

AOP – Annex 1, assessment of the relative level of confidence in the overall AOP based on rank ordered weight of evidence elements.

IR appears to be a “complete” carcinogen in the mammary gland in that the toxin acts as an initiator through the formation of oxidative stress and pro-mutagenic DNA damage and (the MIEs) and as a promoter through increasing inflammation and proliferation, similar to many chemical carcinogens (Russo and Russo 1996). We have high confidence in the evidence linking stressor (IR) with adverse outcome (breast cancer). The weight of evidence for the first pathway from RONS and DNA damage to Mutation and Proliferation is High while the weight of evidence for the second pathway from RONS to Inflammation to Proliferation and Breast Cancer is Moderate. These evaluations are based on the supporting evidence for all KEs and the considerations in Annex 1, and based on the need for additional evidence in the essentiality of Inflammation for the genesis of breast cancer.

This AOP could not address the large number of related topics that interact with the key events described here. These topics include events following IR that may interact with these key events such as immune surveillance (which may change with the inflammatory environment after IR (Schreiber, Old et al. 2011; Barcellos-Hoff 2013; Lumniczky and Safrany 2015); IR effect on survival/apoptosis and interactions of apoptosis with inflammation, mutation, compensatory proliferation, and selection process; changes to DNA repair; and the role of epigenetics in carcinogenesis from IR (Daino, Nishimura et al. 2018). This AOP also does not address other influences on these key events beyond reproductive hormones and typical breast development. Subsequent contributions to this AOP should elaborate on these points.

	Defining question	High (Strong)	Moderate	Low (Weak)
<b>2. Support for essentiality of KEs</b>	Are downstream KEs and/or the AO prevented if an upstream KE is blocked?	Direct evidence from specifically designed experimental studies illustrating essentiality for at least one of the important KEs	Indirect evidence that sufficient modification of an expected modulating factor attenuates or augments a KE	No or contradictory experimental evidence of the essentiality of any of the KEs.
MIE: Increase in reactive oxygen and nitrogen species (RONS)	<b>Essentiality is High.</b> <i>The most significant support comes from the relatively large number of studies using antioxidants or other interventions to reduce RONS, which show a reduction in DNA damage and mutations. Additional support comes from experiments increasing external oxidants like H2O2, which show that RONS are independently capable of causing DNA damage and mutations. Uncertainties arise from the smaller effects of RONS on DNA damage compared with ionizing radiation. Mammary gland relevance is less certain due to the relatively few experiments in breast tissue.</i>			
KE/AO: Increase in DNA damage	<b>Essentiality is High.</b> <i>The essentiality of this MIE to cancer is generally accepted. Supporting evidence comes from application of mutagenic agents: the increase in DNA damage precedes mutations, proliferation, and tumorigenesis. Further indirect evidence comes from evidence for MIE1, in which antioxidants that reduce DNA damage also reduce mutations and chromosomal damage. Finally, mutations in DNA repair genes increase the risk of tumors.</i>			

KE/AO: Increase in mutation	<b>Essentiality is High.</b> The contribution of this MIE to cancer is generally accepted. Evidence comes from knock-out and knock-in experiments, which find that mutations in certain key genes increase tumorigenesis. However, an ongoing debate pits the singular importance of mutations against a significant role for the tissue microenvironment. This debate is fueled by transplant studies that show the importance of tissue environment for tumorigenesis and suggesting that mutations may not be sufficient for tumorigenesis.
KE: Increase, Cell Proliferation (epithelial cells)	<b>Essentiality is High.</b> Cellular proliferation is a key characteristic of cancer cells and can lead to hyperplasia, an intermediate phase in the development of tumorigenesis. Proliferation also increases the number of cells with mutations, which can further promote proliferation and/or changes to the local microenvironment.
KE/AO: Increase, Ductal Hyperplasia	<b>Essentiality is High.</b> Evidence comes from transplant experiments showing that non-proliferating tissue is less tumorigenic than proliferating lesions, and from interventions that reduce both proliferation and tumors. Further evidence comes from animals that are resistant to both mammary gland proliferation and tumors from ionizing radiation. Uncertainty arises from conflicting evidence on the tumorigenicity of hyperplasia, the absence of hyperplasia observed before some tumors, and spontaneous regression of tumors.
KEs: Tissue Resident Cell Activation, Increased Pro-inflammatory mediators, Leukocyte recruitment/activation	<b>Essentiality is Moderate.</b> These key events were reviewed as a group. Evidence comes from using genetic modifications, antibodies, and antioxidants to reduce inflammatory and anti-inflammatory factors. These interventions reduce DNA damage, mutations, and mechanisms contributing to tumorigenesis and invasion. Uncertainty arises from conflicting effects in different genetic backgrounds and in different organs.

	Defining question	High (Strong)	Moderate	Low (Weak)
<b>1. Support for biological plausibility of KERs</b>	a. Is there a mechanistic relationship between KEup and KEdown consistent with established biological knowledge?	Extensive understanding of the KER based on extensive previous documentation and broad acceptance	KER is plausible based on analogy to accepted biological relationships, but scientific understanding is incomplete	Empirical support for association between KEs, but the structural or functional relationship between them is not understood.
<i>MIE Increase in RONS leads to Increase in DNA damage (intermediate AO)</i>		<b>High.</b> Reactive oxygen and nitrogen species from oxygen and respiratory activity are generally acknowledged to damage DNA under a range of cellular conditions.		
<i>DNA damage leads to Increase in Mutations (intermediate AO)</i>		<b>High.</b> DNA damage in the form of nucleotide damage, single strand and double strand breaks, and complex damage can generate mutations, particularly when a damaged cell undergoes replication.		
<i>Increase in Mutations leads to Increase, Cell Proliferation (epithelial cells)</i>		<b>High.</b> Multiple mechanisms limit the proliferation of cells in normal biological systems. Mutations in many of the genes controlling these mechanisms promote proliferation.		
<i>Increase, Cell Proliferation (epithelial cells) leads to Increase in Mutation</i>		<b>High.</b> Biological plausibility is high since proliferation is generally acknowledged to increase mutations through incorporating or amplifying the impact of unrepaired DNA damage as mutations.		
<i>Increase, Cell Proliferation (epithelial cells) leads to Increase, Ductal Hyperplasia (intermediate AO)</i>		<b>Not Specified.</b> This relationship is generally accepted, but evidence has not been compiled for this AOP.		

