THE ROLE OF PROINFLAMMATORY CYTOKINE INTERLEUKIN-18 IN RADIATION INJURY

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Abstract—Massive radiation-induced inflammatory factors released from injured cells may cause innate and acquired immune reactions that can further result in stress response signal activity-induced local and systemic damage. IL-1 family members IL-1 β , IL-18, and IL-33 play key roles in inflammatory and immune responses and have been recognized to have significant influences on the pathogenesis of diseases. IL-1 β , IL-18, and IL-33 share similarities of cytokine biology, but differences exist in signaling pathways. A key component of the inflammatory reaction is the inflammasome, which is a caspase-1-containing multiprotein oligomer. Pathological stimuli such as radiation can induce inflammasome and caspase-1 activation, and subsequently cause maturation (activation) of pro-forms of IL-1 and IL-18 upon caspase-1 cleavage. This caspase-1 dependent and IL-1 and IL-18 associated cell damage is defined as pyroptosis. Activated IL-1 and IL-18 as proinflammatory cytokines drive pathology at different immune and inflammatory disorders through Toll-like receptor (TLR) signaling. While the mechanisms of IL-1 β -induced pathophysiology of diseases have been well studied, IL-18 has received less attention. The author recently reported that gamma radiation highly increased IL-1 β , IL-18 and IL-33 expression in mouse thymus, spleen and/or bone marrow cells; also circulating IL-18 can be used as a radiation biomarker to track radiation injury in mice, minipigs, and nonhuman primates. This mini-review focuses on the role of IL-18 in response to gamma radiation-induced injury. *Health Phys.* 111(2):212–217; 2016

Key words: health effects; radiation damage; radiation effects; tissue, body

INTRODUCTION

IT HAS been suggested that radiation causes cellular and tissue damage leading to “danger signals” and antigen release. These signals and antigens, such as damage-associated molecular

patterns (DAMPs), are important pro-inflammatory factors that play a pivotal role in stress response signal activation and induce inflammatory and immune reactions in target cells (Shan et al. 2007; Williams and McBride 2011). Recently, many DAMPs have been identified, and their roles in the inflammatory response were reported (Venereau et al. 2015). These include high mobility group box (HMGB) 1 protein (Scaffidi et al. 2002; Shi et al. 2003), damaged nuclear and mitochondrial DNA, extracellular adenosine triphosphate (ATP) (Krysko et al. 2011; Idzko et al. 2014), and oxidized low-density lipoprotein (Kim et al. 2013; Kapetanovic et al. 2015).

Inflammation is an important part of the complex biological responses of tissues to harmful radiation stimuli; it can be independent of DNA damage and occurs within minutes of exposure to radiation through post-transcriptional mRNA stabilization and early gene expression (Iwamoto and Barber 2007; Schaeue and McBride 2010). A massive release of radiation-induced proinflammatory cytokines will induce apoptosis, pyroptosis, senescence, autophagy, or necrosis in irradiated cells (McBride et al. 1989; Li et al. 2012; Zhang et al. 2012; Fukumoto et al. 2013; Ha et al. 2013; Haldar et al. 2015). In this sense, acute radiation syndrome (ARS) can be considered an acute inflammatory disease. Interleukin-18 (IL-18) is an interleukin-1 (IL-1) family member discovered in 1995 (Okamura et al. 1995), and it is induced in restricted inflammatory cells by inflammatory stimuli and secreted through activation of the inflammasome (Brydges et al. 2013). Inflammasomes are multiprotein oligomers consisting of caspase-1, NALP (NACHT, LRR, and PYD domains-containing protein), PYCARD (Apoptosis-associated speck-like protein containing a CARD or ASC), and sometimes caspase-5 (also known as caspase-11 or ICH-3). They are expressed in myeloid cells and are a component of the innate immune system. Stress-induced DAMPs (Savage et al. 2012; Venereau et al. 2015) and reactive oxygen species (ROS) released from damaged mitochondria (Fukumoto et al. 2013) are frequent stimulants of inflammasomes, and the inflammasome promotes the maturation of the inflammatory cytokines Interleukin-1 β

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(IL-1 β), IL-18 through NALP3 (cryopyrin) and caspase-1 activation (Rathinam et al. 2012).

