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Editorial: DNA Damage & Immunity

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The genetic material of all organisms is constantly exposed to a wide variety of genotoxic attacks. Cells are equipped with an arsenal of specialized but partially overlapping DNA repair systems to detect and repair a plethora of distinct chemical and structural alterations in the genetic material. Erroneous repair can lead to mutations and chromosomal rearrangements that can alter the genetic information. When tumor suppressor or oncogenes are affected, cells can transform into cancer cells. Thus, DNA damage is causal for cancer development. DNA damage can also lead to loss of cellular function when mutations alter the function of proteins, or when persistent DNA damage blocks transcription or replication. Depending on the cell type, unrepaired DNA damage can trigger constitutive activation of DNA damage checkpoints that halt proliferation transiently – or permanently during cellular senescence – or induce apoptotic demise of the affected cells. Consequently, tissue regeneration is hampered and tissues lose their integrity as DNA damage accumulates during aging. DNA damage is, therefore, a driving factor of the aging process and directly contributes to age-related diseases.

Cell-autonomous DNA damage responses have been extensively investigated since the discovery of DNA damage checkpoint genes in yeast nearly thirty years ago. The importance of such DNA damage checkpoints for preventing tumorigenesis by allowing time for DNA repair and, if necessary, removal of genomically compromised cells has been widely recognized. In recent years, studies conducted predominantly on model organisms ranging from nematodes to mice have brought to light how non-cell-autonomous DNA damage responses impact the organism far beyond the effects in individual, genomically compromised cells. The role of the innate immune system in orchestrating these types of responses is currently a rapidly developing area of research.

As described by Williams and Schumacher, in bacteria it was recognized that through the SOS response, adaptive responses to DNA damage could impact the preservation of the

species (Williams and Schumacher, 2016). Conceptually consistent, in the metazoan *Caenorhabditis elegans*, an important model organism for the community of gerontology researchers, the innate immune system responds to DNA damage in germ cells, which triggers the *DNA damage-induced systemic stress resistance* (GDISR) response that promotes elevated endurance of somatic tissues and, as a result, allows reproductive lifespan extension until genomic integrity of germ cells is restored and generation of offspring can resume. Gasser et al. provide an overview of how the immune system in mammals senses the different forms of damaged DNA, in addition to foreign DNA that cells use the immune response to defend against (Gasser et al., 2016). Notably, factors traditionally associated with DNA repair play important roles in triggering immune responses when genome integrity is compromised. The reprogramming of gene expression patterns is guided through alterations in the nuclear architecture as described by Stratigi et al. (Stratigi et al., 2016). DNA repair systems exert intriguing roles in shaping the immune defense, as outlined by Lescale and Deriano (Lescale and Deriano, 2016). In this regard, DSB induction by the RAG endonuclease reshuffles the V(D)J locus to allow the diversity of immune defenses but requires a strict control of genome integrity. Soria-Valles et al. discuss the mechanisms of immune responses to DNA damage and the role of chronic inflammation in age-related pathology and cancer development. They also outline intervention strategies aiming to counteract inflammatory tissue damage and provide insights into therapeutic concepts to enhance clearance of cancer cells by the immune system (Soria-Valles et al., 2016). The concept of systemic consequences of genome instability is further elaborated by Poliezhaieva and Ermolaeva, who point out that, while the inflammatory responses triggered by persistent DNA damage compromises tissue integrity, the regeneration and repair of tissues requires tissue remodeling that can be promoted by inflammatory cytokine secretion (Poliezhaieva and Ermolaeva, 2016).

This collection of complementary review articles provides a timely account of the emerging field of systemic DNA damage responses that play a key role in the adaptations of the aging organism to the accumulation of DNA damage. Understanding how the immune system responds to compromised cells also has important implications for the future of cancer therapy. Finally, targeting inflammatory DNA damage responses might also provide a major route for preventive therapies of age-related diseases, which have become major public health challenges due to the aging of the global population.

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