Increase, Ductal Hyperplasia increases risk of Breast Cancer (AO)	<b>High.</b> It is generally accepted that proliferation and hyperplasia increase the risk of breast cancer. Evidence comes from transplant experiments showing that non-proliferating tissue is less tumorigenic than proliferating lesions, and from interventions that reduce both lesions and tumors. Further evidence comes from animals that are resistant to both mammary gland hyperplasia and tumors from ionizing radiation. Uncertainty arises from conflicting evidence on the tumorigenicity of hyperplasia, the absence of hyperplasia observed before some tumors, and spontaneous regression of tumors.
Increase in DNA damage leads to Tissue resident cell activation	<b>High.</b> Biological plausibility is high since DNA damage generates inflammatory signals (DAMPS).
Increase in RONS leads to Tissue resident cell activation	<b>Moderate.</b> Damage from RONS can activate some inflammatory and anti-inflammatory pathways (TLR, TGF- $\beta$ ), and RONS are an essential part of the primary signaling pathways of multiple inflammatory and anti-inflammatory pathways (TLR4, TNF- $\alpha$ , TGF- $\beta$ , NFkB).
Tissue resident cell activation leads to Increase in Pro-inflammatory mediators	<b>High.</b> This relationship is well established.
Pro-inflammatory mediators lead to Leukocyte recruitment/activation	<b>High.</b> This relationship is well established.
Pro-inflammatory mediators, Leukocyte recruitment/activation lead to an Increase in RONS	<b>High.</b> Inflammation is commonly understood to generate RONS via inflammatory signaling and activated immune cells.
Pro-inflammatory mediators lead to Increase, Cell Proliferation (epithelial cells)	<b>High.</b> Inflammation is generally understood to lead to proliferation during recovery from inflammation.
Pro-inflammatory mediators promote Breast Cancer	<b>Moderate.</b> Tissue environment is known to be a major factor in carcinogenesis, and inflammatory processes are implicated in the development and invasiveness of breast and other cancers.

	Defining questions	High (Strong)	Moderate	Low (Weak)
<b>3. Empirical support for KERs</b>	Does empirical evidence support that a change in KEup leads to an appropriate change in KEdown? Does KEup occur at lower doses and earlier time points than KE down and is the incidence of KEup > than that for KEdown? Inconsistencies?	Multiple studies showing dependent change in both events following exposure to a wide range of specific stressors. No or few critical data gaps or conflicting data	Demonstrated dependent change in both events following exposure to a small number of stressors. Some inconsistencies with expected pattern that can be explained by various factors.	Limited or no studies reporting dependent change in both events following exposure to a specific stressor; and/or significant inconsistencies in empirical support across taxa and species that don't align with hypothesized AOP
MIE Increase in RONS leads to Increase in DNA damage (intermediate AO)	<b>High.</b> Multiple studies show an increase in DNA damage with RONS treatment as well as dependent changes in both RONS and DNA damage in response to stressors. DNA damage increases with RONS dose, and temporal concordance between RONS and DNA damage events following ionizing radiation is consistent with a causative relationship, although few studies examine multiple doses and time points. A small number of studies do not find double strand breaks at physiological doses, or report an increase in one key event but not the			

	<i>other.</i>
<i>DNA damage leads to Increase in Mutations (intermediate AO)</i>	<b>High.</b> It is generally accepted that DNA damage leads to mutations. Empirical support comes in part from the observation that agents which increase DNA damage also cause mutations, that DNA damage precedes the appearance of mutations, and that interventions to reduce DNA damage also reduce mutations. None of the identified studies measure both outcomes over the same range of time points. This constitutes a readily addressable data gap.
<i>Increase in Mutations leads to Increase, Cell Proliferation (epithelial cells)</i>	<b>Moderate.</b> Mutations that promote proliferation are frequently found in cancers, and both mutation and proliferation occur in response to tumorigenic stressors like ionizing radiation. Although not measured together after stressors, mutations appear over the same time frame or prior to the appearance of proliferation. Multiple uncertainties and conflicting evidence weaken this key event relationship. The two key events differ in their dose response- mutation but not proliferation increases with ionizing radiation dose. Furthermore, a single mutation is not necessarily sufficient to increase proliferation- proliferation typically requires multiple mutations or a change in the surrounding environment. In mammary tissue, stromal state strongly influences the proliferative nature of epithelial cells – even epithelial cells with mutated tumor suppressors may be unable to form tumors in the absence of stromal changes.
<i>Increase, Cell Proliferation (epithelial cells) leads to Increase in Mutation</i>	<b>High.</b> We did not evaluate the empirical support for this KER in response to IR. However proliferation or mitosis is required for some types of DNA damage to be made permanent and heritable, and further DNA damage including mutation promoting double strand breaks can occur when cells divide before DNA repair is complete.
<i>Increase, Cell Proliferation (epithelial cells) leads to Increase, Ductal Hyperplasia (intermediate AO)</i>	<b>Not specified.</b> This relationship is generally accepted, but evidence has not been compiled for this AOP.
<i>Increase, Ductal Hyperplasia increases risk of Breast Cancer (AO)</i>	<b>High.</b> Carcinogenic agents increase proliferation and hyperplasia as well as tumors. Proliferation and hyperplasia appear prior to or at the same time as tumors, grow into carcinomas, and form mammary tumors more effectively than non-proliferating tissue. Disruption of proliferation is associated with decreased tumor growth, and tumor resistant rats do not show proliferation. However, the discrepancy between the non-linear proliferative and linear mammary tumor response to carcinogen dose coupled with evidence of independent occurrences of proliferation and tumorigenesis suggests that while proliferation and hyperplasia likely promote carcinogenesis, additional factors also contribute to carcinogenesis.
<i>Increase in DNA damage leads to Tissue resident cell activation</i>	<b>Not Specified.</b> Biological plausibility is high since DNA damage generates inflammatory signals (DAMPs), but evidence has not been compiled for this AOP.
<i>Increase in RONS leads to Tissue resident cell activation</i>	<b>Moderate.</b> Both RONS and inflammation increase in response to agents that increase either RONS or inflammation. Multiple studies show dose-dependent changes in both RONS and inflammation in response to stressors including ionizing radiation and antioxidants. RONS have been measured at the same or earlier time points as inflammatory markers, but additional studies are needed

