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Published in:
Biochimica et biophysica acta-Reviews on cancer

DOI:
10.1016/j.bbcan.2021.188661

Publication date:
2022

BBA - Reviews on Cancer 1877 (2022) 188661

Contents lists available at ScienceDirect

BBA - Reviews on Cancer

journal homepage: www.elsevier.com/locate/bbacan

Review

Genomic instability, inflammatory signaling and response to cancer immunotherapy

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ARTICLE INFO

Keywords:
DNA damage repair
Homologous recombination
Chromosomal instability
cGAS/STING pathway
Type I interferon
Immune checkpoint inhibition
Immune evasion

ABSTRACT

Genomic and chromosomal instability are hallmarks of cancer and shape the genomic composition of cancer cells, thereby determining their behavior and response to treatment. Various genetic and epigenetic alterations in cancer have been linked to genomic instability, including DNA repair defects, oncogene-induced replication stress, and spindle assembly checkpoint malfunction. A consequence of genomic and chromosomal instability is the leakage of DNA from the nucleus into the cytoplasm, either directly or through the formation and subsequent rupture of micronuclei. Cytoplasmic DNA subsequently activates cytoplasmic DNA sensors, triggering downstream pathways, including a type I interferon response. This inflammatory signaling has pleiotropic effects, including enhanced anti-tumor immunity and potentially results in sensitization of cancer cells to immune checkpoint inhibitors. However, cancers frequently evolve mechanisms to avoid immune clearance, including suppression of inflammatory signaling. In this review, we summarize inflammatory signaling pathways induced by various sources of genomic instability, adaptation mechanisms that suppress inflammatory signaling, and implications for cancer immunotherapy.

1. Introduction

The inability to maintain the structural and numerical integrity of our genome is one of the hallmarks of cancer [1]. 'Genomic instability' can involve both structural and numerical alterations to the genome. Structural abnormalities include mutations and chromosomal rearrangements, whereas numerical abnormalities involve gain or loss of entire chromosomes, is also referred to as 'chromosomal instability' and results in aneuploidy. Genomic instability in cancer can be caused by various mechanisms, including germline or somatic defects in DNA repair [2], oncogene-induced replication stress [1], defective mitotic chromosome segregation [3], collisions between the replication and transcription machinery [4] or genotoxic anti-cancer treatment [5]. Importantly, genomic instability facilitates the acquisition of oncogenic features that allow tumors to proliferate and metastasize [6–9].

Increasing evidence shows that defects in genome maintenance make tumor cells susceptible to recognition by the immune system. Recognition by immune cells is for instance mediated through the presentation of neo-antigens caused by point mutations or genomic rearrangements [10]. Additionally, inflammatory signaling induced by cytoplasmic DNA triggers the activation of immune cells [11,12]. Consequently, one important barrier that tumor cells need to overcome during tumorigenesis is clearance by the immune system. Our understanding of how tumor cells have evolved mechanisms to escape clearance by the immune system has greatly advanced over the recent decades, including the discovery of how tumor cells control 'immune checkpoints'. Under physiological conditions, immune checkpoints limit immune cell activation, thereby maintaining immune homeostasis, and preventing autoimmunity [13]. Cancer cells frequently upregulate immune checkpoint components to reduce T cell activation [13]. To counter these effects, immune checkpoint inhibitors (ICIs) were developed, and have resulted in a breakthrough in cancer treatment [14]. These ICIs induce durable responses across tumor types, preferentially in cancers with high levels of mutational burden [15].

Paradoxically, the clinical response rates in patients with genomically unstable cancers with high expected immunogenicity, such as tumors with defects in DNA repair genes, are limited [16,17]. Therefore, a better understanding is required of how genomic instability leads to inflammatory signaling, what the consequences are of inflammatory signaling in these cancer cells and their environment, and how

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https://doi.org/10.1016/j.bbcan.2021.188661
Received 20 July 2021; Received in revised form 2 November 2021; Accepted 13 November 2021
Available online 17 November 2021

genomically unstable cancers evade anti-cancer immune responses. Insight into these processes could improve the optimal implementation of cancer immunotherapy, and could extend the benefit of immunotherapy to other cancer subtypes. In this review, we describe how cancer-associated genomic instability results in inflammatory signaling, and how this affects anti-cancer immune responses. Moreover, we summarize how these tumors adapt to escape immune clearance and discuss potential targets for combination treatment approaches to potentiate cancer immune therapy.

2. Mechanisms underlying cancer-associated genomic instability

To maintain their genomic integrity, cells depend on many processes that regulate DNA replication and repair. In addition, cells require mechanisms to secure the correct distribution of chromosomes during mitosis. Evidently, defects can occur at many different levels in these genome maintenance pathways. Indeed, genomic instability in cancer can be caused by a plethora of defects, affecting several pathways (Fig. 1).

2.1. DNA repair defects in cancer

The DNA damage response (DRR) involves a group of evolutionary conserved pathways that respond to damaged DNA. Combined, these DDR pathways preserve genomic stability. Defects in genome maintenance pathways, as observed in a variety of cancers, lead to an accumulation of genomic alterations, which facilitate the acquisition of oncogenic traits and contribute to aggressive phenotypes. Here, we describe key DNA repair pathways that are altered in cancer. In addition, we describe how DNA replication can be perturbed by oncogene overexpression, another important cancer-associated cause of genomic instability.