IL-18 and IL-1 β display both similarities and important differences in response to stress and inflammatory stimuli (Bergsbaken et al. 2009). For example, an IL-18 precursor is present constitutively in almost all cells including hematopoietic cells, mesenchymal cells, and epithelial cells of the gastrointestinal (GI) tract in healthy humans and animals, whereas the IL-1 β precursor is rarely found in these cells (Dinarello et al. 2013). IL-1 β is produced by monocytes, macrophages, dendritic cells (DC), B-lymphocytes, and nature killer (NK) cells (van de Veerdonk and Netea 2013). It was reported that IL-1 β administration induced cyclooxygenase (COX)-2 expression and fever in wild-type but not in *COX2*^{-/-} C57BL/6 J mice, whereas IL-18 caused less COX-2 expression and did not induce fever in these mice (Li et al. 2003). In addition, IL-1 β activation of cells usually needs picograms (pg) to nanograms (ng) per milliliter (mL), whereas IL-18 requires 10–20 ng mL⁻¹ or even more (Lee et al. 2004). Deletion of the IL-18 receptor gene (*Il18r*) resulted in partial rescue of skin and visceral disease in young but not aging mice with cryopyrin-associated periodic syndromes (CAPS), suggesting that early disease is driven primarily by IL-18. In contrast, inhibition of IL-1 or IL-1R effectively cured CAPS, indicating the effects of IL-1 and IL-18 are at different stages of the disease process (Brydges et al. 2013).

IL-18, IL-18 RECEPTORS, AND IL-18 BINDING PROTEIN

IL-18 as a T helper 1 (Th1) cell cytokine was originally discovered as an interferon (IFN)- γ -inducer (Okamura et al. 1995) and has been detected in many cell types. Similar to IL-1 β , IL-18 is first synthesized as low levels of inactive precursor. This cytokine precursor lacks a signal peptide and depends on caspase-1 cleavage, becoming a mature active factor secreted in response to disease, stress, and inflammatory stimuli (Liew and McInnes 2002; Dinarello et al. 2013). Radiation stress induces cells to express DAMP signaling through pattern recognition receptors (PRRs) (Weber et al. 2010; Schaeue et al. 2012), which control production of pro-inflammatory cytokines (such as IL-1 and IL-18). IL-18 stimulates neutrophil migration and activation as well as Th1, Th2, and Th17 cell differentiation and IL-2, IL-12, GM-CSF and IFN- γ secretion in a variety of cell types through TLR signaling (Nakanishi et al. 2001; Carta et al. 2013).

Two IL-18 receptors (IL-18R) are required for initiation of IL-18 signaling. The IL-18R α is required for ligand binding with low affinity. After binding of IL-18 to the IL-18R α , the accessory chain, IL-18R β , is recruited into a high affinity signaling complex (Kim et al. 2001). This

complex is recognized by TLRs, which is an essential signal through the adapter protein MyD88 (myeloid differentiation primary protein 88). MyD88 activates the transcription factors NF κ B (Nuclear factor κ B), c-Jun N-terminal kinase (JNK)/AP-1 (activator protein-1), MAPK kinases through IL-1R-associated kinases (IRAK), and interferon regulatory factors (IRF) to trigger inflammatory signal pathways (Fig. 1). This IL-18 activation-induced pathway was defective in *Myd88*^{-/-} mice (Adachi et al. 1998; Hafer et al. 2007).

