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Understanding the Unusual Radiation Resistance of Insect Cells-Valuable Lessons for Stress Biology and Oncology Studies

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EDITORIAL

Insects are unarguably the most abundant, variegated and naturally talented class of organisms on earth, with an unfathomable variety of morphological and physiological features that make them the most formidable survivors on the planet. Following the biggest extinction event that seem to have occurred during Permian-Triassic transition period (nearly 252 million years ago/MYA), majority of the modern day insects are thought to have co-evolved later along with flowering plants during the Cretaceous period of Mesozoic era (<145 MYA) followed by Cenozoic era (<66 MYA), and have retained some of the highly efficient and exemplary survival skills acquired since that age.

While insects make an abundant part of our ecosystem's food chain as prey for numerous predators, these are also responsible for spreading a large number of vector-borne diseases. Insects also carry a number of unusual morphological, physiological and biochemical characteristics that are considered to be of great value for the mankind. In fact, studying insects has remained of utmost priority for the insatiable human quest for understanding nature's secrets, including the intricate mechanisms regulating eukaryotic gene expression and disease progression and pathogenesis. For decades, Drosophila has played tremendous role in our understanding of genetic mechanisms. One of the less talked yet amongst the most intriguing qualities of insects (of course besides the enormously energy-efficient and remarkably agile flying skills), is the high level of resistance these organisms display against various physical and chemical stressors including hyperthermia, ultraviolet radiation, ionizing radiation as well as chemotherapeutic drugs.

An excessive level of radiation resistance is a major characteristic of insects, especially the capacity to tolerate very high doses of ionizing (X-rays, gamma-rays) radiation. Until the early 1970's, this radiation resistance of insects was mainly attributed to an abundance of non-proliferating cells in adult insects, especially since larval and pupal stages had demonstrated relatively higher radiosensitivity. However, a number of studies were conducted by TM Koval and co-workers on cultured insect cells during 1970's and 1980's, which surprisingly proved that this radioresistance was an inherent characteristic of insect cells rather than being a systemic response of the organism. Using mostly the ovarian origin cell lines derived from insects of different orders, cells from Lepidoptera (moths and butterflies) were found to demonstrate much higher radioresistance than Diptera (flies and mosquitos) or orthoptera (cockroaches); the lepidopteran cells/insects tolerating X-ray doses up to 400Gy. It must be noted here for simple comparison that a usual daily fraction in a normal radiotherapy regime may not exceed 2Gy dose of X-rays focused on the tumour mass. Therefore, doses tolerated by whole insects or their cells are more than 100 times the radiation doses that can be tolerated by human system. What makes this even more interesting is the fact that insect cells carry numerous structural and functional homologies with human cells, including the presence of certain highly conserved canonical stress response pathways.

Studies carried out during the last 15 years, many of which are contributed from our laboratory, have revealed the existence of an intriguing set of alternate stress responses in Lepidopteran insect cells (Sf9 ovarian cells derived from Spodoptera frugiperda, the fall Armyworm). We have initially reported in 2004 that that these cells are unusually resistant to radiation-induced apoptotic cell death, despite carrying a highly conserved eukaryotic apoptotic death pathway with minor atypical features. While the post-mitochondrial apoptotic signaling is well conserved in these

cells, the mitochondrial capacity for calcium sequestration following stress induction was found to be considerably higher. This was aided by an interesting set of highly resilient responses, viz., an unusual resistance to intracellular calcium mobilization from calcium reservoirs such as endoplasmic reticulum, leading to strong attenuation of pro-apoptotic calcium spikes or waves. Further, these cells were additionally protected by an unusually silent nitric oxide synthase (NOS) response (despite the presence of NOS orthologue) at such high radiation doses that could cause significant calcium mobilization, thereby preventing the amplification and propagation of pro-death signals. This unusual intracellular attenuation of death signals observed in this higher eukaryotic system seems to act as an effective radioprotective mechanism, and has major implications for future studies in biological radiation protection. Besides this, we have recently observed that Lepidopteran cells carry an alternate p53-mediated mechanism that imparts radioprotection. It is affected through regulation of microRNA-31 overexpression by a radiation-inducible p53 response. In our effort to explore the existence of a similar mechanism in human system, we have recently come across evidences from literature that a partially analogous mechanism may be encountered in certain tumors wherein the p53 may be dysfunctional or partially inactivated. This may have important implications in designing future strategies for therapy, which are being investigated in our laboratory.

Overall, the Lepidopteran insect cells carry certain very effective alternate switches within the highly conserved canonical stress signaling pathways, with apparently important biomedical implications in the fields of stress biology and oncology. The multifold higher radioresistance compared even with the Dipteran insects (e.g., *Drosophila melanogaster*), makes Lepidopteran cells a favoured model system for radiation biology and oncology studies. Further in-depth investigations are in progress in our laboratory, with an aim to harness the extra-ordinary and untapped biomedical research potential of these unusual cells.