2.1.1. Homologous recombination (HR) defects

Repair of double-strand breaks (DSBs) can be essentially conducted by two main mechanisms: non-homologous end joining (NHEJ) and homologous recombination (HR). HR can only be used to repair DSBs during S and G2 phase of the cell cycle, as it involves the sister chromatid as a template for repair [18]. For this reason, HR is a more accurate DSB repair mechanism when compared to NHEJ. Upon induction of DNA DSBs, the 5′ ends of the DSB are resected by the MRN complex in conjunction with CtIP, DNA2 and EXO1 nucleases, followed by binding of RPA to the ssDNA tract [18,19]. The decision to engage in 5′ end resection and commit to HR is largely controlled by CDK kinase activity, and thereby linked to cell cycle status [20]. BRCA1 facilitates the recruitment of HR repair components PALB2 and BRCA2. Subsequently, BRCA2 promotes the displacement of RPA by the RAD51 recombinase, which forms the RAD51 nucleoprotein filament [21]. The RAD51 filament performs the search for homologous DNA sequences on the sister chromatid, leading to joint DNA molecules called D-loops [22]. Then, RAD51 is removed to allow for DNA synthesis. After DNA synthesis, the newly synthesized DNA can be ligated to the original DNA strand (SDSA). Alternatively, the elongation of the D-loop through DNA

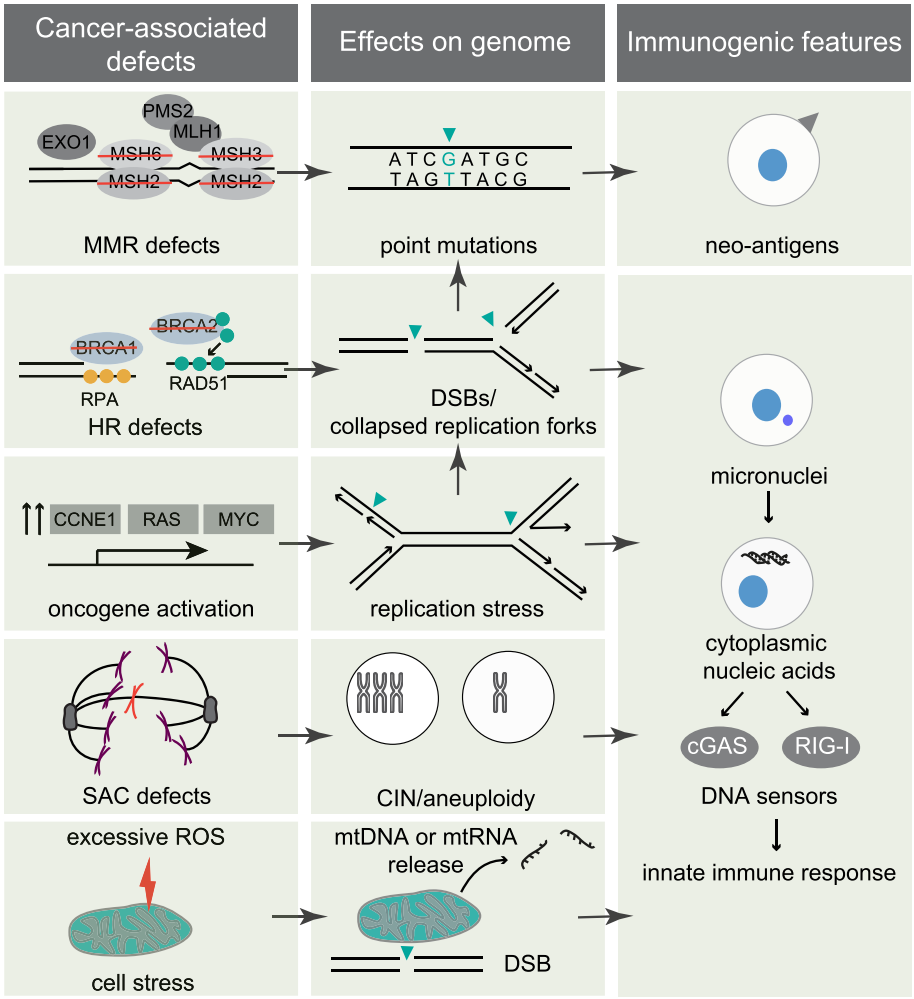

Fig. 1. Mechanisms of inflammatory signaling induced by genomic instability MMR defects lead to point mutations, resulting in neo-antigens. HR defects, SAC defects and oncogene overexpression lead to genomic instability and subsequent formation of micronuclei. Rupture of micronuclei releases DNA to the cytoplasm and activates DNA sensors. Also, cytoplasmic mitochondrial DNA or RNA results in activation of DNA and RNA sensors. Both neo-antigens and cytoplasmic DNA and RNA trigger immune responses. MMR: mismatch repair; HR: homologous recombination; DSB: double-strand break; SAC: spindle assembly checkpoint; CIN: chromosomal instability; ROS: reactive oxygen species; mtDNA: mitochondrial DNA; mtRNA: mitochondrial RNA.

synthesis allows for capture of the second DNA end, leading to the formation of Holliday Junctions (HJs). These HJs can be 'dissolved' by the BLM/Top3/RMI1/RMI2 complex or 'resolved' by the MUS81/EME1, GEN1 and SLX1-SXL4 endonucleases to complete HR repair [23].