IL-18 binding protein (IL-18BP) is a novel natural antagonist of IL-18 discovered by two independent groups in 1999 (Aizawa et al. 1999; Novick et al. 1999). This protein belongs to the immunoglobulin-like class of receptors and is not cleaved on the cell surface. IL-18BP is a secreted protein in serum. It binds to the receptor-binding site of IL-18 with high affinity to block the IL-18 and IL-18R complex formation and subsequently inhibits IL-18 activation (Fig. 1). There are four isoforms of IL-18BP (a, b, c, and d) in humans and mice (Kim et al. 2000). Among them, IL-18BP isoforms a and c inhibit IL-18 at equimolar ratios, and isoforms b and d have no function for IL-18 inhibition. Human and mouse IL-18BPs share approximately 61% amino acid sequence identity. IL-18BP is abundant in both human and mouse serum and can be determined by ELISA using polyclone anti-IL-18BP antibody (Novick et al. 2001). Levels of IL-18 and IL-18BP are not always positively correlated. Disease-induced IL-18 increases with or

Fig. 1. IL-18 signal pathway. After caspase-1 cleavage, the activated IL-18 is bound by IL-18R α , which recruits IL-18R β to form a high affinity complex. This complex is recognized by TLRs and associated with a Toll/interleukin-1 receptor (TIR) domain, which is an essential signal through the adapter protein MyD88. The TLR signal pathway further anchors IRAK to trigger downstream stress-response proteins such as NF κ B and MAPK. IL-18BP is a constitutively secreted protein in human and animal serum. IL-18BP is a natural inhibitor of IL-18, which binds to mature IL-18 and neutralizes the activation of IL-18.

without enhanced IL-18BP in serum have been observed (Shan et al. 2009; Ji et al. 2014; Yoshida et al. 2014). In humans and animals, increased disease severity can be associated with an imbalance of IL-18 to IL-18BP. Thus, IL-18BP has a role in destructive inflammatory disorders.

EFFECTS OF IL-18 ON RADIATION INJURY

Acute exposure to ionizing radiation induces danger signals and antigens such as endogenous DAMPs. DAMPs can be recognized by pattern recognition receptors (PRRs) and inflammasomes, which subsequently initiate immune and inflammatory signal transduction pathways through TLR and interleukin receptors (IL-R) and associated adaptor proteins containing a Toll/interleukin-1 receptor (TIR) homology domain (Fig. 1) (Janeway 1992; Kluwe et al. 2009; Santoni et al. 2015). IL-18R has a TIR domain (Sandor et al. 2003; Meijer et al. 2004). Shan et al. (2007) reported that total-body irradiation (TBI) between 0.05 and 4 Gy resulted in radiation dose-dependent IL-12 and IL-18 secretion and increased TLR4-MD2 and MyD88 expression in mouse peritoneal macrophages. Furthermore, radiation-induced NLRP3 inflammasome activation and caspase-1 cleavage correlated with apoptosis in mouse immune cells have been reported (Stoecklein et al. 2015). The investigators demonstrated that the circulating IL-1 β , IL-18, IL-6, and IL-12 were significantly lower in *caspase-1*^{-/-} or *Nlrp3*^{-/-} mice than in wild type (WT) mice after TBI. Both *caspase-1*^{-/-} or *Nlrp3*^{-/-} mice showed lower inflammatory-type responses to radiation exposure and lesser radiation-induced cell death than genetically normal mice did, suggesting that the caspase-1 and NLRP3 inflammasome play key roles in radiation-induced injury in animal cells.

The author recently reported that IL-1 β , IL-18, and IL-33 were upregulated in mouse thymus, spleen, and bone marrow after TBI (Ha et al. 2014). Interestingly, IL-18 but not IL-1 β or IL-33 significantly and stably increased in mouse serum from 1 d after sublethal (5–7 Gy) and lethal doses (8–12 Gy) of TBI (Li et al. 2015) in a radiation dose-dependent manner. High levels of circulating IL-18 (2.5–24-fold higher than control) were tightly associated with lethal doses of radiation exposure up to 13 d post-TBI. That finding was further confirmed by the author in total-body lethal dose γ -irradiated nonhuman primates (NHPs) (Farese et al. 2012) and minipigs (Moroni et al. 2011), and demonstrated that radiation significantly enhanced IL-18 in serum from NHPs 2–4 d after 7 Gy and in minipig plasma 1–3 d after 1.6 Gy of TBI. The statistical data from this study were summarized in Table 1. Finally, circulating IL-18 were compared with the lymphocyte and neutrophil counts in blood of mice, minipigs and NHPs and demonstrated close correlations between increases of

Table 1. Radiation significantly increased circulating IL-18 in mice, minipigs and NHPs^a.