	<i>to characterize the inflammatory response at the earliest time points to support causation. Uncertainties come from the positive feedback from inflammation to RONS potentially interfering with attempts to establish causality, and from the large number of inflammation related factors with differing responses to stressors and experimental variation.</i>
<i>Tissue resident cell activation leads to Increase in Pro-inflammatory mediators</i>	<b>Moderate.</b> <i>This relationship is generally accepted, but empirical evidence has not been compiled for this KER in mammary gland.</i>
<i>Pro-inflammatory mediators lead to Leukocyte recruitment/activation</i>	<b>Moderate.</b> <i>This relationship is generally accepted, but evidence has not been compiled for this KER in mammary gland.</i>
<i>Increase in Pro-inflammatory mediators and Leukocyte recruitment/activation leads to an Increase in RONS lead to an Increase in RONS</i>	<b>High.</b> <i>Signals arising from inflammation can be both pro- and anti-inflammatory, and both can have effects on RONS and downstream key events. Multiple inflammation-related factors increase RONS or oxidative damage, and ionizing radiation increases both inflammation-related signaling and RONS or oxidative damage over the same time points. Interventions to reduce inflammation also reduce RONS. The dose-dependence of the response to stressors is generally consistent between the two key events, although this is based on a small number of studies with some conflicting evidence.</i>
<i>Pro-inflammatory mediators lead to Increase, Cell Proliferation (epithelial cells)</i>	<b>High.</b> <i>We did not evaluate the empirical support for this KER in response to IR. However, inflammation is generally understood to promote proliferation and survival</i>
<i>Pro-inflammatory mediators promote Breast Cancer</i>	<b>Moderate.</b> <i>Interventions to increase inflammatory factors increase the carcinogenic potential of targeted and non-targeted cells. Inflammation is documented at earlier time points than tumorigenesis or invasion- within minutes or hours compared to days to months for carcinogenesis, consistent with an inflammatory mechanism of tumorigenesis and invasion. Inhibition of cytokines, inflammatory signaling pathways, and downstream effectors of inflammation activity prevent transformation, tumorigenesis, and invasion following IR or stimulation of inflammatory pathways. However, the key event and the adverse outcome differ in their dose-response to ionizing radiation: inflammation always does not increase linearly with dose, while breast cancer and invasion does. Uncertainty arises from the multifunctional nature of inflammation-related pathways which may be pro- or anti-inflammatory and pro- or anti-carcinogenic based on context. Both pro- and anti-inflammatory factors may contribute to carcinogenesis- further research will be required to identify the context of each.</i>

Supporting Information for Essentiality Call to be Included in Annex 1:

### Overall assessment of KEs

IR appears to be a “complete” carcinogen in the mammary gland in that the stressor acts as an initiator through the formation of oxidative stress and pro-mutagenic DNA damage and (the MIEs) and as a promoter through increasing inflammation and proliferation, similar to many chemical carcinogens (Russo and Russo 1996). We have high confidence in the evidence linking stressor (IR) with adverse

outcome (breast cancer). The weight of evidence for the first pathway from RONS to DNA damage, Mutation, and Proliferation is High while the weight of evidence for the second pathway from RONS to Inflammation to Proliferation and Breast Cancer is Moderate. These evaluations are based on the supporting evidence for all KEs and the considerations in Annex 1, and based on the need for additional evidence in the essentiality of Inflammation for the genesis of breast cancer.

### **MIE1: Increase in RONS**

**Essentiality is High.** *The most significant support comes from the relatively large number of studies using antioxidants or other interventions to reduce RONS, which show a reduction in DNA damage and mutations. Additional support comes from experiments increasing external oxidants like H<sub>2</sub>O<sub>2</sub>, which show that RONS are independently capable of causing DNA damage and mutations. Uncertainties arise from the smaller effects of RONS on DNA damage compared with ionizing radiation. Mammary gland relevance is less certain due to the relatively few experiments in breast tissue.*

Multiple studies support the hypothesis that elevated RONS is a key part of the adverse outcome pathway for breast cancer from ionizing radiation. The strongest evidence comes from studies showing that reducing RONS also reduces DNA damage in irradiated cells and bystander cells, including genomic instability observed at later time points after IR. Free radical and NADPH oxidase inhibitors reduce the effect of IR on DNA nucleotide damage, double strand breaks, chromosomal damage, and mutations in isolated DNA and cultured cells (Winyard, Faux et al. 1992; Douki, Ravanat et al. 2006; Choi, Kang et al. 2007; Jones, Riggs et al. 2007; Ameziane-El-Hassani, Boufraquech et al. 2010; Ameziane-El-Hassani, Talbot et al. 2015; Manna, Das et al. 2015) and on nucleotide damage and double strand breaks in vivo (Pazhanisamy, Li et al. 2011; Ozyurt, Cevik et al. 2014). RONS reduction after ionizing radiation also reduces genomic instability in animals and in cloned cell lines (Dayal, Martin et al. 2008; Dayal, Martin et al. 2009; Pazhanisamy, Li et al. 2011; Bensimon, Biard et al. 2016). RONS are similarly implicated in IR effects in bystander cells. Antioxidants (including a nitric oxide scavenger) and oxidase inhibitors added before or after radiation reduce micronuclei and gamma-H2AX formation in bystander cells (Azzam, De Toledo et al. 2002; Yang, Asaad et al. 2005; Yang, Anzenberg et al. 2007). Antioxidant activity also reduces the inflammatory response to IR in animals and cultured skin cells (Berruyer, Martin et al. 2004; Das, Manna et al. 2014; Ozyurt, Cevik et al. 2014; Haddadi, Rezaeyan et al. 2017; Zhang, Zhu et al. 2017).

