

Health & Physiology

What happens to our genes in the twilight of death?

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Death -- the ultimate end of everyone's journey. What is there to study? Is anything interesting happening? Aside from religious and philosophical discourses, valuable knowledge might be obtained from tangible physical facts. Consider an analogy: a disaster happens in a chemical plant that results in its halt and potential destruction. A chemical plant is a complex chain of reactors linked together by a multitude of control networks that normally determine its functionality. Most disaster-like processes involve a sequence of events that occurs due to the availability of residual energy and materials. Understanding this process helps us determine whether it may be stopped and reverted. It might even provide information on what parts are salvageable. Similar to a disaster at a chemical plant, our study investigated gene expression in postmortem animals in order to project our findings to adult humans that have suddenly died.

Humans are complex creatures capable of elaborate functions, such as the ability to talk, walk, and monitor the environment -- all at the same time. This capacity is due to the coordinated "turning-on" and "turning-off" of thousands of genes at the right time, in the right place, and in the right amount (1). The genes that are "turned-on" (*i.e.*, activated) produce messages (transcripts) that ultimately enable elaborate functions. There is a lack of information about these processes in death, such as when a person suddenly dies from a massive heart attack or severe brain injury. Several studies have investigated the effects of cell death on gene expression; however, the study of gene expression in death has received

little to no attention so far.

We extracted gene transcripts (*i.e.* messages from genes which are "turned-on") from dead zebrafish and the livers and brains of dead mice that were incubated for times spanning from life to 48-96 h postmortem. At each time sample, the abundances of gene transcripts were precisely determined by using a technique called "[Gene Meter](#)" (2,3). A gene was identified as being activated (*i.e.*, "turned-on") when its transcripts were more abundant in the dead tissue than in flash-frozen, *i.e.*, "live" tissue. We determined the functions of the activated genes by surveying the literature and they were characterized into major categories, ranging from genes involved in embryo development to those involved in detecting infection or injury.

Hundreds of genes were activated in the twilight of death -- the period of time between the cessation of elaborate functions and the death of all cells. Interestingly, the genes were activated reproducibly in several individuals. They were not all activated at the same time -- nor were they activated at random. Rather, the genes were activated sequentially, suggesting an *order* to the activation of genes in death. These findings are relevant to forensic science because the timing of the activations could be used to precisely determine the time of death (*i.e.*, postmortem interval) in suspicious crimes and natural deaths (4).

As expected, genes involved in survival and in stress response were activated in the twilight of death. Products from these genes are designed to cope with perturbations and to help restore homeostasis.

What was unexpected was that genes involved in embryo development and cancer were activated. Developmental genes, typically activated during embryonic stages, are usually silenced (for life) following those stages (7). Activation of these genes suggests that they are no longer silenced presumably because either the postmortem physiological conditions resemble those during development or simply because “the brakes are burned”. It is possible that the activation of these genes involves the unwinding of the compacted genomic DNA that in turn allows access to other genes that were previously silenced (*e.g.*, development genes). The activation of cancer-associated genes was a serendipitous finding, discovered through a survey of cancer databases. Apparently, the number of activated cancer genes increased from minutes after death to up to 24 h postmortem and then stopped. This has implications to liver transplant recipients because cancer-associated genes may be activated in the donor and transferred to the recipient, resulting in an increased risk of cancer. Apparently, patients with liver transplants have a higher incidence of cancer than control groups (5,6).

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