PNAS COMMENTARY

Scars and PARs in a close relative

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Fig. 1. Even baboons need to pick the right mother.

When viewed through the all-encompassing lens of biology interacting with environment, we are nothing more than the cumulative luck we have been handed, with the luck of early life playing a foundational role. Was your childhood environment harsh or bountiful? Was your mother poor, did she die when you were young? Was your neighborhood crowded, did you have a younger sibling competing for attention and calories? For any observer of the primate predicament, it is clear that the consequences of bad luck early in life will echo long afterward, and for those who study the social determinants of health, the question is how. In a remarkable study on page XXX-YYY (1), Anderson and colleagues give us a glimpse into the gene regulatory consequences of early life adversity in the context of the rich social world of a close primate relative.

The study subjects were a population of wild savanna baboons in the grasslands of Kenya's Amboseli National Park. Baboons, living in groups of 50 to 100 individuals, spend their lives in a highly stratified society filled with aggression and competition, as well as cooperation and affiliation. This particular population has been observed continuously for more than 50 y, an unprecedented study pioneered by Jeanne and Stuart Altmann of the University of Chicago. The resulting longitudinal dataset has generated detailed behavioral, health, and reproductive histories for more than 250 individuals, supplemented with intermittent blood sampling (2). This has allowed the authors to generate enormously interesting findings, such as that being a low-, rather than high-ranking female trims about

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10 y off of an ~18-y life expectancy (3), and that the offspring of females whose own childhoods were filled with adversity have a lower survival rate (4; Fig. 1).

In the current study, the authors examine the epigenetic consequences of early life adversity for these adult baboons. A textbook epigenetic mechanism is methylation, the addition of a methyl group at cytosine/guanine dimers in DNA (i.e., CpG sites); classically, methylation of CpG sites in a regulatory stretch of DNA causes long-lasting silencing of the downstream gene. Patterns of methylation at 450,000+ CpG sites in the baboon genome were examined in blood samples, in order to determine whether early life adversity produces a distinct methylation signature in adults. Adversity came in two categories: the first concerned environmental stressors in the form of a baboon having experienced a drought in childhood and whether they were born into an ecologically low-quality habitat (with the contrast with a high-quality one arising from one population of baboons having shifted their home territory due to declining habitat quality). The second types of childhood adversity were social, namely having had a low-ranking mother, a younger sibling close in age, losing a mother to death, or living in a particularly large group. It should be noted that "environmental" stressors and "social" ones are highly intertwined (for example, the nutritional disadvantages of having a low-ranking mother are more severe during a drought than during a time of plenty).

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As the main finding, early life adversity produced a discernable signature of DNA methylation in baboons as much as a quarter century after their childhoods. A demonstration in a wild primate that the subtleties of early experience are embedded in the adult epigenome is an extraordinary example of coupling the molecular approaches of the laboratory with the best of observational field primatology.

This, of course, immediately raises the question of whether all these versions of early life adversity produced a methylation signature and, if so, the same one; this was not the case. With each source of adversity considered individually, only being born into a low-quality habitat significantly predicted increased incidences of methylation, in this case at more than 3,000 CpG sites. That the overall ecological quality of a wild primate's childhood neighborhood leaves the most persistent epigenetic trace in adulthood is not unexpected; nonetheless, does this mean that other forms of adversity leave no epigenetic signature? This is highly unlikely, given that there are additional mechanisms of epigenetic change (e.g., chromatin modification); moreover, because only blood samples could be taken when animals were briefly anesthetized, methylation could only be studied in peripheral blood mononuclear cells (PBMCs). For those of us with a fondness for neuroscience, it would not be surprising if massively interesting methylation changes in response to adversity also occurred in the brain in a region-specific manner.

That habitat quality, but not the other sources of adversity, caused PBMC methylation changes makes the key point that different early life stressors produce different adult outcomes. This is well established in other domains where, for example, different types of prenatal stressors program the hypothalamic–pituitary–adrenal stress axis in different ways (5, 6) and carry different risks for adult psychopathology and metabolic disorders (7, 8); similarly, natural versus human-made disasters have different outcomes on Post Traumatic Stress Disorder (PTSD) risk (9, 10). This seemingly runs counter to the usual treatment of Adverse Childhood Experience (ACE) scores (11), where the ten different categories of stressors are treated as fungible and additive in generating a single cumulative adversity score (and where higher scores predict increased risks of antisocial behavior, mood disorders, and substance abuse in adulthood). However, collapsing the array of types of adversity into a single ACE score is more about public policy expediency than viewing, say, the childhood experience of physical abused versus parental divorce as being qualitatively equivalent (12, 13).