Besides repairing DSBs, HR components also protect stalled replication forks. Specifically, BRCA2 and BRCA1 were demonstrated to prevent nucleolytic degradation of nascent DNA at stalled replication forks by MRE11 [24,25]. The conserved C-terminal site of BRCA2, which is involved in stabilizing RAD51 filaments, is essential for fork protection, but dispensable for HR, indicating that these are separate genome maintenance pathways [24]. Of note, the Fanconi anemia (FA) component FANCD2 is also required for protection of nascent DNA at stalled replication forks [25].

Loss or reduced function of HR components leads to unrepaired DSBs, collapsed replication forks and ensuing genomic rearrangements [24–26]. In line with a role for HR in maintaining genome stability, individuals with germline *BRCA1/2* mutations have a severely enhanced risk of developing early onset breast and ovarian cancers [27].

Defective HR leads to a defined genomic landscape, characterized by extensive copy number alterations and complex genomic rearrangements [28,29]. Mechanistically, repair of DNA lesions by error-prone repair pathways and mitotic transmission of unresolved recombination intermediates in HR-defective cancer cells leads to the mutational signatures that are associated with '*BRCAness*' [30,31]. The downstream consequences of these copy number aberrancies were demonstrated to facilitate the acquisition of malignant traits that determine metastatic ability and resistance to anti-cancer agents [32,33]. Moreover, tumors with overall higher degree of somatic copy number alterations showed increased immune evasion and resistance to immunotherapy [9].

2.1.2. Mismatch repair defects

Mismatch repair (MMR) is active during and after DNA replication, and repairs incorrectly incorporated base pairs and small insertions and deletions (indels) [34]. The MMR complex consists of two major complexes. A heterodimer of the MSH2 and MSH6 proteins is involved in repair of base substitutions and mismatched loops, whereas the MSH2/MSH3 complex is required for repair of larger loop structures. [35]. Both the MSH2/MSH6 and MSH2/MSH3 dimers recruit a second heterodimer, consisting of MLH1 and PMS2 [34,36]. Subsequently, recruitment of exonuclease-1 (EXO1), which performs nucleolytic removal of the nascent strand, results in a region of single-stranded DNA (ssDNA). Upon stabilizing the ssDNA by Replication factor A (RPA), a complex of DNA polymerase Pol δ and PCNA fills the ssDNA gap, after which DNA ligase-1 catalyzes nick ligation, thereby finishing repair [37]. In addition to resolving DNA mismatches, MMR proteins have non-canonical functions in post-replicative DNA repair processes [38], and in promoting faithful homologous recombination (HR) [39].

Germline mutations in one of the MMR genes (*MLH1*, *MSH2*, *MSH3, MSH6* or *PMS2*), as observed Lynch syndrome patients, lead to accumulation of point mutations and deletion/insertions predominantly at repetitive sequences such as microsatellites [40–43]. This phenomenon is known as microsatellite instability (MSI), and involves alterations in the length of microsatellite repeats. MSI is known to be an important read-out of genomic instability and is frequently observed in colorectal cancer [44]. Interestingly, besides MMR defects, loss of DNA polymerase proofreading by DNA polymerase ε and/or σ (encoding for *POLE* and *POLD1*) also contributes to MSI, although the resulting MSI signatures are distinct [45]. As stated above, MMR proteins also have non-canonical functions in post-replicative DNA repair [38], and in promoting faithful HR [39]. Interestingly, a recent study has shown that MLH1 is rapidly recruited to DNA breaks [46]. In the absence of MLH1, EXO1, which is also involved in DNA end-resection in HR, is hyperactivated, resulting in genome instability and increased chromosomal aberrancies [46]. Invariably, tumors with MMR defects show high frequencies of mutations [47]. This feature has been correlated to rapid tumor growth and acquisition of drug resistance, but has also been linked to favorable responses to immune-checkpoint inhibitors [47].

2.1.3. Oncogene-induced replication stress

Replication stress (RS) is generically defined as the process of slowing of stalling of replication forks, and drives genome instability in cancer cells predominantly at difficult-to-replicate genomic loci, such as common fragile sites (CFSs) [48]. A major cause of replication stress in cancer cells is oncogene expression, which induces DNA damage in early stages of cancer development [49,50]. Oncogene-induced RS has been linked to various genomic aberrancies, including chromosome mis-segregration, DSBs and degradation of nascent DNA at stalled forks [51–54]. Several possible underlying mechanisms have been described that link oncogene expression to perturbed replication [55–57]. One of these mechanisms involves the depletion of the nucleotide pool. Indeed, overexpression of cyclin E or viral oncogenes was associated with nucleotide shortage, likely due to uncoordinated firing of replication origins [50,55]. In parallel, the aberrant origin firing upon overexpression of the *CCNE1* or *MYC* oncogenes also occurs at intragenic regions, and leads to collisions between the transcription and replication machineries [55,56]. Interestingly, cells with oncogene-induced replication stress often show mitotic DNA synthesis (MiDAS), pointing towards under-replicated DNA at the time of mitotic entry. Of note, MiDAS in oncogene-overexpressing cells preferentially occurred in transcribed, origin-poor genetic regions, suggesting that analysis of MiDAS activity might help to identify cancers suffering from replication stress [58]. Also in clinical samples, oncogene expression has been linked to high levels of genomic instability, with defined mutational signatures. Amplification of *CCNE1*, for instance, has been associated with tandem duplications [59]. Combined, oncogene-induced replication stress is increasingly recognized as an important cause of genomic instability.