RONS are sufficient to trigger subsequent key events in this AOP. Extracellularly applied or intracellularly generated ROS (which also facilitates the formation of RNS) are capable of creating DNA damage in vitro including base damage, single and double strand breaks, and chromosomal damage (Oya, Yamamoto et al. 1986; Dahm-Daphi, Sass et al. 2000; Nakamura, Purvis et al. 2003; Gradzka and Iwanenko 2005; Ismail, Nystrom et al. 2005; Driessens, Versteyhe et al. 2009; Berdelle, Nikolova et al. 2011; Lorat, Brunner et al. 2015; Stanicka, Russell et al. 2015) and mutations (Sandhu and Birnboim 1997; Ameziane-El-Hassani, Boufraquech et al. 2010; Seager, Shah et al. 2012; Sharma, Collins et al. 2016). Similarly, decreased antioxidant activity and higher RONS is observed in cells with genomic instability (Dayal, Martin et al. 2008; Buonanno, de Toledo et al. 2011). To our knowledge, no experiments have tested whether elevating intracellular RONS alone in one group of cells can cause bystander effects in another.

### **Evidence in Mammary Gland**

The increase of RONS following IR has been shown in a wide range of cells, in vivo and in vitro, including epithelial cells, and in two studies in mammary epithelial cells (Jones, Riggs et al. 2007; Bensimon, Biard et al. 2016). Both mammary cell studies also show increased RONS and DNA damage over a day after IR in vitro and link DNA damage with elevated RONS.

### **Uncertainties or Inconsistencies**

The mitigating effects of antioxidants on IR-generated DNA damage support the essentiality of RONS in producing DNA damage and mutations. However, externally applied RONS is less effective than IR at generating double strand breaks and mutations (Sandhu and Birnboim 1997; Dahm-Daphi, Sass et al. 2000; Gradzka and Iwanenko 2005; Ismail, Nystrom et al. 2005). One possible explanation for this discrepancy is that IR may elicit a higher concentration of localized RONS than can be achieved with external application of H<sub>2</sub>O<sub>2</sub>. IR deposits energy and oxidizes molecules within a relatively small area over a rapid timescale potentially permitting a very high local concentration which could precede or overwhelm local buffering capacity. In contrast, extracellularly applied H<sub>2</sub>O<sub>2</sub> would interact with many antioxidants and other molecules on its way to the nucleus, where the concentration would slowly reach a lower steady state.

As expected for RONS as a key event for DNA damage from IR, DNA damage from IR and H<sub>2</sub>O<sub>2</sub> are additive in cells (Dahm-Daphi, Sass et al. 2000; Driessens, Versteijhe et al. 2009). Unexpectedly however, inhibiting glutathione (which should increase or sustain the effects of RONS), increases DNA damage from H<sub>2</sub>O<sub>2</sub> but not IR. This lack of effect of glutathione inhibition on IR conflicts with multiple studies showing decreased DNA damage from IR with anti-oxidants. One possible explanation is that the concentration or reaction rate of glutathione is already inadequate to buffer the elevated RONS from IR, so further inhibition has no measurable effect.

### **KE/AO: Increase in DNA damage**

***Essentiality is High.*** *The essentiality of this MIE to cancer is generally accepted. Supporting evidence comes from application of mutagenic agents: the increase in DNA damage precedes mutations, proliferation, and tumorigenesis. Further indirect evidence comes from evidence for MIE1, in which antioxidants that reduce DNA damage also reduce mutations and chromosomal damage. Finally, mutations in DNA repair genes increase the risk of tumors.*

Increases or decreases in DNA damage are associated with corresponding increases or decreases in downstream key events in the pathway to breast cancer. An external agent (ionizing radiation) that increases DNA damage (Padula, Ponzinibbio et al. 2016) also causes chromosomal damage and increased mutations (Sandhu and Birnboim 1997; Jones, Riggs et al. 2007; Denissova, Nasello et al. 2012; Fibach and Rachmilewitz 2015), transforms cells (Yang, Craise et al. 1992; Yang, Georgy et al. 1997; Unger, Wienberg et al. 2010), and causes tumors (Poirier and Beland 1994; Little 2009). Polymorphisms or mutations in DNA repair genes affect tumor formation after ionizing radiation in animals (Yu, Okayasu et al. 2001; Umesako, Fujisawa et al. 2005) and in people (Millikan, Player et al. 2005; Andrieu, Easton et al. 2006; Broeks, Braaf et al. 2007; Bernstein, Haile et al. 2010; Brooks, Teraoka et al. 2012; Pijpe, Andrieu et al. 2012; Bernstein, Thomas et al. 2013). Consistent with these findings, antioxidants that

reduce DNA damage from stressors like IR also reduce chromosomal aberrations and micronuclei arising from those stressors (Azzam, De Toledo et al. 2002; Choi, Kang et al. 2007; Jones, Riggs et al. 2007).

### **Evidence in mammary gland**

The majority of research on the effects of IR on DNA damage has been performed in tissues other than mammary gland, but several studies suggest that effects in the mammary gland (and its consequences) would be consistent with other tissues. Oxidative DNA damage in mammary cells increases immediately after exposure to IR (Haegele, Wolfe et al. 1998), and double stranded breaks, micronuclei, and (later) chromosomal aberrations appear two hours to six days after IR exposure in vivo and in vitro (Soler, Pampalona et al. 2009; Snijders, Marchetti et al. 2012; Hernandez, Terradas et al. 2013). Genomic instability was reported in genetically susceptible cells after a month of higher doses of IR (4 doses of 1.8 Gy but not 0.75 Gy) (Snijders, Marchetti et al. 2012).