TBI vs. 0 Gy	Mice		Minipigs	NHP
	5 Gy (N = 6)	7–12 Gy (N = 30)	1.6 Gy (N = 4)	7 Gy (N = 5)
Time post-radiation (days)	<i>p</i> -value	<i>p</i> -value	<i>p</i> -value	<i>p</i> -value
+1	<0.01	<0.01	<0.05	
+2				<0.05
+3	<0.05	<0.01	<0.05	
+4				
+7		<0.01		
+9		<0.01		
+13		<0.01		

^aStatistical analysis: Differences between means were compared by one way analysis of variance (ANOVA) with Dunnett's Post-Hoc test and multivariate analysis of variance (MANOVA). *P* < 0.05 was considered statistically significant (Ha et al. 2014).

IL-18 and decreases in lymphocyte and neutrophil counts after radiation (Ha et al. 2014).

Lymphocytes are very sensitive to radiation. IL-18-induced lymphocyte count reductions were also found in NHPs (Herzyk et al. 2002). A single intravenous injection of IL-18 at 1 or 10 mg kg⁻¹ in cynomolgus monkeys caused a transient decrease of lymphocyte counts in peripheral blood. The authors suggested that the effect of IL-18 on lymphocytes is indicative of lymphocytes trafficking out of circulation to tissue sites, instead of IL-18-induced lymphocyte death. How IL-18 mediates its role in radiation-induced reduction of lymphocyte counts in peripheral blood needs further investigation.

Radiation-induced neuroinflammation and radiation somnolence syndrome (RSS) was described as a late effect of whole-brain radiotherapy in children. Radiation-induced proinflammatory cytokines, including IL-18 secretion, may be responsible for this disorder (Ballesteros-Zebadua et al. 2012). In addition, Hwang et al. (2006) reported that a single dose of 15 Gy irradiation to a whole rat brain increased glial fibrillary acidic protein in astrocytes and initiated neuron gliosis. They further demonstrated radiation dose-dependent increases in IL-18 and multiple pro-inflammatory cytokine mRNAs in microglia cells and suggested an association between inflammatory complications and radiotherapy-induced astrocyte gliosis.

Recently, radiocontrast administration-caused increases in plasma creatinine and spot urine IL-18 levels in humans were reported by Turkmen et al. (2012). The radiocontrast agents used in 20 patients (11 males, 9 females) were 623 mg mL⁻¹ Iopromidand (1.5 mL Kg⁻¹) and 100 mL of 650 mg mL⁻¹ meglumine diatrizoate as three-way oral and rectal contrast material for abdominal computed tomography (CT). The risk of radiocontrast-induced nephropathy (RIN) in humans was low. However, a statistically significant

increase in spot urine IL-18 levels was observed at 6 and 24 h after radiocontrast administration, followed by plasma creatinine increases at 24 and 48 h, compared with the control group. Radiocontrast administration-induced plasma creatinine increases did not reach the significant levels, but urine IL-18 increases may indicate an early kidney injury by radiocontrast. The author suggested that the level of IL-18 in a patient's urine can be used as an early parameter for kidney injury after radiocontrast administration.

IL-18 production also occurred after other types of radiations that cause inflammatory responses. Ultraviolet radiation (UVR) exposure stimulated abundant IL-18, IL-1, and IL-33 secretion in keratinocytes (Grandjean-Laquerriere et al. 2007; Nasti and Timares 2012). Keratinocytes are the predominant cell type in the epidermis, the outermost layer of the skin, which forms a barrier against environmental damage by pathogenic bacteria, fungi, parasites, viruses, heat, ionizing radiation, UVR, and water loss. UVR exposure causes accumulated DNA mutations that can lead to epidermal malignancies. Cho et al. (2002) reported that IL-18 production was enhanced by UVB irradiation in a dose- and time-dependent manner and is correlated with malignant skin tumors. Furthermore, their results suggested that UVB irradiation-induced IL-18 production is selectively mediated through the generation of ROI (regulator of O-antigen length) and the activation of AP-1.