2.2. Chromosomal instability (CIN)

The spindle assembly checkpoint (SAC) prevents premature chromosome segregation during pro-metaphase of mitosis [3]. Mechanistically, unattached kinetochores catalyze the formation of the mitotic checkpoint complex (MCC), which inhibits the anaphase-promoting complex/cyclosome (APC/C), and maintains high levels of mitotic CDK1/Cyclin B activity [60]. When the kinetochores of all the chromosomes have attached to the mitotic spindle and are aligned in metaphase, the APC/C is activated to mediate degradation of securin and cyclin B1 [60]. Degradation of securin releases separase and opens the cohesin ring structure, which separates sister chromatids and initiates anaphase [60]. Conversely, a defective SAC, for instance through loss of the *APC* tumor suppressor gene, causes chromosome segregation errors and ultimately leads to numerical chromosomal abnormalities (i.e., aneuploidy) [61]. Whereas severe CIN often results in cell death, recent findings revealed that some tumors can survive ongoing CIN, which leads to abnormal chromosome numbers and tumor cell heterogeneity [62]. Consequently, CIN is often associated with drug resistance and poor prognosis [63].

Beyond numerical aberrancies, chromosomal instability often leads to structural genome defects. Mis-segregated chromosomes are frequently damaged during cytokinesis, triggering a DNA damage response involving ATM, Chk2 and p53 [64]. As a consequence of the DSBs at mis-segregating chromosomes during mitosis, unbalanced translocations in the daughter cells can arise [64,65]. Taken together, CIN gives rise to whole chromosome aneuploidies and goes along with structural alterations to the genome.

A separate cause of chromosomal instability is telomere dysfunction.

When telomeres reach a critically short length, chromosome ends activate a DNA damage response, and initiate a state of senescence or are cleared through autophagic cell death [66,67]. In cells lacking proper cell cycle control, for instance due to *TP53* or *RB1* mutations, cellular proliferation with dysfunctional telomeres can lead to breakage-fusion-bridge cycles, which drive genomic instability [68,69].

2.3. Mitochondrial genomic instability

Similar to nuclear DNA, the integrity of mitochondrial DNA (mtDNA) also requires maintenance, and an inability to do so has been linked to carcinogenesis [70]. Although mtDNA repair mechanisms are not as extensively studied as nuclear DNA repair, mtDNA is shown to be repaired through HR and microhomology-mediated end joining (MMEJ) [71,72]. Damage to mtDNA leads to less efficient mitochondrial function, resulting in excessive ROS production and further accumulation of damage to mtDNA, as well as damage to nuclear DNA. [73]

Upon apoptotic stimuli, the BCL2 family members BAX and BAK permeabilize the outer membrane of mitochondria, also known as 'mitochondrial outer membrane permeabilization' (MOMP). Interestingly, limited MOMP, induced by sub-lethal apoptotic stress, causes DNA damage via low-level activation of the caspase-activated DNase (CAD) [74]. In fact, a limited MOMP was shown to promote genomic instability and tumorigenesis [74]. In line with this notion, mtDNA has been reported as a mutation hotspot in various tumors [75].

3. Genomic instability, micronuclei and sensing of cytoplasmic DNA and RNA

DNA is normally strictly localized within the nucleus and mitochondria. However, in conditions of cancer-associated genomic or chromosomal instability, DNA may be released into the cytoplasm, predominantly through the formation of micronuclei, which are extranuclear DNA-containing structures [76] **(**Fig. 1**)**. Whereas micronuclei originating from defects in DNA repair typically contain acentric chromosome fragments, chromosomal instability predominantly leads to micronuclei containing whole chromosomes **(**Fig. 1**)** [76]. Of note, chromosomal instability also leads to DNA damage, and micronuclei containing acentric chromosome fragments. Most the micronuclei tend to undergo an irreversible loss of compartmentalization during interphase, due to the collapse of the micronucleus membrane [76]. Although nuclear function was preserved to some degree in intact micronuclei, this was dramatically reduced in disrupted micronuclei. Moreover, disrupted micronuclei suffer from defects in transcription and replication, and are therefore associated with massive accumulation of DNA damage [76,77]. Therefore, micronuclei are increasingly recognized as a critical source of cytoplasmic DNA. [78,79].

Besides through micronucleus rupture, DNA may also directly be released from the nucleus into the cytoplasm. For example, nascent ssDNA fragments can be released from stalled replication forks, as was demonstrated in cells lacking the replication fork protection factor SAMHD1 [51]. Also, mitochondrial DNA and RNA fragments can directly be released into the cytoplasm of the cells upon mitochondrial DNA damage **(**Fig. 1**)** [80].