### **KE/AO: Increase in mutation**

***Essentiality is High.** The contribution of this MIE to cancer is generally accepted. Evidence comes from knock-out and knock-in experiments, which find that mutations in certain key genes increase tumorigenesis. However, an ongoing debate pits the singular importance of mutations against a significant role for the tissue microenvironment. This debate is fueled by transplant studies that show the importance of tissue environment for tumorigenesis and suggesting that mutations may not be sufficient for tumorigenesis.*

Mutations increase transformation in culture (Wang, Su et al. 2011) and proliferation and tumors in mice (Radice, Ferreira-Cornwell et al. 1997; Umesako, Fujisawa et al. 2005; de Ostrovich, Lambertz et al. 2008; Podsypanina, Politi et al. 2008; Francis, Bergsied et al. 2009; Gustin, Karakas et al. 2009; Francis, Chakrabarti et al. 2011; Tao, Xiang et al. 2017). Restoring function in mutated genes regresses tumors in animals (Martins, Brown-Swigart et al. 2006; Podsypanina, Politi et al. 2008). Mutations are common in tumors (Haag, Hsu et al. 1996; Greenman, Stephens et al. 2007; Stratton, Campbell et al. 2009; CGAN (Cancer Genome Atlas Network) 2012; Vandin, Upfal et al. 2012; Garraway and Lander 2013; Vogelstein, Papadopoulos et al. 2013; Yang, Killian et al. 2015) and tumors are largely clonal, suggesting that individual mutations offer the tumor evolutionary advantages (Wang, Waters et al. 2014; Yates, Gerstung et al. 2015; Begg, Ostrovnaya et al. 2016).

### **Evidence in mammary gland**

Many of the studies in support of the proliferative and tumorigenic role of mutations are in mammary gland or breast cancers. Further support for including DNA damage and mutation in the mechanistic pathway linking ionizing radiation with breast cancer comes from the observation that variants in DNA repair genes increase the risk of mammary tumors in animals after IR (Yu, Okayasu et al. 2001; Umesako, Fujisawa et al. 2005) and increase breast cancer after IR (Millikan, Player et al. 2005; Andrieu, Easton et al. 2006; Broeks, Braaf et al. 2007; Bernstein, Haile et al. 2010; Brooks, Teraoka et al. 2012; Pijpe, Andrieu et al. 2012; Bernstein, Thomas et al. 2013). BRCA is perhaps the best known DNA repair gene linked with breast cancer risk, and several studies of these studies have suggested a link between BRCA mutation status and increased susceptibility to breast cancer following ionizing radiation, particularly in women exposed at younger ages (Pijpe, Andrieu et al. 2012).



### **Uncertainties or Inconsistencies**

Mutations alone are not sufficient or even essential for tumor growth in mammary glands. Mammary tumor incidence following ionizing radiation varies significantly by sex and depends on the presence of ovarian hormones (Cronkite, Shellabarger et al. 1960; Segaloff and Maxfield 1971; Shellabarger, Stone et al. 1976; Holtzman, Stone et al. 1979; Holtzman, Stone et al. 1981; Welsch, Goodrich-Smith et al. 1981; Clifton, Yasukawa-Barnes et al. 1985; Solleveld, van Zwieten et al. 1986; Broerse, Hennen et al. 1987; Lemon, Kumar et al. 1989; Inano, Suzuki et al. 1991; Inano, Suzuki et al. 1996; Peterson, Servinsky et al. 2005). Tumor growth from transplanted tumor cells varies with age, parity, and lactational status (Maffini, Calabro et al. 2005; McDaniel, Rumer et al. 2006), and stroma treated with carcinogens or IR supports tumors from pre-malignant epithelial cells (Barcellos-Hoff and Ravani 2000; Maffini, Soto et al. 2004; Nguyen, Oketch-Rabah et al. 2011). While the mechanisms underlying these contextual factors have not been clearly identified, the proliferative effect of hormones on the mammary gland may serve to amplify damaged and mutated cells and modify the stromal environment to increase the likelihood of cellular transformation. Inflammatory responses including the release of cytokines and the activation of inflammatory and anti-inflammatory signaling pathways likely also amplify the effects of DNA damage and mutations through many of the same mechanisms.

### **KE: Increase in proliferation**

*Essentiality is High.* Cellular proliferation is a key characteristic of cancer cells (Hanahan and Weinberg 2011) and can lead to hyperplasia, an intermediate phase in the development of tumorigenesis.

*Proliferation also increases the number of cells with mutations, which can further promote proliferation and/or changes to the local microenvironment.*

### **Evidence in mammary gland**

Multiple studies show that mammary gland proliferates after IR or chemical carcinogen treatment prior to the appearance of mammary tumors. Epithelial cells proliferate following IR in vitro (Mukhopadhyay, Costes et al. 2010) and in vivo (Nguyen, Oketch-Rabah et al. 2011; Snijders, Marchetti et al. 2012; Suman, Johnson et al. 2012; Tang, Fernandez-Garcia et al. 2014). Increasing proliferation leads to hyperplasia (Korkaya, Paulson et al. 2009). Proliferative nodules and hyperplasia appear in mammary terminal end bud, alveolae, and ducts of rats and mice after exposure to chemical carcinogens (Beuving, Bern et al. 1967; Beuving, Faulkin et al. 1967; Russo, Saby et al. 1977; Purnell 1980) and ionizing radiation (Faulkin, Shellabarger et al. 1967; Ullrich and Preston 1991; Imaoka, Nishimura et al. 2006). Proliferating foci precede the development of tumors (Haslam and Bern 1977; Purnell 1980) and form tumors more effectively than non-proliferating tissue (Deome, Faulkin et al. 1959; Beuving 1968; Rivera, Hill et al. 1981).

Supporting the essentiality of these proliferative processes to tumorigenesis, ACI rats that exhibit no mammary proliferation or hyperplasia following IR are resistant to tumors following IR (Kutanzi, Koturbash et al. 2010). Interventions reducing proliferation in susceptible PyVT and BALB/c mice also reduce mammary tumors (Luo, Fan et al. 2009; Connelly, Barham et al. 2011; Tang, Fernandez-Garcia et al. 2014).