The authors then analyzed their data in more detail and revealed what is probably their most important finding. As noted, none of the single childhood adversities of loss of mother to death, large group size, low maternal rank, or a closely aged younger sibling was significantly predictive of adult methylation patterns. However, all of these were when considering the subset of baboons born into a low-quality habitat; seemingly, the latter induces a constitutive vulnerability of decreased resiliency to subsequent adversity. This is reminiscent of classic diathesis/stress models in psychiatry where, for example, a perinatal challenge such as hypoxia sensitizes the brain to subsequent stressors in explaining the emergence of schizophrenia (14, 15). For a baboon, as for a human, multiple types of bad luck early in life synergize in their impact.

This raises a crucial question—Do these methylation signatures actually have functional consequences? While CpG methylation sites are widely dispersed throughout the genome, the basic picture of methylation having epigenetic influences revolves around methylation that occurs in gene regulatory regions; reflecting this, such regions are disproportionately rich in CpG sites (i.e., "CpG islands"). As a key finding, CpG sites that were preferentially methylated in baboons with adverse childhoods were disproportionately clustered in CpG islands and in downstream genes themselves (versus the vast majority of DNA that does not have either of these roles); this strongly suggests functional relevance. Strengthening this further, the authors established a baboon-specific reporter assay and showed that a significant subset of these adversity-dependent clusters of methylation were in stretches of DNA with gene regulatory activity that was dependent on methylation state. In other words, the methylation signature laid down in childhood most probably means something important in the lives of these adult baboons.

But what? Here is where one must consider a crucial dichotomy in thinking about early life adversity. One school of thought frames the consequences in terms of pathology, where early life threat and trauma can give rise to, say, a crippling anxiety disorder in adulthood. This anchors the long-term consequences of stress squarely in a medical

model. In contrast, the consequences of early life adversity can be viewed as "preparative adaptive responses" (PARs). With this thinking, threat and trauma early in life predict more of the same in adulthood such that enhanced vigilance and a lowered threshold for perceiving threat in adulthood will prove beneficial.

Whether early life adversity sets one up for disease or enhanced adaptation depends on at least two factors. First is how long lasting the epigenetic changes persist. In early periods of epigenome research, an epigenetic change was viewed as inevitably life-long and even potentially multigenerational through non-Mendelian inheritance of traits. Only more recently has it been appreciated that some epigenetic markers are reversible (for example, via demethylation) (16). In accord with that, the authors saw that in sampling baboons ranging in age from 2 to 26 y, the methylation signature of a low-quality childhood habitat lessened over time; as such, adult experience can overwrite that of childhood. For these long-lived primates, early life is not methylation destiny set in stone.

As a second related factor, determining if an early life response to adversity will prove beneficial or maladaptive depends on the likelihood of similar adversity occurring in adulthood—is the childhood adversity an anomaly or an accurate harbinger of things to come? Framed that way, the pathology of the famed Dutch Hunger Winter phenomenon reflects inaccuracy. In this classic example, individuals who were starved as fetuses (during the winter of 1944 when the Nazis produced a famine by diverting food from Holland) underwent epigenetic changes throughout the body that produced a life-long "thrifty metabolism" that was highly efficient at extracting and storing calories from food. In this instance, the metabolic shift did not constitute a PAR, in that once the Nazi blockade was lifted after Holland's liberation, people resumed their lifetime of a bountiful Westernized diet. The result of this mismatch was a greatly increased risk in adulthood of metabolic disorders such as type II diabetes (17).

Thus, do the long-lasting methylation changes in these baboons' genomes represent pathologic scars or beneficial PARs? While the authors have already demonstrated one example of early life adversity constituting the former in these baboons (18), they are now poised to be able to examine which genes are epigenetically embedded by adversity; this will produce a goldmine of crucial information about a close primate relative living in its natural habitat. As such, the excellence of this current study is matched by the excitement of future insights likely to come.

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