CONCLUSION

IL-1 family member IL-1 β , IL-18, and IL-33 are proinflammatory cytokines that promote immune and inflammatory responses to a variety of pathologic stimuli. The IL-18 precursor is expressed in many types of mammalian cells including hematopoietic cells, endothelial cells, keratinocytes, mesenchymal cells, and intestinal epithelial cells. IL-18 plays a key role in radiation-induced cell damage through an inflammasome-TLR signal transduction pathway involving radiation stress response factors NF κ B, JNK, AP-1, and MAPK. Pro-IL-18 is cleaved by caspase-1 to form active IL-18, and the latter is secreted from monocyte, macrophage and/or dendritic cells (Dinarello et al. 2013) after radiation exposure to start an inflammatory signal cascade. The elevated circulating IL-18 after radiation proportionally reflects radiation dose and severity of radiation injury and may be used as a potential biomarker for triage and also monitoring of casualties after radiological accidents as well as for therapeutic radiation exposure. Inhibition of IL-18 activation by IL-18 BP and maintaining the balance between IL-18 and IL-18BP may protect animals and humans from radiation injury.

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REFERENCES

- Adachi O, Kawai T, Takeda K, Matsumoto M, Tsutsui H, Sakagami M, Nakanishi K, Akira S. Targeted disruption of the MyD88 gene results in loss of IL-1- and IL-18-mediated function. *Immunity* 9:143–150; 1998.
- Aizawa Y, Akita K, Tanai M, Torigoe K, Mori T, Nishida Y, Ushio S, Nukada Y, Tanimoto T, Ikegami H, Ikeda M, Kurimoto M. Cloning and expression of interleukin-18 binding protein. *FEBS Lett* 445:338–342; 1999.
- Ballesteros-Zebadua P, Chavarria A, Celis MA, Paz C, Franco-Perez J. Radiation-induced neuroinflammation and radiation somnolence syndrome. *CNS Neurol Disord Drug Targets* 11: 937–949; 2012.
- Bergsbaken T, Fink SL, Cookson BT. Pyroptosis: host cell death and inflammation. *Nat Rev Microbiol* 7:99–109; 2009.
- Brydges SD, Broderick L, McGeough MD, Pena CA, Mueller JL, Hoffman HM. Divergence of IL-1, IL-18, and cell death in NLRP3 inflammasomopathies. *J Clin Invest* 123:4695–4705; 2013.
- Carta S, Lavieri R, Rubartelli A. Different members of the IL-1 family come out in different ways: DAMPs vs. cytokines? *Front Immunol* 4:123; 2013.
- Cho D, Seung Kang J, Hoon Park J, Kim YI, Hahm E, Lee J, Yang Y, Jeon J, Song H, Park H, Kim T, Pang S, Kim CW, Il Hwang Y, Jae Lee W. The enhanced IL-18 production by UVB irradiation requires ROI and AP-1 signaling in human keratinocyte cell line (HaCaT). *Biochem Biophys Res Commun* 298: 289–295; 2002.
- Dinarello CA, Novick D, Kim S, Kaplanski G. Interleukin-18 and IL-18 Binding Protein. *Front Immunol* 4:289; 2013.
- Farese AM, Cohen MV, Katz BP, Smith CP, Jackson W III, Cohen DM, MacVittie TJ. A nonhuman primate model of the hematopoietic acute radiation syndrome plus medical management. *Health Phys* 103:367–382; 2012.
- Fukumoto J, Fukumoto I, Parthasarathy PT, Cox R, Huynh B, Ramanathan GK, Venugopal RB, Allen-Gipson DS, Lockey RF, Kolliputi N. NLRP3 deletion protects from hyperoxia-induced acute lung injury. *Am J Physiol Cell Physiol* 305: C182–189; 2013a.
- Fukumoto R, Cary LH, Gorbunov NV, Lombardini ED, Elliott TB, Kiang JG. Ciprofloxacin modulates cytokine/chemokine profile in serum, improves bone marrow repopulation, and limits apoptosis and autophagy in ileum after whole body ionizing irradiation combined with skin-wound trauma. *PLoS ONE* 8:e58389; 2013b.
- Grandjean-Laquerriere A, Antonicelli F, Gangloff SC, Guenounou M, Le Naour R. UVB-induced IL-18 production in human keratinocyte cell line NCTC 2544 through NF-kappaB activation. *Cytokine* 37:76–83; 2007.
- Ha CT, Li XH, Fu D, Moroni M, Fisher C, Arnott R, Srinivasan V, Xiao M. Circulating Interleukin-18 as a biomarker of total-body radiation exposure in mice, minipigs, and nonhuman primates (NHP). *PLoS One* 9:e109249; 2014.
- Ha CT, Li XH, Fu D, Xiao M, Landauer MR. Genistein nanoparticles protect mouse hematopoietic system and prevent proinflammatory factors after gamma irradiation. *Radiat Res* 180: 316–325; 2013.
- Hafer K, Iwamoto KS, Scuric Z, Schiestl RH. Adaptive response to gamma radiation in mammalian cells proficient and deficient in components of nucleotide excision repair. *Radiat Res* 168:168–174; 2007.

