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Review

IFI16, an amplifier of DNA-damage response: Role in cellular senescence and aging-associated inflammatory diseases

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ABSTRACT

DNA-damage induces a DNA-damage response (DDR) in mammalian cells. The response, depending upon the cell-type and the extent of DNA-damage, ultimately results in cell death or cellular senescence. DDR-induced signaling in cells activates the ATM-p53 and ATM-IKKα/β-interferon (IFN)-β signaling pathways, thus leading to an induction of the p53 and IFN-inducible *IFI16* gene. Further, upon DNA-damage, DNA accumulates in the cytoplasm, thereby inducing the IFI16 protein and STING-dependent IFN-β production and activation of the IFI16 inflammasome, resulting in the production of proinflammatory cytokines (*e.g.*, IL-1β and IL-18). Increased expression of IFI16 protein in a variety of cell-types promotes cellular senescence. However, reduced expression of IFI16 in cells promotes cell proliferation. Because expression of the *IFI16* gene is induced by activation of DNA-damage response in cells and increased levels of IFI16 protein in cells potentiate the p53-mediated transcriptional activation of genes and p53 and pRb-mediated cell cycle arrest, we discuss how an improved understanding of the role of IFI16 protein in cellular senescence and associated inflammatory secretory phenotype is likely to identify the molecular mechanisms that contribute to the development of aging-associated human inflammatory diseases and a failure to cancer therapy.

Contents

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1. Introduction

Exposure of mammalian cells to DNA-damaging agents (*e.g.*, ultraviolet light, ionizing radiations, or cancer chemotherapeutic agents) induces a DNA-damage response (DDR) (Lakin and Jackson, 1999; Bargonetti and Manfredi, 2002; Shiloh, 2006; Shiloh and Ziv, 2013). The response activates certain cell signaling pathways, including well-known ataxia telangiectasia mutated (ATM)-p53 (Kastan 2007; Shiloh and Ziv, 2013) and recently identified ATM-IKKα/β-interferon (IFN)-β (Yu et al., 2015) pathways. The activation of ATM-p53 pathway in cells stimulates the transcription of the p53 target genes that encode for the inhibitors of cell cycle progression (*e.g.*, $p21^{WAF1/CIP1}$) (el-Deiry et al., 1993; el-Deiry, 1998). Further, activation of the ATM-IKKα/β-IFN-β signaling pathway in cells increases the expression of the IFN-β (a type I IFN) and its secretion (Yu et al., 2015). Binding of IFN-β to high affinity cell surface receptor in autocrine and paracrine manner activates the JAK/STAT signaling pathway in the target cells (Stark et al., 1998), which stimulates the expression of the IFN-inducible genes that encode for the inhibitors of cell cycle progression and the negative regulators of the telomerase (*e.g.*, IFI16) (Chin et al., 1996; Xin et al., 2003; Xin et al., 2004; Song et al., 2010; Clarke et al., 2010), an enzyme that determines the proliferation potential of cells through maintaining the telomere length (Hahn 2005).

In murine bone marrow-derived macrophages (BMDMs), DNA-damage by ionizing radiations or etoposide treatment releases single and double-stranded DNA into cytoplasm (Härtlova et al., 2015). Upon sensing of cytosolic DNA, the murine structural and functional homologue of the IFI16 protein, p204, recruited the adaptor protein STING to induce the expression of IFN-β through activation of the TBK1 and IRF3. Interestingly, the induction of IFN-β production in BMDMs was dependent upon the ATM kinase. Further, fibroblasts from individuals with Ataxia Telangiectasia (A-T, a premature aging syndrome) also exhibited an increased expression of IFN-β and activation of type I IFN response (an increased expression of the IFN-inducible genes) (Duan et al., 2011a,b). Accordingly, BMDMs from *Atm*-deficient mice exhibited accumulation of DNA into the cytoplasm (without any treatment with DNA-damaging agents) and activated the type I IFN response (Härtlova et al., 2015).

Depending upon the cell-type and the extent of DNA-damage, activation of DDR-induced signaling in cells ultimately results in either a transient cell cycle arrest, cell death, or permanent cell cycle arrest termed replicative or cellular senescence (Levine, 1997; Bargonetti and Manfredi, 2002; Campisi, 2001; Feng et al., 2008; Shiloh and Ziv, 2013). The p53-mediated induction of $p21^{WAF1/CIP1}$ protein levels in a variety of cell types (*e.g.,* fibroblasts and epithelial cells) results in a transient cell cycle arrest, thus allowing cells to continue the cell-cycle progression after completion of DNA repair. In contrast, an extensive DNA-damage in cells results in cellular senescence-associated permanent cell cycle arrest (Levine, 1997; Campisi, 2001; Feng et al., 2008; Shiloh and Ziv, 2013).

