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Exposure to low level environmental agents: The induction of hormesis

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The biological effects and health risks of exposure to low doses of natural or man-made agents, including ionizing radiation, chemicals, drugs or pesticides, that would otherwise cause cancer and degenerative diseases at high doses, remain ambiguous and are the subject of intense debate. Human epidemiological studies would be ideal to predict such deleterious effects; however, these studies are limited due to the necessity of very large cohorts (several millions) to generate data with an acceptable level of confidence. Furthermore, epidemiological surveys examine the effects of exposures that happened several years earlier, and therefore may be biased by many variables during the intervening time until overt detrimental health effects are expressed. Although great uncertainties about a causal relationship between low dose exposure and harmful health effects exist, it is nevertheless clear that for most agents, there is little direct evidence of risk at low doses. However, to meet societal concerns, a linear no-threshold model has been advocated to predict the biological effects of low dose environmental exposures. In that model, it is assumed that harmful effects increase as a function of exposure dose, and the smallest dose has the potential to cause a small increase in risk to humans. Further, the effects of sequential exposures are presumed to be additive.

In their paper in this issue of the journal, Calabrese and colleagues have analyzed published data on the mutagenicity of over 800 chemicals, performed by three independent laboratories [1]. Their findings challenge the assumptions made in the linear-no-threshold model, and provide strong evidence that the dose/effect relation is much more complex than predicted by the linear model. Increases in dose did not simply increase the risk of mutagenic effect; in contrast, at low doses, mutagenicity was significantly lower than the spontaneous rate for a wide range of chemical agents that belong to different classes. These results add to the growing body of evidence that the molecular and biochemical changes induced by low doses of exogenous mutagenic agents differ from those induced by high doses [2,3]; the net effect being the induction of mechanisms that protect not only against the damaging effect of the agent, but also the stress induced by normal oxidative metabolism [4–6]. Such low-dose-induced stimulatory or hormetic biological effects are now widely recognized as real. They are supported by a wealth of cellular and molecular data [7]. For exposures to a wide spectrum of chemical and physical stressors, rather than conforming to a

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linear dose–response relation, effects measured *in vitro* and *in vivo* by a battery of biological endpoints reveal a J-shaped or an inverted U-shaped dose–response (reviewed in [8,9]).

Antioxidant defenses, proteases that remove oxidized proteins, repair enzymes that mend damaged DNA, drug pumps, DNA replication mechanisms designed to protect stem cells, apoptosis and immune responses that remove damaged cells– all of these mechanisms are operating constantly to minimize the mutagenic potential of the byproducts of normal oxidative metabolism [10,11]. When challenged by exogenous carcinogens, including various types of radiation and molecules that enter the body via ingestion or inhalation, distinct signaling pathways that respond to the specific stressful challenge are up-regulated in a manner that depends on the dose of the carcinogen [12]. Common and distinctive changes have been observed subsequent to the exposure of human cells to low or high doses of a series of exogenous agents. Whereas pro-apoptotic pathways may be induced at high doses, pathways that promote healthy survival are induced at low doses [13]. Often, the protective mechanisms that are up-regulated at low doses overcompensate, and result in stimulatory responses that enhance the well-being of the organism long after the exposure [14].

Central to low-dose-induced protective effects is the stability of DNA, in particular DNA in stem cells. Whereas cells are endowed with mechanisms to detoxify harmful compounds before they attack genomic DNA, they also have an array of redundant mechanisms to repair the damage when it occurs. These mechanisms are unleashed immediately or with a delay after the exposure. Frequently, inter-related mechanisms, but yet with unique function, are coordinately regulated to provide maximum protection for the cell and its DNA from damage [10]. For example, exposure of prokaryotic cells to paraquat, one of the most widely used herbicides in the world, resulted in simultaneous induction of antioxidant enzymes and DNA repair enzymes [15]. The latter mechanisms, together with cell cycle checkpoints and other protective processes, were also implicated in mitigating effects against DNA damage induced by exposures to high doses of environmental agents delivered to cultured cells or rodents that were previously pre-exposed to low doses of the same or other related stressful agents [16]. Hence, multiple lines of evidence point to various inducible adaptive responses against damage to DNA. In the case of cells exposed to sparsely ionizing radiations, such as X rays, there is also evidence that the induced protective effects may be propagated from the targeted cells to neighboring non-targeted (bystander) cells in the exposed population [17].

Besides low-dose-induced protective mechanisms, there is also strong evidence for the propagation from cells targeted with chemical agents, or densely ionizing radiations (e.g. α particles and energetic heavy ions), of signaling events that lead to oxidative stress, DNA damage, and enhanced frequency of spontaneous neoplastic transformation in bystander cells with which they had been in co-culture [18]. However, in these instances the targeted cells were subjected to relatively high doses of the stressful agent. For example, traversal of a cell by a single α particle or an energetic heavy ion results in absorbed doses of 15–100 cGy. In the center of the track of the impacting particle, the local dose may reach hundreds of Gy. In contrast, a cell traversed by a single electron track resulting from an exposure to X rays receives a small dose of 0.1 cGy [19]. Hence, as in the case of targeted effects, the nature of propagated non-targeted effects is dose-dependent, with low doses to the targeted

cells triggering the propagation of an adaptive response and high doses to the targeted cells of agents such as ionizing radiation or chemotherapeutic drugs inducing the spread of toxic effects [20,21].

With the development of sensitive methods to examine biochemical, molecular and cytogenetic changes, we are increasingly being able to quantify the effects of low doses of physical and chemical agents in cultured cells and in tissues of whole body-exposed animals. This knowledge is contributing to greater understanding of the system responses to stress, and is enhancing our knowledge of the mechanisms underlying hormetic effects such as those observed by Calabrese and colleagues. The net result is expected to be greater public awareness of the risks of low dose exposures, and the implementation of environmental regulations that adequately protect workers and the general public, and make the most effective use of economic resources.

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