- Haldar S, Dru C, Choudhury D, Mishra R, Fernandez A, Biondi S, Liu Z, Shimada K, Arditi M, Bhowmick NA. Inflammation and pyroptosis mediate muscle expansion in an interleukin-1 β (IL-1 β)-dependent manner. *J Biol Chem* 290: 6574–6583; 2015.
- Herzyk DJ, Soos JM, Maier CC, Gore ER, Narayanan PK, Nadwodny KL, Liu S, Jonak ZL, Bugelski PJ. Immunopharmacology of recombinant human interleukin-18 in non-human primates. *Cytokine* 20:38–48; 2002.
- Hwang SY, Jung JS, Kim TH, Lim SJ, Oh ES, Kim JY, Ji KA, Joe EH, Cho KH, Han IO. Ionizing radiation induces astrocyte gliosis through microglia activation. *Neurobiol Dis* 21:457–467; 2006.
- Idzko M, Ferrari D, Eltzschig HK. Nucleotide signalling during inflammation. *Nature* 509:310–317; 2014.
- Iwamoto KS, Barber CL. Radiation-induced posttranscriptional control of M6P/IGF2r expression in breast cancer cell lines. *Mol Carcinog* 46:497–502; 2007.
- Janeway CA Jr. The immune system evolved to discriminate infectious nonself from noninfectious self. *Immunol Today* 13: 11–16; 1992.
- Ji Q, Zeng Q, Huang Y, Shi Y, Lin Y, Lu Z, Meng K, Wu B, Yu K, Chai M, Liu Y, Zhou Y. Elevated plasma IL-37, IL-18, and IL-18BP concentrations in patients with acute coronary syndrome. *Mediators Inflamm* 2014:165742; 2014.
- Kapetanovic R, Bokil NJ, Sweet MJ. Innate immune perturbations, accumulating DAMPs and inflammasome dysregulation: a ticking time bomb in ageing. *Ageing Res Rev* 24:40–53; 2015.
- Kim M, Choi SH, Jin YB, Lee HJ, Ji YH, Kim J, Lee YS, Lee YJ. The effect of oxidized low-density lipoprotein (ox-LDL) on radiation-induced endothelial-to-mesenchymal transition. *Int J Radiat Biol* 89:356–363; 2013.
- Kim SH, Eisenstein M, Reznikov L, Fantuzzi G, Novick D, Rubinstein M, Dinarello CA. Structural requirements of six naturally occurring isoforms of the IL-18 binding protein to inhibit IL-18. *Proc Natl Acad Sci USA* 97:1190–1195; 2000.
- Kim SH, Reznikov LL, Stuyt RJ, Selzman CH, Fantuzzi G, Hoshino T, Young HA, Dinarello CA. Functional reconstitution and regulation of IL-18 activity by the IL-18R β chain. *J Immunol* 166:148–154; 2001.
- Kluwe J, Mencin A, Schwabe RF. Toll-like receptors, wound healing, and carcinogenesis. *J Mol Med (Berl)* 87:125–138; 2009.
- Krysko DV, Agostinis P, Krysko O, Garg AD, Bachert C, Lambrecht BN, Vandenabeele P. Emerging role of damage-associated molecular patterns derived from mitochondria in inflammation. *Trends Immunol* 32:157–164; 2011.
- Lee JK, Kim SH, Lewis EC, Azam T, Reznikov LL, Dinarello CA. Differences in signaling pathways by IL-1 β and IL-18. *Proc Natl Acad Sci USA* 101:8815–8820; 2004.
- Li S, Goorha S, Ballou LR, Blatteis CM. Intracerebroventricular interleukin-6, macrophage inflammatory protein-1 β and IL-18: pyrogenic and PGE(2) -mediated? *Brain Res* 992: 76–84; 2003.
- Li XH, Ha CT, Fu D, Landauer MR, Ghosh SP, Xiao M. Delta-tocotrienol suppresses radiation-induced MicroRNA-30 and protects mice and human CD34 $^{+}$ cells from radiation injury. *PLoS One* 10:e0122258; 2015.
- Li XH, Ha CT, Fu D, Xiao M. REDD1 protects osteoblast cells from gamma radiation-induced premature senescence. *PLoS ONE* 7:e36604; 2012.
- Liew FY, McInnes IB. Role of interleukin 15 and interleukin 18 in inflammatory response. *Ann Rheum Dis* 61(Suppl 2): ii100–102; 2002.
- McBride WH, Mason K, Withers HR, Davis C. Effect of interleukin 1, inflammation, and surgery on the incidence of adhesion formation and death after abdominal irradiation in mice. *Cancer Res* 49:169–173; 1989.
