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Perspective

Interplay Between DNA Damage Response and NF-κB Signaling in Aging Cells: A Molecular Crossroad of Senescence and Inflammation

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DESCRIPTION

Aging is a complex, multifactorial process driven by the gradual accumulation of cellular damage and loss of homeostatic control. Two prominent hallmarks of aging genomic instability and chronic low-grade inflammation are orchestrated by two interconnected cellular systems: the DNA Damage Response (DDR) and the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway. Emerging evidence suggests that their interplay forms a critical molecular axis regulating cell fate decisions, including senescence, apoptosis and pro-inflammatory secretory behavior. Understanding this crosstalk has profound implications for age-related diseases, tissue degeneration and therapeutic interventions. The DDR is a highly conserved cellular mechanism that detects and repairs DNA lesions, preserving genomic integrity. In response to Double-Strand Breaks (DSBs), a cascade involving ATM (ataxia-telangiectasia mutated), ATR (ATM and Rad3-related) and DNA-PK is activated, leading to the phosphorylation of histone H2AX (γ-H2AX), cell cycle arrest and recruitment of repair complexes. However, when damage is excessive or persistent as often observed in aged or stressed cells the DDR fails to fully resolve lesions, resulting in chronic signaling that shifts the cell into a senescent state.

Senescent cells remain metabolically active but exhibit permanent growth arrest and a distinct pro-inflammatory phenotype known as the senescence-associated secretory phenotype (SASP). NF-κB is a major transcriptional driver of the SASP and its sustained activation in response to persistent DDR signaling has been identified as a key link between DNA damage and age-related inflammation. Mechanistically, ATM activation in response to DNA damage can initiate NF-κB signaling through the phosphorylation of NEMO (NF-κB essential modulator), promoting the nuclear translocation of p65/p50 NF-κB complexes. These factors bind promoter regions of pro-inflammatory genes including IL-6, IL-8 and TNF-α, initiating chronic cytokine release. While this may serve as an initial damage alarm or immune recruitment signal, long-term activation creates a pro-inflammatory environment that contributes to tissue dysfunction, stem cell exhaustion and even cancer initiation.

Interestingly, NF-κB not only responds to DDR but can also feed back to modulate DNA repair efficiency and cellular stress resistance. Chronic NF-κBactivation has been shown to repress genes involved in DNA repair, including *BRCA1* and *RAD51*, promoting further genomic instability. Conversely, under certain contexts, NF-κB can promote survival pathways, enabling damaged cells to evade apoptosis and persist in tissues a hallmark of aging known as inflammaging. This bidirectional interplay is particularly evident in age-associated diseases. In neurodegenerative disorders such as Alzheimer's disease, elevated DNA damage and persistent NF-κB activation co-exist, leading to glial cell senescence and neuroinflammation. Similarly, in atherosclerosis and osteoarthritis, the accumulation of senescent cells and their SASP products is directly linked to chronic tissue inflammation and degeneration. The dual contribution of DDR and NF-κB to these pathological processes makes them compelling targets for therapeutic intervention.

Recent research has focused on pharmacologically targeting this interplay. Agents such as senolytics, which selectively eliminate senescent cells and NF-κB inhibitors, which reduce SASP expression, are being explored in clinical trials for age-related diseases. Furthermore, molecules that enhance DNA repair or modulate ATM/NEMO signaling may suppress aberrant NF-κB activation at its source. However, caution is required, as indiscriminate suppression of DDR or NF-κB could compromise host defense and tumor surveillance. Therefore, the challenge lies in developing context-specific modulators that restore balance without disrupting protective functions. A key future direction involves mapping the temporal dynamics and cellular specificity of DDR-NF-κB interactions. Single-cell transcriptomics and proteomics are providing new tools to dissect how different cell types respond to persistent DNA damage and how this contributes to organismal aging. Additionally, understanding how lifestyle factors such as diet, exercise and environmental stress affect DDR and NF-κB signaling could help design non-pharmacological interventions to delay age-related decline.

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CONCLUSION

The interplay between DNA damage response and NF-κB signaling lies at the heart of aging biology. Together, these pathways form a molecular feedback loop that integrates genomic surveillance with inflammatory signaling, ultimately influencing cellular aging and systemic health. While DDR maintains genomic stability, its chronic activation fuels NF-κB-mediated inflammation, promoting senescence and functional decline. Targeting this axis holds transformative potential for treating age-related diseases and extending healthspan. However, successful interventions will require precision and specificity, ensuring the protective roles of DDR and NF-κB are preserved while mitigating their harmful consequences in aging tissues. As research advances, unraveling this intricate crosstalk promises to redefine our approach to aging and regenerative medicine.