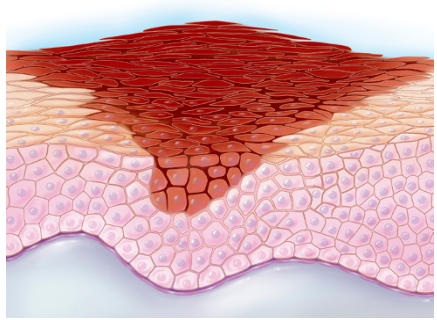
Illuminating melanoma at the molecular level

The early detection of a cancer can be crucial for its successful treatment. In the case of melanoma, the stage at diagnosis can mean the difference between simple, minimally invasive excision, and more intensive treatment involving radiation and/or chemotherapy. According to the American Cancer Society, 5-year survival rates for melanoma exceed 90% if intervention occurs at the earliest stages, but can drop as low as 15% if it has grown untreated and metastasized to other tissues.

Approximately 80% of human moles carry a mutation to the *Braf* gene. This gene encodes a protein involved in signaling pathways for normal cell proliferation and differentiation during embryonic development, but is also classified as an oncogene for its potential to induce tumor growth when mutated. Despite the frequency of *Braf* mutations in moles, very few become cancerous. What drives those that do?

Charles Kaufman and his colleagues are illuminating the processes behind melanoma initiation and development using a zebrafish melanoma model (*Science* **351**, 6272; 2016). Melanoma originates from melanocytes, pigmentation cells derived from embryonic neural crest cells. The study visualized early melanoma in zebrafish carrying a *Braf* mutation by attaching a fluorescent protein to the gene *crestin*, found in embryonic neural crest progenitors and in adult melanoma. Their technique allowed the researchers to detect the expression of *crestin* before tumors became visible on the scales of the fish. All thirty cells observed with fluorescent *crestin* developed into melanoma over the course of the study.

The team continued their research with an investigation of potential melanoma regulators. They manipulated the expression of *sox10*, a gene involved in regulating *crestin* during embryonic development that has also been documented in melanoma. By increasing the expression of *sox10*, they found that melanoma development accelerated, while inactivating the gene with CRISPR/Cas9 slowed the onset of tumors. These results support their conclusion that the reemergence of neural crest progenitors is closely involved with triggering



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malignancy and suggest that disease development could potentially be influenced by modifying regulatory genes.

Kaufman and his team's fluorescent zebrafish model enabled them to visualize melanoma before the appearance of visible tumors and follow its progression from a single cell, providing evidence that neural crest progenitor reemergence is an important element involved in initiating malignancy in otherwise benign moles containing *Braf* gene mutations. The model and results should be valuable in future efforts to discern suspicious moles at the earliest stages.

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THE TRANSGENERATIONAL IMPACTS OF HYPOXIA

There is growing evidence that an organism's environment can have profound impacts on the expression of its genes, without necessarily altering its underlying genetic code. These 'epigenetic' changes can be passed down from generation to generation. Environmental factors that can lead to epigenetic modifications include external substances, such as toxins or pollutants, as well as exposure to sources of stress. One such increasingly common environmental stressor is hypoxia. Hypoxia refers to a condition found in aquatic ecosystems where dissolved oxygen in the water is depleted to detrimental concentrations; it can occur naturally, but pollution exacerbates the condition and has expanded its prevalence, particularly in estuaries and coastal ecosystems. Although variable in scale, duration, and severity, hypoxic events are problematic throughout the globe. The impacts to individuals that are directly exposed to hypoxia have been frequently studied in numerous species, but it was previously unknown if those effects were inheritable and could continue to impair future generations. Simon Wang and his colleagues in Hong Kong explored the transgenerational effects of hypoxia in a recently published study (*Nat. Commun.* **7**, 12114; 2016).

The research team tracked reproductive impairments across three generations of male marine medaka fish (*Oryzias melastigma*) in three treatments: a normoxic group, in which all fish had sufficiently oxygenated, or normoxic, water; a hypoxic group chronically exposed to low dissolved oxygen; and a transgenerational group where the parent experienced hypoxia but subsequent generations were raised in normoxic water after they were spawned. Compared to the normoxic control generations, both the hypoxic and transgenerational fish displayed decreased sperm motility, lowered sperm production, and reduced fertilization success. Underlying those impairments were changes in DNA methylation—an epigenetic mechanism capable of modifying gene expression—to genes involved in spermatogenesis. Importantly, the observed changes in the transgenerational treatment offspring, which were never directly exposed to hypoxia, provides evidence that deleterious modifications induced by hypoxia in an individual can be inherited by its offspring.

Wang's study is the first to establish that low dissolved oxygen can adversely impact the reproductive potential of subsequent generations in addition to the individual directly exposed, suggesting that environmental managers and regulatory bodies may need to consider longer-term costs when evaluating the harm caused by aquatic hypoxia. It also raises questions about whether hypoxia in other species, including humans, can lead to transgenerational consequences.

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