How Moms Program Their Offspring to Fight Disease

Preview for "Burton *et al*. Cysteine synthases CYSL-1 and CYSL-2 mediate C. elegans heritable adaptation to P. vranovensis infection. Nat Commun. 2020 Apr 8;11(1):1741. doi: 10.1038/s41467-020-15555-8."

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Whether environment-driven transgenerational responses exist in humans has long been a hot topic for debate. However, since it is hard to acquire the relevant data for population studies, the answer is still in the air. Several cohort studies have spun out from the Dutch famine of 1944-1945, including ones examining the transgenerational effect of starvation. Veenendaal et al reported that the adult offspring of prenatally exposed fathers have higher weights and BMIs, while the adult offspring of prenatally exposed mothers show no increase in weights or BMIs[1]. Furthermore, Lumey et al discovered that there is a moderate (50-100g) change in offspring birth weight for prenatally exposed mothers, but it's considered inconclusive due to the small sample size and big variation[2]. Nevertheless, other studies that also examined the cohort subjected to the Dutch famine indicated no transgenerational effect on offspring birth weight[3,4]. While it's still not quite conclusive in humans, adaptations to environmental stress by transgenerational response have been observed in many other species. Dantzer et al discovered that population density is associated with an increase in adaptive offspring growth in free-ranging red squirrels[5]. In *C. elegans*, temperature induced expression change of *daf-21* (Hsp90) can last for 14 generations via altered trimethylation of histone H3 lysine 9 (H3K9me3)[6]. Additionally, pathogenic avoidance to *P. aeruginosa* can be learned and passed down to the next few generations via epigenetic change in *C. elegans*[7]. While most transgenerational responses are transmitted through epigenetic alteration, the authors of this study revealed a novel non-epigenetic related pathway in *C. elegans* driving heritable adaptation to *P. vranovensis* infection[8].

In this paper, *Burton et al* describe a pathway in which parental exposure to a pathogen modulates embryonic gene expression, conferring immunity to the offspring. The authors identified a novel *C. elegans* pathogen, *Pseudomonas vranovensis,* which induces a pathogen-specific, heritable immune response. Surprisingly, this response was not mediated by known mechanisms of intergenerational inheritance, such as small RNA pathways, histone modification, or DNA methylation. Through an as-yet unknown mechanism, parental pathogen exposure activates the stress response transcription factor SKN-1 and induces expression of the detoxification genes *cysl-1* and *cysl-2* during embryogenesis*.* Each of these factors is required for offspring survival in the presence of *P. vranovensis.*

In order to establish an adaptive pathogen response model, the authors began by screening a panel of bacterial pathogens for the ability to induce immunological priming in *C. elegans.* They found that embryos exposed to *Pseudomonas vranovensis* exhibited enhanced survival if the parent had also been exposed to the same pathogen. This effect typically only persisted for one generation, although mild transgenerational effects could be seen after three consecutive

generations of pathogen exposure. Heritable adaptation to *P. vranovensis* appears to be mediated by a novel mechanism, as it was still observed in a number of *C. elegans* mutants defective for epigenetic modifications.

The authors next performed RNA-seq to investigate how parental exposure to *P. vranovensis* affects embryonic gene expression. By comparing these data with published gene expression profiles of *C. elegans* mutants, they determined that many of the observed transcriptional changes could be explained by increased activity of the stress response transcription factor SKN-1. Indeed, *skn-1* mutants exhibited reduced heritable adaptation to *P. vranovensis.* Both indirect genetic activation of SKN-1 and parental pathogen exposure induce expression of *cysl-1* and *cysl-2,* among other genes. These two genes encode cysteine synthases that have previously been implicated in breaking down bacterial toxins. Accordingly, *C. elegans* mutants lacking either CYSL-1, CYSL-2, or their upstream activator RHY-1 are unable to adapt to pathogen exposure. Together, these data support a model in which parental exposure to *P. vranovensis* activates embryonic SKN-1 transcription factor activity, leading to the expression of pathogen-response genes including *cysl-1* and *cysl-2*.

Burton *et al*. established a transgenerational pathogen response model that consecutive exposure of pathogenic bacteria *Pseudomonas vranovensis* across generations can promote the survival of the host nematode offspring. This protective mechanism is novel, involving the cysteine synthases *cysl-1* and *cysl-2* and the regulator of hypoxia inducible factor *rhy-1*. As most of the transgenerational effects in C elegans rely on microRNA or epigenetic modification, this work may provide new opportunities for future investigation of adaptive immunity as well as intergenerational genetic inheritance. There are several unanswered but important question following this work:

1. The mechanism of *Pseudomonas vranovensis* toxicity
   The protective effect of the primed pathogen exposure is strikingly impressive, with 1~5% survival rate for descendants of parents fed normal diets and 40~75% for those adapted to *P. vranovensis*. A priority for future research is to identify the source of toxicity in this soil bacteria. The authors suggested hydrogen cyanide as a potential *P. vranovensis-derived toxin*, yet this hypothesis is unlikely given the super-sensitivity of previously reported cyanide-resistant *rhy-1* mutants to *P. vranovensis*. The authors might perform metabolomic analysis on P. *vranovensis* to identify potential toxic metabolites*. They might also examine the P. vranovensis genome for cyanide synthase genes or biosynthetic gene clusters and determine whether any of these are sufficient to induce a similar response when heterologously expressed in E. coli.*

2. Molecular pathway of the transgenerational adaptive response
   Although the authors have identified three key factors during this process, it is far from clear how the worm senses bacteriaand induces transcriptional responses featuring *cysl-1* and *cysl-2*. It should not be difficult to examine the role of major pathways, especially those important in stress response(daf-2, daf-16), oxidative stress(skn-1, mek-1, pmk-1 which is tested in the paper) and folding stress. Understanding how this epigenetic information is transduced through generations in the germline is necessary for full mechanistic understanding.

3. The evolutionary significance

It is unclear how the phenomenon described in this paper would translate to an ecologically relevant setting with more diverse microbial species. Can diluted *P. vranovensis also* trigger the response at prolonged exposure? Does this adaptive response apply to other pathological bacteria? How long can this protective “memory” last? Answering these questions will add value to this worm specific observation, providing novel understanding of the origin of adaptive immunity, and even yielding new pest control drug targets.

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