Cells are equipped with various cytoplasmic sensors of DNA and RNA, including cGAS, RIG-I, IFI16, ZBP1, AIM2 and TLRs (described in more detail elsewhere [81]). These cytoplasmic nucleic acid sensors are evolved to respond to microbial pathogens, but can also be activated in response to 'self' DNA in the cytoplasm. Two of these DNA/RNA-sensing pathways have been linked to genomic instability in particular and are described in more detail below.

3.1. cGAS/STING pathway

One of the most widely recognized DNA sensors that are activated upon the presence of cytoplasmic DNA is cGAS. Mechanistically, *cyclic GMP-AMP synthase* (cGAS, encoded by the *MB21D1* gene) rapidly localizes to micronuclei when the micronucleus envelope ruptures [12]. Subsequently, cGAS catalyzes the synthesis of the second messenger 2′-3′-cyclic GMP-AMP (cGAMP) [82]. cGAMP then activates *Stimulator of Interferon Genes* (STING, encoded by the *Trans Membrane Protein 173* gene (*TMEM173*)), which in turn recruits and activates TANK-binding kinase-1 (TBK1) by a conserved PLPLRT/SD motif within the C-terminal tail of STING [83]. Subsequently, TBK1 and its homolog IκB kinase (IKK), are involved in the activation of downstream transcription factors, which activate a wide range of interferon-stimulated genes [82,84,85] **(**Fig. 2**)**. Notably, the cGAS-STING pathway connects genomic instability and the recognition of self-DNA to innate immune responses mediated by cytoplasmic DNA originating from ruptured micronuclei or directly from the nucleus [12]. For example, cell cycle progression through mitosis following DNA damage results in micronuclei, which activate the cGAS-STING pathway [86]. Taken together, recognition of cytoplasmic self-DNA by cGAS/STING has been demonstrated to be an important cell-intrinsic immune surveillance mechanism.

It is important to note that cGAS autoinduction is extensively regulated to prevent its activation in physiological situations. During mitosis, the nuclear envelope is temporarily disassembled, providing access of cytoplasmic factors to chromatin. The mitotic chromatin conformation, however, prevents the activation of a cytoplasmic DNA response [87,88]. In addition, mitotic phosphorylation of cGAS by Aurora kinase B prevents its activation, and allows for mitotic progression without triggering inflammatory signaling [88]. Conversely, cGAS was shown to promote apoptosis without triggering inflammation in situations of prolonged, aberrant mitoses [87]. Combined, these mechanisms ensure that cGAS activity is attenuated under physiological circumstances, while its activity is triggered during aberrant cell division.

3.2. RIG-I/MAVS pathway

RIG-I (*retinoic acid inducible gene-I*) is increasingly considered to be an important player in immune activation in genomic unstable cancers [89]. RIG-I is triggered upon sensing of cytoplasmic RNA, and subsequently binds to the adaptor molecule MAVS **(**Fig. 2**)** [90,91]. Similar to the cGAS/STING pathway, MAVS activates IKK and/or TBK1 upon stimulation, ultimately resulting in activation of the type I interferon (IFN) pathway, via downstream transcription factors [92]. Beyond direct activation by RNA, RIG-I can also be activated by DNA. For example, RNA polymerase III was shown to bind cytosolic DNA and induce type I interferons through the RIG-I pathway [93]. In this context, cytosolic poly(dA-dT) DNA was shown to be converted into 5′-ppp RNA, and to trigger the induction of gene expression of pro-inflammatory cytokines [93]. Conversely, the induction of pro-inflammatory cytokines was reduced in RIG-I-depleted cells upon treatment with Poly(dA:dT) [94]. Interestingly, crosstalk between the RIG-I/MAVS and cGAS/STING pathways has been described. Specifically, STING was shown to directly transmit RIG-I/MAVS-mediated signaling [95].

4. Genomic instability and inflammatory signaling

Genomic instability has been demonstrated to cause activation of immune responses. An important distinction in this context has to be made between adaptive immune responses that result from alterations in the DNA sequence versus innate immune responses in response to cytoplasmic DNA or RNA. For example, neo-antigens that arise due to point mutations in cancers with defective mismatch repair can be presented on MHC-1 molecules and trigger activation of an adaptive T-cell response with subsequent tumor cell clearance **(**Fig. 1**)** [11,96].

In contrast to mutation-driven adaptive immune responses, cancer-associated genomic instability that leads to DNA fragments was shown to trigger innate inflammatory responses via cGAS/STING signaling and