## Uncertainties or Inconsistencies

Some studies report carcinogenesis in the absence of hyperplasia (Sinha and Dao 1974) and others do not find increased tumorigenesis from transplanted hyperplasia (Beuving, Bern et al. 1967; Haslam and Bern 1977; Sinha and Dao 1977). The failure of some proliferative foci to form tumors and the regression of some tumors when formed (Haslam and Bern 1977; Purnell 1980; Korkola and Archer 1999) suggests that proliferation may not be sufficient for sustained tumorigenesis in mammary gland.

## KE/AO: Increase, ductal hyperplasia

**Essentiality is High.** Evidence comes from transplant experiments showing that non-proliferating tissue is less tumorigenic than proliferating lesions, and from interventions that reduce both proliferation and tumors. Further evidence comes from animals that are resistant to both mammary gland proliferation and tumors from ionizing radiation. Uncertainty arises from conflicting evidence on the tumorigenicity of hyperplasia, the absence of hyperplasia observed before some tumors, and spontaneous regression of tumors.

Hyperplasia signals the presence of excess proliferation (a key characteristic of cancer cells (Hanahan and Weinberg 2011)) and represents an intermediate phase in the development of tumorigenesis.

## Evidence in mammary gland

Multiple studies show that mammary gland proliferates after IR or chemical carcinogen treatment prior to the appearance of mammary tumors. Proliferative nodules and hyperplasia appear in mammary terminal end bud, alveolae, and ducts of rats and mice after exposure to chemical carcinogens (Beuving, Bern et al. 1967; Beuving, Faulkin et al. 1967; Russo, Saby et al. 1977; Purnell 1980) and ionizing radiation (Faulkin, Shellabarger et al. 1967; Ullrich and Preston 1991; Imaoka, Nishimura et al. 2006). Proliferating foci precede the development of tumors (Haslam and Bern 1977; Purnell 1980) and form tumors more effectively than non-proliferating tissue (Deome, Faulkin et al. 1959; Beuving 1968; Rivera, Hill et al. 1981). Adenocarcinomas in rats appear to preferentially form from terminal end bud hyperplasia (Haslam and Bern 1977; Russo, Saby et al. 1977; Purnell 1980), similar to the origin of many breast cancers for humans and for some mice after IR (Medina and Thompson 2000).

Supporting the essentiality of these proliferative processes to tumorigenesis, ACI rats that exhibit no mammary proliferation or hyperplasia following IR are resistant to tumors following IR (Kutanzi, Koturbash et al. 2010). Interventions reducing proliferation in susceptible PyVT and BALB/c mice also reduce mammary tumors (Luo, Fan et al. 2009; Connelly, Barham et al. 2011).

## Uncertainties or Inconsistencies

Some studies report carcinogenesis in the absence of hyperplasia (Sinha and Dao 1974) and others do not find increased tumorigenesis from transplanted hyperplasia (Beuving, Bern et al. 1967; Haslam and Bern 1977; Sinha and Dao 1977). The failure of some lesions to form tumors and the regression of some tumors when formed (Haslam and Bern 1977; Purnell 1980; Korkola and Archer 1999) suggests that hyperplasia alone may not be sufficient for sustained tumorigenesis in mammary gland.

## **KEs: Tissue resident cell activation, Increase, Pro-inflammatory mediators, Leukocyte Recruitment/Activation**

*Essentiality is Moderate.* These key events were reviewed as a group. Evidence comes from using genetic modifications, antibodies, and antioxidants to reduce inflammatory and anti-inflammatory factors. These interventions reduce DNA damage, mutations, and mechanisms contributing to tumorigenesis and invasion. Uncertainty arises from conflicting effects in different genetic backgrounds and in different organs.

Tumors and tumor cells exhibit features of inflammation, and inflammation is generally understood to promote transformation and tumor progression by supporting multiple hallmarks of cancer including oxidative activity and DNA damage, survival and proliferation, angiogenesis, and invasion and metastasis (Iliopoulos, Hirsch et al. 2009; Hanahan and Weinberg 2011; Esquivel-Velazquez, Ostoa-Saloma et al. 2015).

Many of these cancer promoting effects of inflammation can be seen following exposure to ionizing radiation (Bisht, Bradbury et al. 2003; Elahi, Suraweera et al. 2009; Nguyen, Oketch-Rabah et al. 2011; Bouchard, Bouvette et al. 2013; Nguyen, Fredlund et al. 2013; Illa-Bochaca, Ouyang et al. 2014). Inflammatory pathways are commonly activated in breast and mammary cancers following IR (Nguyen, Oketch-Rabah et al. 2011; Nguyen, Fredlund et al. 2013; Illa-Bochaca, Ouyang et al. 2014). Polymorphisms in inflammation genes are associated with breast cancer risk from IR in radiation technologists (Schonfeld, Bhatti et al. 2010) and with susceptibility to intestinal adenoma following IR in mice (Elahi, Suraweera et al. 2009). Cytokines TGF- $\beta$  and IL6 transform primary human mammospheres and pre-malignant mammary epithelial cell lines in vitro and make them tumorigenic in vivo (Sansone, Storci et al. 2007; Iliopoulos, Hirsch et al. 2009; Nguyen, Oketch-Rabah et al. 2011), and inflammation related factors COX2 and TGF- $\beta$  are required for the full effect of IR on DNA damage and transformation in vitro and mammary tumor growth and invasion in vivo (Bisht, Bradbury et al. 2003; Nguyen, Oketch-Rabah et al. 2011).