- Meijer AH, Gabby Krens SF, Medina Rodriguez IA, He S, Bitter W, Ewa Snaar-Jagalska B, Spaijk HP. Expression analysis of the Toll-like receptor and TIR domain adaptor families of zebrafish. *Mol Immunol* 40:773–783; 2004.
- Moroni M, Lombardini E, Salber R, Kazemzadeh M, Nagy V, Olsen C, Whitnall MH. Hematological changes as prognostic indicators of survival: similarities between Göttingen minipigs, humans, and other large animal models. *PLoS ONE* 6: e25210; 2011.
- Nakanishi K, Yoshimoto T, Tsutsui H, Okamura H. Interleukin-18 regulates both Th1 and Th2 responses. *Annu Rev Immunol* 19: 423–474; 2001.
- Nasti TH, Timares L. Inflammasome activation of IL-1 family mediators in response to cutaneous photodamage. *Photochem Photobiol* 88:1111–1125; 2012.
- Novick D, Kim SH, Fantuzzi G, Reznikov LL, Dinarello CA, Rubinstein M. Interleukin-18 binding protein: a novel modulator of the Th1 cytokine response. *Immunity* 10:127–136; 1999.
- Novick D, Schwartzburd B, Pinkus R, Suissa D, Belzer I, Stoecker Z, Keane WF, Chvatchko Y, Kim SH, Fantuzzi G, Dinarello CA, Rubinstein M. A novel IL-18BP ELISA shows elevated serum IL-18BP in sepsis and extensive decrease of free IL-18. *Cytokine* 14:334–342; 2001.
- Okamura H, Tsutsui H, Komatsu T, Yutsudo M, Hakura A, Tanimoto T, Torigoe K, Okura T, Nukada Y, Hattori K. Cloning of a new cytokine that induces IFN- γ production by T cells. *Nature* 378:88–91; 1995.
- Rathinam VA, Vanaja SK, Fitzgerald KA. Regulation of inflammasome signaling. *Nat Immunol* 13:333–342; 2012.
- Sandor F, Latz E, Re F, Mandell L, Repik G, Golenbock DT, Espevik T, Kurt-Jones EA, Finberg RW. Importance of extra- and intracellular domains of TLR1 and TLR2 in NF κ B signaling. *J Cell Biol* 162:1099–1110; 2003.
- Santoni G, Cardinali C, Morelli MB, Santoni M, Nabissi M, Amantini C. Danger- and pathogen-associated molecular patterns recognition by pattern-recognition receptors and ion channels of the transient receptor potential family triggers the inflammasome activation in immune cells and sensory neurons. *J Neuroinflammation* 12:21; 2015.
- Savage CD, Lopez-Castejon G, Denes A, Brough D. NLRP3-inflammasome activating DAMPs stimulate an inflammatory response in glia in the absence of priming which contributes to brain inflammation after injury. *Front Immunol* 3:288; 2012.
- Scaffidi P, Misteli T, Bianchi ME. Release of chromatin protein HMGB1 by necrotic cells triggers inflammation. *Nature* 418: 191–195; 2002.
- Schaue D, Kachikwu EL, McBride WH. Cytokines in radiobiological responses: a review. *Radiat Res* 178:505–523; 2012.
- Schaue D, McBride WH. Links between innate immunity and normal tissue radiobiology. *Radiat Res* 173:406–417; 2010.
- Shan NN, Zhu XJ, Peng J, Qin P, Zhuang XW, Wang HC, Hou M. Interleukin 18 and interleukin 18 binding protein in patients with idiopathic thrombocytopenic purpura. *Br J Haematol* 144:755–761; 2009.
- Shan YX, Jin SZ, Liu XD, Liu Y, Liu SZ. Ionizing radiation stimulates secretion of pro-inflammatory cytokines: dose-response relationship, mechanisms and implications. *Radiat Environ Biophys* 46:21–29; 2007.
- Shi Y, Evans JE, Rock KL. Molecular identification of a danger signal that alerts the immune system to dying cells. *Nature* 425:516–521; 2003.
- Stoecklein VM, Osuka A, Ishikawa S, Lederer MR, Wanke-Jellinek L, Lederer JA. Radiation exposure induces inflammasome pathway activation in immune cells. *J Immunol* 194:1178–1189; 2015.