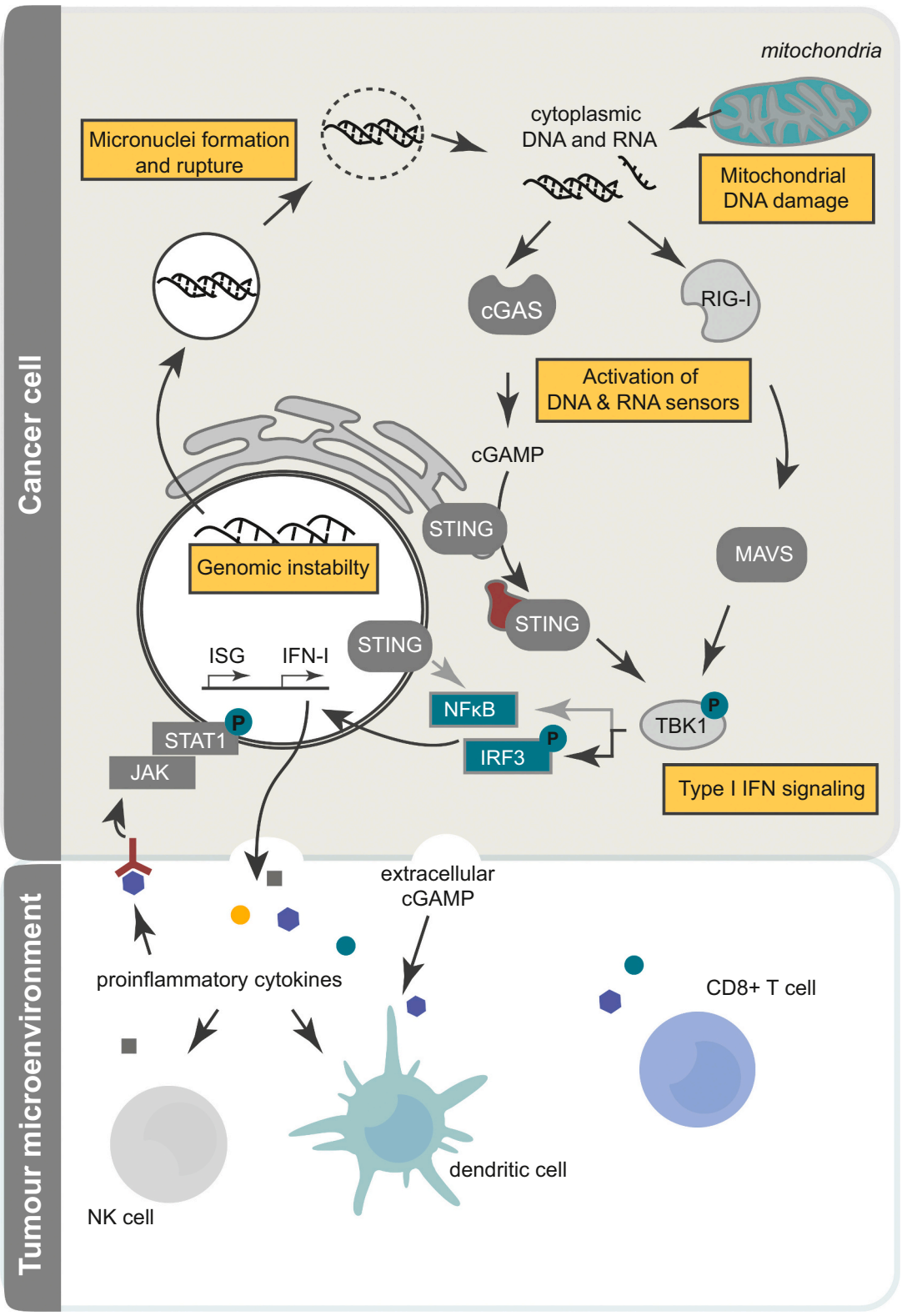

Fig. 2. Inflammatory pathways induced by genomic instability in cancer Genomic instability is associated with the formation of micronuclei. Cytoplasmic DNA and RNA released from either ruptured micronuclei or mitochondria activate DNA or RNA sensors, including cGAS and RIG-I. Upon activation of cGAS, the synthesis of 2′3’-cGAMP is catalyzed. cGAMP activates STING, which in turn recruits and activates TBK1. Subsequently, TBK1 phosphorylates IRF3, or activates NF-κB, which translocate to the nucleus. Alternatively, STING can also be activated upon nuclear DNA damage. In parallel, RIG-I binds to the adaptor molecule MAVS, which also activates IRF3. Upon phosphorylation, IRF3 induces a type I interferon response, resulting in secretion of pro-inflammatory cytokines. The inflammatory microenvironment recruits and activates $CD8^+$ T cells. Meanwhile, tumor-associated dendritic cells (DCs) and natural killer cells (NKs) are also activated to enhance immune responses.
cGAMP: cyclic GMP-AMP; IFN-I: type I interferon; ISG: interferon-stimulated genes.

related pathways [12,97–99]. Importantly, cGAS-mediated innate immune responses can also be induced by genotoxic anti-cancer treatments, including radiation therapy [86].

The inflammatory signaling and immune-modulatory effects that are induced upon cytoplasmic DNA or RNA detection are complex, and can lead to a variety of cellular outcomes [100]. Moreover, the consequences of inflammatory responses depend on the extent and duration of inflammatory signaling [98]. As a consequence, acute high levels of DNA damage that arise upon external stimuli (such as radiation or genotoxic chemotherapeutics) likely initiate different cellular responses when compared to chronic DNA damage upon endogenous sources (such as DNA repair defects). Unfortunately, many qualitative and quantitative aspects of DNA damage-induced inflammatory signaling are still unclear. Nevertheless, some common immune pathways were demonstrated to play important roles in the type I interferon response induced by genomic instability **(**Fig. 2**)**.