One mechanism of cancer promotion involves oxidative activity and DNA damage: inflammation in response to IR increases oxidative activity in a positive feedback loop leading to increased DNA lesions and mutations. Oxidative activity mediates the increase in inflammatory markers (TNF- $\alpha$  and neutrophil markers) in bladder and kidney (Ozyurt, Cevik et al. 2014), and TNF- $\alpha$  and neutrophils increase oxidative activity (Jackson, Gajewski et al. 1989; Stevens, Bucurenci et al. 1992; Zhang, Zhu et al. 2017). Inflammatory activity from neutrophils and TNF- $\alpha$  and NF-kB-dependent COX2 and NO damage DNA and increase mutations by increasing oxidative activity (Jackson, Gajewski et al. 1989; Zhou, Ivanov et al. 2005). The mutations can be reduced by blocking the inflammatory factors NF-kB, COX2, TNF- $\alpha$ , or nitric oxide, or with antioxidants (Jackson, Gajewski et al. 1989; Zhou, Ivanov et al. 2005; Zhou, Ivanov et al. 2008; Zhang, Zhu et al. 2017). Antibodies to TNF- $\alpha$  or TGF- $\beta$  reduce DNA damage in bone marrow (Burr, Robinson et al. 2010; Rastogi, Coates et al. 2012) and CHO cells (Han, Chen et al. 2010). Inhibiting TNF- $\alpha$  also reduces genomic instability in directly irradiated (but not bystander) lymphocytes (Moore, Marsden

et al. 2005) and in bone marrow of CBA/Ca mice susceptible to IR-induced leukemia but not resistant C57BL/6 mice (Lorimore, Mukherjee et al. 2011). Inhibiting inflammatory factors NF- $\kappa$ B or iNOS reduces IR-induced bystander mutations in lung fibroblasts (Zhou, Ivanov et al. 2008).

Inflammatory pathways activated by IR are also capable of promoting tumor growth and metastasis. Exposure to IR or RONS sensitizes mammary epithelial cells to respond to TGF- $\beta$  - which is widely activated by IR (Ehrhart, Segarini et al. 1997). IR and TGF- $\beta$  signaling leads to an epithelial to mesenchymal (EMT)-like transition, which disrupts the expression and distribution of cell adhesion molecules and multicellular organization and promotes invasion (Park, Henshall-Powell et al. 2003; Andarawewa, Erickson et al. 2007; Andarawewa, Costes et al. 2011; Iizuka, Sasatani et al. 2017). This mechanism resembles wound healing (Koh and DiPietro 2011; Perez, Vago et al. 2014; Landen, Li et al. 2016), but also resembles malignancy - invasive breast cancer cell lines overexpress TGF- $\beta$  and respond to TGF- $\beta$  with increased invasion (Kim, Kim et al. 2004; Gomes, Terra et al. 2012).

The response to TGF- $\beta$  likely involves an increase in senescence in fibroblasts. IR-induced senescence releases a suite of signaling molecules including pro-inflammatory IL6 and proteases (MMPs) (Tsai, Chuang et al. 2005; Liakou, Mavrogonatou et al. 2016; Perrott, Wiley et al. 2017). The signaling molecules released by IR-senescent fibroblasts promote the disorganized tissue structure of mammary epithelial cells and the growth, EMT, and invasion of breast cancer epithelial cells or mutant epithelial cells (Tsai, Chuang et al. 2005; Liakou, Mavrogonatou et al. 2016; Perrott, Wiley et al. 2017) and 3D mammary tumor models (Sourisseau, Harrington et al. 2011). The induction of senescence in fibroblasts by IR requires TGF- $\beta$  (Liakou, Mavrogonatou et al. 2016), and the release of the pro-invasive signaling molecules involves an IL-1 dependent activation of NF- $\kappa$ B (Perrott, Wiley et al. 2017). Senescence following IR also selects for a post-senescent variant of epithelial cell that is more conducive to tumorigenesis (Mukhopadhyay, Costes et al. 2010).

IL6 may play an important function in the carcinogenic response to IR. IL6 is expressed in mouse mammary gland after IR (Bouchard, Bouvette et al. 2013). IL6 is produced by IR-senescent fibroblasts, but may also be expressed by epithelial cells after IR since primary human mammospheres and pre-malignant mammary epithelial cell lines respond to IL6 with increased IL6 expression (Sansone, Storci et al. 2007; Iliopoulos, Hirsch et al. 2009). IL6 promotes the mobility and tumorigenesis of normal and breast cancer epithelial cells (Sansone, Storci et al. 2007; Sasser, Sullivan et al. 2007; Studebaker, Storci et al. 2008; Iliopoulos, Hirsch et al. 2009; Iliopoulos, Jaeger et al. 2010). This activity depends on transcription factor NOTCH3, which supports the renewal of stem-like cell populations (Sansone, Storci et al. 2007), and NOTCH has been implicated in multiple other studies in the proliferative response to IR in mammary epithelia (Nguyen, Oketch-Rabah et al. 2011; Marusyk, Tabassum et al. 2014; Tang, Fernandez-Garcia et al. 2014). The NF- $\kappa$ B/IL6/STAT3 signaling pathway generates cancer stem cells in multiple types of breast cancer cells (Iliopoulos, Hirsch et al. 2009; Iliopoulos, Jaeger et al. 2010; Iliopoulos, Hirsch et al. 2011) and is also implicated in colon and other cancers (Iliopoulos, Jaeger et al. 2010). The inflammation related transcription factor NF- $\kappa$ B also contributes to mammary tumorigenesis and metastasis in PyVt mice, in which mammary tumors are induced by expression of an MMTV-driven oncogene (Connelly, Barham et al. 2011). Interestingly, breast cancer fibroblasts and fibroblasts from common sites of breast cancer metastasis (bone, lung) express IL6. IL6 is required for the growth and

tumor promoting effects of these fibroblasts on ER-positive cancer cells in vitro and in vivo. ER-negative breast epithelial cells release autocrine IL6 and may therefore be less dependent on IL6 from fibroblasts, although IL6 also transforms these cells (Sasser, Sullivan et al. 2007; Studebaker, Storci et al. 2008; Iliopoulos, Hirsch et al. 2009).

Inflammation is suspected to play a role in the indirect effects of radiation, in which cells not directly targeted by radiation exhibit effects including DNA damage and RONS (Lorimore and Wright 2003; Mukherjee, Coates et al. 2014; Sprung, Ivashkevich et al. 2015). In addition to the IR-induced release of inflammatory signals that are diffusible and can trigger systemic immune responses, inflammatory factors COX2 and TGF- $\beta$  are produced in bystander cells that are not directly irradiated but are exposed to irradiated cells or media (Zhou, Ivanov et al. 2005; Zhou, Ivanov et al. 2008; Chai, Calaf et al. 2013; Chai, Lam et al. 2013; Wang, Wu et al. 2015).