Cellular senescence (or replicative senescence) is a phenotype, which is accompanied by a failure to re-enter the cell division cycle in response to mitogenic stimulation and by an acquired resistance to oncogenic challenge (Bringold and Serrano, 2000; Campisi, 2001; Campisi, 2013; Salama et al., 2014; Sharpless and Sherr, 2015). In addition to DDR, cellular senescence in human normal cells can be induced by short telomeres (due to an exhaustion of the replication potential), oncogenes (or supra-physiological mitogenic signals), and overexpression of certain tumor suppressor genes (Campisi, 2013; Salama et al., 2014; Sharpless and Sherr, 2015). Further, the activity of both p53 and retinoblastoma tumor suppressor protein (pRb) plays an important role in inducing cellular senescence-associated cell cycle arrest in human normal cells (Bringold and Serrano, 2000; Itahana et al., 2001; Thomas et al., 2003; Feng et al., 2008;). Because senescent cells are unable to proliferate, the induction of cellular senescence in human cells is thought to suppress tumorigenesis (Campisi, 2001, 2013; Salama et al., 2014). Although, senescent cells are resistant to oncogenic challenge and do not proliferate, these cells exhibit a secretory phenotype (senescence-associated secretory phenotype or SASP) that is associated with secretion of proinflammatory cytokines and "exosomes" (Lehmann et al., 2008; Hoare and Narita, 2013; Franceschi and Campisi, 2014; Salama et al., 2014). Exosomes (microvesicles, 50–100 nm) contain pathogen-associated and damage-associated molecular patterns (PAMPs and DAMPs), cytokines, a number of proteins (*e.g.,* CD81 and HMGB1), and DNA (up to ~1000 bp) (Lehmann et al., 2008; Zhu et al., 2014). Notably, SASP is closely associated with aging of muticellular tissues and organs (Zhu et al., 2014). Further, accumulation of senescent cells (and associated SASP) in tissues and organs is thought to contribute to organismal aging and inflammation-associated human diseases, including the development of certain human cancers (Collado et al., 2007; Franceschi and Campisi, 2014; Childs et al., 2015). Notably, accumulation of senescent cells has been reported in tumors after radiation and/or chemotherapy of cancer patients (Salama et al., 2014; Sharpless and Sherr, 2015).

All cell types produce low constitutive levels of IFN-β (Taniguchi and Takaoka, 2001). This low constitutive IFN-β production, which is maintained in part by activation of the IRF7 transcription factor, is important to maintain various physiological functions and regulate signaling of other cytokines (Taniguchi and Takaoka, 2001). However, an increased production of IFN-β in response to viral infections or activation of DDR, plays an important role in antiviral and DNA-damage responses (Stark and Darnell, 2012). Binding of secreted IFN-β to cell surface high affinity receptor (a heterodimer of the IFNAR1 and IFNAR2 subunits) activates the JAK-STAT signaling pathway in IFN-responsive cells (Stark et al., 1998). The pathway activates STAT1 transcription factor through its phosphorylation on Tyr-701 (indicated as PY-STAT1) by JAK kinase. The activated STAT1 and STAT2, along with IRF9, form the phosphorylated ISGF3 (P-ISGF3) transcription factor, which in the nucleus, stimulates the transcription of >2000 IFN-stimulated genes (ISGs) (Der et al., 1998). Proteins encoded by these genes mediate various biological and physiological activities of the type I IFNs. Notably, treatment of cells with the IFN-β also activates DDR through the generation of reactive oxygen species (ROS) that results in an increased expression of p53 (Takaoka et al., 2003) and activation of the ATM-p53 pathway (Moiseeva et al., 2006; Kim et al., 2009; Duan et al., 2011a,b). Activated p53 induces the expression of the p53-responsive genes, including the *IFI16* and $p21^{CIP1}$ (el-Deiry et al., 1993; Song et al., 2008). Increased expression of a set of ISGs, including the *IFI16*, in a variety of cell types is associated with cellular senescence-associated cell cycle arrest (Fridman and Tainsky, 2008; Purcell et al., 2014). Further, the expression of certain ISGs is