Downstream of the cGAS and RIG-I nucleic acid detectors, the adaptor proteins STING and MAVS are both signaling hubs that balance the activation of the IRF3 and nuclear factor-κB (NF-κB) transcription factors **(**Fig. 2**)** [101,102]. Phosphorylation of IRF3 is promoted by the recruitment and activation of TBK1 [103]. In turn, phosphorylated IRF3 transactivates the expression of many interferon-stimulated genes (ISGs), which contain interferon-stimulated response elements (ISREs) in their promoter regions [104]. Ultimately, IRF3 induces the expression and secretion of many pro-inflammatory cytokines, including IFNβ, TNFα and CCL5 [92]. In parallel, the NF-κB pathway is a well-established pathway in inflammation and tumor progression, which promotes cell survival and induces a variety of cytokines and chemokines [105]. NF-κB can be activated in both a canonical and a non-canonical way, which is extensively reviewed elsewhere [106]. How inflammatory signaling is activated upon genomic instability and how it determines cell fate is described in more detail below.

4.1. DNA repair defects and inflammatory signaling

Mutations or loss of HR genes including *BRCA1* and *BRCA2* has been shown to yield DNA lesions that originate during S phase, but remain unresolved upon mitotic entry [107,108]. As a consequence, inactivation of BRCA1 or BRCA2 leads to inflammatory responses, characterized by the presence of cGAS-positive micronuclei, and a subsequent cGAS/STING-mediated interferon response, which encompasses expression of various pro-inflammatory cytokines **(**Fig. 1**)** [97–99] and enhanced sensitivity to TNFα [97]. These observations likely reflect a generic response of cells to defective genome maintenance, as FANCD2 depletion or replication fork stalling using hydroxyurea treatment resulted in similar effects [97,99]. In a similar study, chronic inactivation of BRCA2 also resulted in cytoplasmic DNA, which triggers cell-intrinsic cGAS/STING signaling cascade, and predominantly upregulation of interferon signaling [98].

Defective HR also comes with therapeutic vulnerabilities, with *BRCA1/2* mutant tumors showing sensitivity to inhibitors of poly (ADP-ribose) polymerase (PARP) [109–111]. Interestingly, treatment of BRCA1/2-deficient cancer cells with PARP inhibitor augments the formation of micronuclei and activation of cGAS/STING signaling, and increases the interferon response [98,108,112].

Besides inducing cGAS/STING signaling, defective DDR function is also associated with signaling via RIG-I, and MAVS [89]. For instance, combined loss of p53 and ATR resulted in activation of both cGAS- and RIG-I-dependent anti-tumor immunity, underscoring the similar modes of action of these pathways [113]. Likewise, PARP depletion induces expression of a large number of ISGs and multiple proteins involved in pattern recognition pathways through the RIG-I/MAVS pathway [114]. Also, RIG-I was demonstrated to be an important inducer of immune signaling upon irradiation-induced DNA damage [89]. Specifically, RIG-I was shown to be recruited to sites of DNA damage upon irradiation, and suppress NHEJ activity [115]. These observations also highlight the close connections between DNA repair and inflammation, since DNA damage repair proteins, including MRE11 and XRCC4, have - been shown to reciprocally participate in the sensing of intracellular DNA [115,116].

Key for the induction of an innate immune response upon DNA damage appears to be the protein STING. Indeed, STING inactivation prevented pro-inflammatory signaling, and abolished olaparib-induced T-cell infiltration in HR-defective tumors [117,118]. Notably, besides being activated upon HR defects, STING also is activated upon lesions caused by mismatch repair defects. In particular, loss of the MMR protein MLH1 resulted in unrestrained DNA excision by EXO1, leading to increased ssDNA formation, DNA breaks and the activation of STING [46].

HR defective cells upregulate alternative DNA repair pathways to survive their extensive genomic instability, including microhomology-mediated end joining (MMEJ) [119]. Specifically, HR-deficient cells rely on the MMEJ factor polymerase theta (POLQ) for their viability [119]. Of note, loss of POLQ not only augments genome instability in HR-deficient tumors, but also leads to activation of the cGAS/STING pathway [120]. Similarly, mutations in ribonuclease H2, an enzyme involved in DNA replication, were also found to stimulate a cGAS/STING-mediated innate immune response [121]. Collectively, loss of critical DNA repair components, including HR factors, results in inflammatory signaling. These effects can be enhanced by PARP inhibition or other replication-perturbing agents [99].

4.2. Differential STING activation by nuclear versus cytosolic DNA

STING activation and function are strongly linked to its subcellular localization. Prior to activation, STING is localized in the cytoplasm and tethered to the endoplasmic reticulum (ER) [122]. Upon its activation, STING shows strong perinuclear localization, which can be used as a marker of STING pathway activation [123,124]. In line with these observations, perinuclear-localized STING expression was associated with a favorable prognosis in breast cancer [123]. In contrast, tumors with low levels of perinuclear-localized STING were associated with chromosomal instability [123], suggesting that these cancers have adapted to prevent STING activation. Interestingly, whereas perinuclear localization of STING is associated with activation of IRF3, nuclear STING was suggested to be involved in NF-κB activation [125,126]. Specifically, this non-canonical activation of STING was shown to be mediated via the DNA binding protein IFI16, ATM and PARP-1 [125]. These observations indicate that nuclear DNA damage and cytosolic DNA may result in differential STING activation, resulting in differential downstream effects. In fact, different DNA repair proteins might be involved in this process of fine-tuning. Although extensive data is lacking, some links were provided of STING-mediated NF-κB signaling. Specifically, PARP-1 was shown to be important for radiation-induced NF-κB [127]. Moreover, TBK1 associated with STING was shown to promote dsDNA-mediated canonical activation of NF-κB to facilitate pro-inflammatory gene transcription [128]. However, other studies reported NF-κB activation in a TBK1-independent manner upon nuclear DNA damage in myeloid cells [85,125].