- Turkmen F, Isitmangil G, Berber I, Arslan G, Sevinc C, Ozdemir A. Comparison of serum creatinine and spot urine interleukin-18 levels following radiocontrast administration. *Indian J Nephrol* 22:196–199; 2012.
- van de Veerdonk FL, Netea MG. New insights in the immunobiology of IL-1 family members. *Front Immunol* 4:167; 2013.
- Venereau E, Ceriotti C, Bianchi ME. DAMPs from cell death to new life. *Front Immunol* 6:422; 2015.
- Weber A, Wasiliew P, Kracht M. Interleukin-1 (IL-1) pathway. *Sci Signal* 3:cm1; 2010.
- Williams JP, McBride WH. After the bomb drops: a new look at radiation-induced multiple organ dysfunction syndrome (MODS). *Int J Radiat Biol* 87:851–868; 2011.
- Yoshida T, Friehs I, Mummidi S, del Nido PJ, Addulnour-Nakhoul S, Delafontaine P, Valente AJ, Chandrasekar B. Pressure overload induces IL-18 and IL-18R expression, but markedly suppresses IL-18BP expression in a rabbit model. IL-18 potentiates TNF-alpha-induced cardiomyocyte death. *J Mol Cell Cardiol* 75:141–151; 2014.
- Zhang M, Yin L, Zhang K, Sun W, Yang S, Zhang B, Salzman P, Wang W, Liu C, Vidyasagar S, Zhang L, Ju S, Okunieff P. Response patterns of cytokines/chemokines in two murine strains after irradiation. *Cytokine* 58:169–177; 2012.