Inflammatory factors TGF- $\beta$ , TNF- $\alpha$ , COX2, and NO are implicated in the RONS (Shao, Folkard et al. 2008; Zhou, Ivanov et al. 2008; Wang, Wu et al. 2015), DNA damage (Dickey, Baird et al. 2009; Han, Chen et al. 2010; Dickey, Baird et al. 2012; Chai, Calaf et al. 2013; Chai, Lam et al. 2013; Wang, Wu et al. 2015) and mutations (Zhou, Ivanov et al. 2005; Zhou, Ivanov et al. 2008) observed in bystander cells and in the appearance of genomic instability (Moore, Marsden et al. 2005; Natarajan, Gibbons et al. 2007; Lorimore, Chrystal et al. 2008; Lorimore, Mukherjee et al. 2011) after IR. Further evidence for inflammation in indirect effects of IR come from tumors arising from mammary epithelial cells transplanted into IR exposed cleared fat pads: inflammation-related genes and pathways are upregulated or enriched in the gene expression patterns of these indirectly IR-induced tumors (Nguyen, Oketch-Rabah et al. 2011; Nguyen, Fredlund et al. 2013; Illa-Bochaca, Ouyang et al. 2014).

### **Evidence in mammary gland**

Many of the studies above that link inflammatory signals with increased oxidative activity, senescence, EMT, bystander effects, genomic instability, and tumorigenesis, and metastasis use mammary tissue. Since inflammation-related signals are reported after IR in mammary gland (Barcellos-Hoff, Derynck et al. 1994; Dickey, Baird et al. 2009; Datta, Hyde et al. 2012; Snijders, Marchetti et al. 2012; Bouchard, Bouvette et al. 2013; Wang, Wu et al. 2015) inflammation likely contributes to many of the effects of IR in this tissue.

### **Uncertainties or inconsistencies**

The effects of inflammation can be both pro and anti-tumorigenic. For example, in addition to TGF- $\beta$ 's role in EMT, in mammary epithelial cells TGF- $\beta$  is essential to apoptosis of DNA damaged cells including damage following ionizing radiation (Ewan, Henshall-Powell et al. 2002), thus limiting genomic instability (Maxwell, Fleisch et al. 2008). Inflammatory factors TNF- $\alpha$  and COX2 play a similar role in bone marrow of C57BL/6 mice (Lorimore, Rastogi et al. 2013). By eliminating cells with severe DNA damage and curtailing genomic instability, apoptosis (and therefore TGF- $\beta$  or TNF- $\alpha$ ) limits the appearance of major (possibly carcinogenic) mutations following ionizing radiation. However, apoptosis (and thus TGF- $\beta$  or TNF- $\alpha$ ) can indirectly promote tumorigenesis through compensatory proliferation (Loree, Koturbash et al. 2006; Fogarty and Bergmann 2017).

Genetic background also influences the interaction between inflammation and tumorigenesis. Polymorphisms in inflammatory genes influence susceptibility to intestinal cancer following IR (Elahi, Suraweera et al. 2009). In the SPRET outbred mouse higher baseline TGF- $\beta$  during development decreases tumor incidence following lower doses of IR (0.1 Gy), possibly by reducing ductal branching and susceptibility (Zhang, Lo et al. 2015). Conversely, the BALB/c mouse susceptible to mammary tumors after IR has a lower baseline TGF- $\beta$  (and a polymorphism in a DNA damage repair-related gene). Early (4 hours) after low dose (0.075 Gy) IR BALB/c mice have suppressed immune pathways and macrophage response but increased IL6, COX2, and TGF- $\beta$  pathway activation in mammary gland compared to the tumor-resistant C57BL/6 mouse (Snijders, Marchetti et al. 2012; Bouchard, Bouvette et al. 2013). By 1 week after IR, the BALB/c mice show TGF- $\beta$  -dependent inflammation in the mammary gland, and by 1 month after IR, their mammary glands show proliferation (Nguyen, Martinez-Ruiz et al. 2011; Snijders, Marchetti et al. 2012), suggesting that TGF- $\beta$  is associated with inflammation, proliferation, and mammary tumorigenesis in these mice. Consistent with this pattern, BALB/c mice that are heterozygous for TGF- $\beta$  are more resistant to mammary tumorigenesis following IR (Nguyen, Oketch-Rabah et al. 2011). However, the BALB/c mouse also has a polymorphism in a DNA repair gene associated with IR-induced genomic instability (Yu, Okayasu et al. 2001), making it difficult to distinguish potentially overlapping mechanisms.

While inflammatory signals are associated with bystander effects including DNA damage, genomic instability, and mutation, these effects vary between organs in vivo (Chai, Calaf et al. 2013; Chai, Lam et al. 2013), by genotype (Coates, Rundle et al. 2008; Lorimore, Chrystal et al. 2008; Lorimore, Mukherjee et al. 2011), and by cell type (Chai, Calaf et al. 2013). Further research will be required to identify all the underlying factors determining differences in bystander effects, but one variable is the appearance of a protective apoptotic response to cytokines under some conditions (Lorimore, Mukherjee et al. 2011; Lorimore, Rastogi et al. 2013).

One major piece of conflicting evidence comes from a direct test of the essentiality of inflammation to IR-induced carcinogenesis. In a mouse model of lymphoma, a mutation preventing the PIDD/NEMO dependent activation of NF- $\kappa$ B blocks early IR-induced activation of NF- $\kappa$ B (4-24 h) and production of TNF- $\alpha$  (5-48 h) but not lymphoma, suggesting that activation of these inflammatory factors is not essential in this time period (Bock, Krumschnabel et al. 2013). However, this study examined only day one post-IR time points for NF- $\kappa$ B activity, and did not block production of IL6. Later activation of NF- $\kappa$ B or activation of other inflammation-related factors including IL6 and TGF- $\beta$  could therefore potentially have contributed to lymphoma.

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