能改变所有在与 Rett 综合症作斗争的人的生活。我们希望这些文字能够反映出我们对这项工作的热情，以及我们对 RSRT 及其所有支持者的感激之情。

Over the nearly 30 years since Dr. Adrian Bird's laboratory discovered MeCP2, researchers have learned a great deal about how this protein works. These discoveries have largely relied on genetically engineered mice and cultured cells because it has not been feasible to directly study MeCP2 function in humans. One of the main reasons that studying MeCP2 in humans has been difficult is because girls with Rett Syndrome have a mixture of cells that express either mutant or normal MeCP2 within their brain, and there has not been a way to easily distinguish between them. In our recent *Nature Neuroscience paper*, we developed a new approach to overcome this challenge, enabling the direct study of MeCP2 function in autopsy brain tissue from individuals with Rett Syndrome.
自从 Adrian Bird 博士的实验室发现了 MeCP2 蛋白质，在之后约 30 年的时间里研究人员已经对这种蛋白质的工作原理了解了很多。这些发现在很大程度上依赖于基因工程小鼠和培养的细胞，因为直接研究人类的 MeCP2 功能在技术上还不可行。之所以在人类身上研究 MeCP2 很困难，其中一个主要原因是在 Rett 女性患者的大脑里，表达突变型或正常型的 MeCP2 蛋白质的脑细胞是混合在一起的，而且一直没有办法能方便地将这两种细胞区分开来。在我们最近在 *Nature Neuroscience* 杂志发表的论文中，我们研发了一种能克服这种困难的新方法，使我们能够直接研究 MeCP2 在一位 Rett 综合症患者的尸体中解剖出的脑组织中的作用。

Our new approach for studying gene expression abnormalities in Rett leverages advances in single-cell sequencing technology to determine which cells express mutant or normal MeCP2. We then compared mutant and normal cells within the same brain tissue from donors who had Rett Syndrome caused by R255X mutations in MeCP2. We observed that genes that contained high levels of DNA methylation and were very long were significantly upregulated when MeCP2 is mutated, an effect that has also been observed in cell lines and mouse models. This conserved molecular signature of Rett Syndrome gives us clues about how MeCP2 functions and ways we might be able to overcome its mutation in human neurons.
我们用来研究 Rett 患者体内基因表达异常的新方法依托了单细胞测序技术的发展，这可以用来确定哪些细胞表达突变型，而哪些细胞表达正常型的 MeCP2 蛋白。然后，我们对一位 Rett 综合症患者的脑组织进行研究，这位捐赠者的 MeCP2 基因突变位点是 R255X。我们对比了这位患者脑组织中的突变细胞和正常细胞。我们观察到，

当 MeCP2 有突变时，那些非常长且有高水平 DNA 甲基化的基因的表达会显著上调。这种效应在细胞系和小鼠模型中也同样观察到了。Rett 综合症患者体内这种保守的分子特征给我们提供了 MeCP2 如何发挥作用的线索，这也同时暗示了我们如何在人类神经细胞中克服 MeCP2 突变影响的方法。

By studying brain cells individually rather than mixing them together as we used to do prior to single-cell sequencing, we observed that MeCP2 mutations lead to the misregulation of different gene programs in different types of neurons within the same individual. We still do not know, however, which of these genes are directly controlled by MeCP2 and which are changed because of adaptations many steps removed from MeCP2's direct function. Because gene expression changes in MeCP2-mutant cells are different in each cell type, our best chances to reverse Rett Syndrome outside of gene therapy may be to focus on MeCP2's most direct function, which is likely to be shared across all cell types, rather than the numerous and variable secondary consequences of MeCP2 mutations. Ongoing studies in the lab are focused on better understanding these direct mechanisms of MeCP2 that are common across cell types in hopes of guiding novel therapeutic design.
通过研究单个的脑细胞，而不是像有单细胞测序技术之前那样将所有脑细胞混合在一起研究，我们观察到 MeCP2 突变会导致同一个体不同类型神经细胞中不同基因功能的失调。不过，我们仍然不知道这些基因中哪些是由 MeCP2 直接控制的，哪些是由于 MeCP2 直接控制的功能缺少后又经过许多步骤后影响的。因为不同类型的细胞中因 MeCP2 突变导致的各种基因表达的变化也是不同的，所以除了基因疗法，逆转 Rett 综合症的最好机会就是集中注意力到 MeCP2 最直接的，几乎影响到所有细胞类型的功能上，而不是去考虑那些由 MeCP2 突变导致的数量繁多的各种间接影响。当前实验室正在进行的研究正是集中在更好地理解 MeCP2 在不同细胞类型中普遍存在的这些直接作用机制，以期能对新型治疗方法的研发提供思路。

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