What's Making MeCP2 Toxic in Duplication Syndrome?

是什么导致 MECP2 重复综合征中 MeCP2 蛋白质的毒性？

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I'm a post-doc in the lab of Adrian Bird. The lab has historically studied MeCP2 in the context of Rett Syndrome – but now we are using everything we've discovered about MeCP2 to also better understand its role in MECP2 Duplication Syndrome (MDS).

我是 Adrian Bird 实验室中的一位博士后。我们实验室过去一直基于雷特综合征的背景研究 MeCP2 蛋白质，但现最近我们开始利用我们已发现的关于 MeCP2 蛋白的一切知识来更好地了解它在 MECP2 重复综合征(MECP2 Duplication Syndrme，MDS)中的作用。

Professor Bird discovered MeCP2 in the early 1990s. Since then we have learned a lot about what it does, how it works, and which parts of it are important. We know that in neurons, MeCP2 is very abundant. We also know that it is very important to have the right amount of MeCP2. Too little of it causes Rett Syndrome, and too much of it causes MeCP2 Duplication Syndrome (MDS)。

Bird 教授在 20 世纪 90 年代早期发现了 MeCP2。从那以后，我们已经学到了很多东西，关于它是干什么的，它是如何工作的，以及它的哪些部分是重要的。我们知道在神经元中，MeCP2 蛋白质的表达量是非常丰富的。我们还知道，MeCP2 蛋白保持在一个适当的数量是非常重要的。过少会导致雷特综合征，过多会导致 MECP2 重复综合征(MDS)。

Our lab wanted to know if the problems caused by too much MeCP2 are simply a consequence of too much protein in neurons or if there were specific regions within MeCP2 which are important for MDS. We have recently published this work.

我们实验室想知道，过多的 MeCP2 导致的问题是否仅仅是因为神经元中这种蛋白质过多的结果，还是 MeCP2 中存在对某个对 MDS 非常重要的特定区域。最近我们也发表了这项研究成果。

In order to learn more about MeCP2's role in MDS we developed a series of mouse models. The models were based on one originally developed in the Jaenisch lab. In these mice, an extra copy of MECP2 is added into a gene called Tau – so you can have up to three MECP2 copies in the mouse; one from its normal location, and one or two from the Tau locus.

为了能更好的了解 MeCP2 在 MDS 中的角色， 我们基于最初由 Jaenisch 实验室开发的一个模型进一步开发了一系列小鼠模型。在这些小鼠中，一个额外的 MECP2 基因拷贝被插入到一个名为 Tau 的基因中，因此在小鼠中可以有最多 3 个 MECP2 拷贝：一个来自它的正常位置，另有一个或两个来自 Tau 所在的基因位点。

The experiments showed that mice which had two Tau-MeCP2 genes and the normal MeCP2 protein were very sick – clearly demonstrating that too much MeCP2 had a detrimental effect.

实验表明，有两个 Tau-MeCP2 转基因和一个正常基因表达 MeCP2 蛋白质的小鼠有非常严重的病情，这清楚地表明过量的 MeCP2 蛋白质会产生有害的影响。

We then inserted mutations into the Tau-MeCP2 gene – mutations which frequently occur in Rett Syndrome patients and which deactivate one of two critical regions of MeCP2: the NID (NCoR Interaction Domain) or the MBD (methyl-CpG-binding domain).

然后我们将一些突变插入到 Tau-MeCP2 转基因中，这些突变是雷特综合征患者中经常发生的基因突变，它们导致 MeCP2 蛋白的两个关键区域——NID (NCoR 相互作用域)和 MBD(甲基化 CpG 结合域)——中的一个的失活。

We started by inserting a mutation that inactivates the NID, Tau-MeCP2-R306C. Mice which don't have any normal MeCP2, but only have Tau-MeCP2-R306C developed Rett like symptoms, similar to knock-in mouse models of MeCP2-R306C.

我们首先插入一种导致 NID 失活的突变，Tau-MeCP2-R306C。那些没有正常 MeCP2，只有 Tau-MeCP2-R306C 突变基因的小鼠呈现出类似 Rett 的症状，这和 MeCP2-R306C 的敲入小鼠模型表现的类似。

We then analysed mice which had normal MeCP2, plus 2 copies of Tau-MeCP2-R306C. Interestingly the mice were pretty normal. This clearly showed that the problems in MDS are not just because of too much MeCP2 protein – the extra MeCP2 needs to be functional.

然后我们分析了又有正常 MeCP2，同时还有 2 份 Tau-MeCP2-R306C 突变基因拷贝的小鼠。有趣的是，这些老鼠都很正常。这清楚地表明 MDS 的问题并不仅仅是因为 MeCP2 蛋白总量过多，而是多出来的 MeCP2 蛋白质发挥了功能性的作用。

Next, we repeated the experiment with Rett mutations that destroy the MBD – R133C and T158M. Mice with normal MeCP2 and 2 copies of either Tau-MeCP2-R133C or Tau-MeCP2-T158M survived, but showed a hindlimb clasping phenotype. This suggests that having surplus MeCP2 with a mutated MBD but a functional NID causes problems.

接下来，我们重复上述的实验，这次换用另外 2 种 Rett 突变点位 R133C 和 T158M——这些突变破坏的是 MBD。我们发现具有正常 MeCP2 和 2 份 Tau-MeCP2-R133C 或 Tau-MeCP2-T158M 拷贝的小鼠都存活了下来，但呈现一种后肢相互紧扣的表型。这表明当存在多余的 MeCP2 蛋白质，且蛋白质的 MBD 存在突变而 NID 功能正常的话，就会引起问题。

This series of experiments demonstrate that the NID is the key part of MeCP2 which mediates the toxic effect of MeCP2 in MDS.

这一系列实验证明，NID 是 MeCP2 在 MDS 中引起蛋白过量毒性的关键部分。

The NID allows MeCP2 to bind to a big protein complex called NCoR which contains a lot of different proteins, including one called HDAC3. We hypothesized that perhaps MDS is the result of too much MeCP2 recruiting too much HDAC3 – so if we could reduce the activity of HDAC3, this should counteract having too much MeCP2.

NID 允许 MeCP2 与一种名为 NCoR 的包含许多不同蛋白质的复合物相结合，这种复合物中包括一种名为 HDAC3 的蛋白质。我们有了一种假设：MDS 有可能是由过多的 MeCP2 结合了过多的 HDAC3 引起的——因此如果我们能够降低 HDAC3 的活性，就应该可以抵消 MeCP2 蛋白过量的影响。

We therefore crossed our Tau-MeCP2 mice with mice from the Lazar lab, which have reduced HDAC3 activity. Against our prediction, this did not rescue the lethal phenotype observed for Tau-MeCP2. This showed us, that HDAC3 is not the crucial NCoR component.

我们随即将 Tau-MeCP2 小鼠与 Lazar 实验室中具有降低的 HDAC3 活性的小鼠杂交。与我们的预测相反，这并没有拯救其后代 Tau-MeCP2 基因型的小鼠，其表型仍是致命的。这表明，HDAC3 并不是 NCoR 蛋白复合体中的关键组分。

Future work will focus on other NCoR components, and their potential roles in MDS. Identifying the part of NCoR which mediates the toxicity could lead to the development of drugs specifically reducing the function of this component – and by that hopefully help in treating MeCP2 Duplication patients.

我们未来的工作将关注 NCoR 蛋白复合体中其它的组分，以及它们在 MDS 中起的潜在作用。确定 NCoR 中引起毒性的组分有可能会指导那些注重于降低这些相关组分功能的药物的开发，从而有望帮助治疗 MeCP2 重复综合征患者。