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Abstract

Cellular senescence, widely recognized as a potent suppressor of tumorigenesis, represents response to cellular stress and DNA damage which results in irreversible cell growth arrest. Growing evidence signalizes crucial role of cytokine production in senescence phenomenon. Recently, many research groups have efforted to define exact character of senescence-associated secretory phenotype and its function in senescence development and maintentance. Factors secreted by senescent cells, mainly of proiflammatory character, were found to have pronounced effects on their environment as well as on its own producer. These observations were obtained preferentially on models of replicative senescence and oncogene-induced senescence.
In this study, we aimed to define character of cytokine production in senescence induced by combination of genotoxic agents bromodeoxyuridine and distamycin A. In this model, we found sustained activation of interferon signaling followed by upregulation of interferon-target genes including tumor suppressors PML, STAT1 and IRF1. Moreover, screening of more then 160 cytokines and their receptors revealed significantly elevated levels of two dozen of cytokines including pro-inflammatory species such as IL-1, IL-6 and IL-8. Our results suggest that cytokine signaling associated with drug-induced senescence represents complex and robust action which is sustained by positive feedback loops.
PML (promyelocytic leukemia) protein and PML NBs (nuclear bodies) are known to be involved in tumor suppression, cell growth arrest and induction of cellular senescence. PML NBs represent sites where activation of many regulators of cell cycle progression proceeds.
Being an interferon-stimulated gene, PML is strongly upregulated at the transcriptional level in response to interferon signaling which is usually followed by multiplication or magnification of PML NBs.
We observed upregulation of PML and multiplication of PML NBs in drug-induced and replicatively senescent cells suggesting an activation of interferon signaling in these cells. Under these conditions, upregulation of PML compartment was linked to formation of specific nucleoli-associated PML structures. PML and PML NBs were previously found to be involved in sequestering of regulatory proteins into nucleolus upon stress conditions resulting in cell growth arrest. Thus we suggest that upregulation of PML and formation of nucleoli-associated PML structures is functionally involved in senescence progression.
Using inhibitors of histone deacetylases, we showed in detailed study of regulation of PML expression that interferon-mediated up-regulation of PML gene is linked to activity of histone deacetylases.
In summary, this study reveals the complex cytokine network activated with drugs during cellular senescence and its important role in expression of tumor suppressors participating in premature senescence.