Combined, these studies show that STING can activate both NF-κB and IRF3 in response to damage lesions, and that the choice between these downstream pathways is influenced by the source of DNA fragments being nuclear or cytosolic.

4.3. Chromosomal instability and inflammatory signaling

Similar to DNA damage-induced chromosome fragments that end up in the cytoplasm during mitosis, also whole chromosomes can end up in the cytoplasm when defective spindle assembly checkpoint function leads to chromosome missegregation. Again, missegregation of chromosomes triggers activation of the cGAS/STING pathway or other inflammatory signaling **(**Fig. 1**)** [129]. Indeed, chromosomal instability

was found to cause micronuclei, subsequent DNA damage and interferon signaling in acute myeloid leukemia cells [130]. Similarly, cells with chromosomal trisomies accumulate cytoplasmic dsDNA, thereby activating cGAS/STING pathway [131]. Interestingly, whole chromosome aneuploidy was shown to induce local inflammation via promoting a senescence-associated secretory phenotype (SASP), which involves various interferon-stimulated genes [132]. Notably, the short-term inflammatory response that is induced by CIN suppresses activated oncogenes [133], while the chronic inflammatory responses may lead to tissue destruction and cancer [133]. In good agreement, ongoing CIN in an *in vivo* cancer models promoted chronic inflammatory signaling through cGAS/STING, and caused aggressive metastatic tumor growth [134].

Conversely, recent findings revealed that the cGAS/STING/TBK1 pathway can prevent the proliferation of CIN cells through upregulation of the cell cycle inhibitor p21 [135]. Specifically, inactivation of STING, TBK1 or IRF3 leads to increased micronuclei formation and chromosome missegregation [135]. Likewise, STING depletion resulted in premature entry to S-phase and mitosis, and increased chromosome instability [136]. Collectively, chromosomal instability and inflammatory signaling show reciprocal interaction to determine genomic integrity and tumor evolution.

4.4. *Mitochondrial DNA damage and inflammatory signaling*

Damage to mitochondrial DNA (mtDNA) was demonstrated to also activate the cGAS/STING and RIG-I pathways [137]. Aberrant mtDNA packaging caused by deficiency of the mitochondrial transcription factor TFAM causes the release of mtDNA into the cytosol [138]. Similar to cytoplasmic DNA that originates from the nucleus, cGAS binds to cytoplasmic mtDNA and activates STING/IRF3-dependent signaling to instigate a type I interferon response (Fig. 1) [138]. In addition, DSBs in mtDNA activate BAK/BAX-mediated herniation of the mitochondrial membrane, which releases mtRNA in the cytoplasm and triggers a RIG-I/MAVS-dependent immune response [80,137]. Therefore, mtDNA breaks synergize with nuclear DNA damage in boosting a cellular immune response [80].

Interestingly, the inflammatory signaling induced by mitochondrial DNA was demonstrated to protect genome stability. In fact, damage to and release of mtDNA was shown to enhance nuclear DNA repair [139]. Also, cytoplasmic accumulation of mtRNA may be part of an intrinsic immune surveillance mechanism, allowing cells to deal with mtDSBs, including breaks caused by genotoxic agents [80]. How these opposite roles of mitochondria are regulated mechanistically remains unclear, but their balance likely determines whether mitochondria promote immune evasion or instigate a pro-inflammatory type of cell death [140].

Taken together, defects in mtDNA maintenance may be a critical cell-intrinsic source of innate immunity, while the induced inflammatory signaling may play a role in promoting genomic stability. Further studies are still needed to elucidate the relationship between mtDNA stress and innate immune response in cancer.

5. Consequences of inflammatory signaling in genomically unstable cancers and their tumor microenvironment

The inflammatory responses induced by genomic instability exert both pro- and anti-tumor activity, in a context-dependent manner. This observation not only stems from experimental models, but is also observed clinically. For instance, in patients with HR-deficient cancers, the subgroup that showed activation of cytoplasmic nucleic acid-sensing pathway genes showed a longer overall survival [141], suggesting that inflammatory signaling indeed promotes tumor clearance. In this context, tumor cells will need to evolve mechanisms to suppress immune responses, thereby facilitating immune escape. In contrast, long-term inflammation in the tumor microenvironment has been associated with enhanced proliferation, immune evasion and metastasis of cancers [134]. In this context, inflammatory signaling is beneficial for tumor cell survival, providing a competitive advantage to cancer cells that maintain inflammatory signaling. How and when the type I interferon response leads to pro- or anti- tumor effects, and how inflammatory

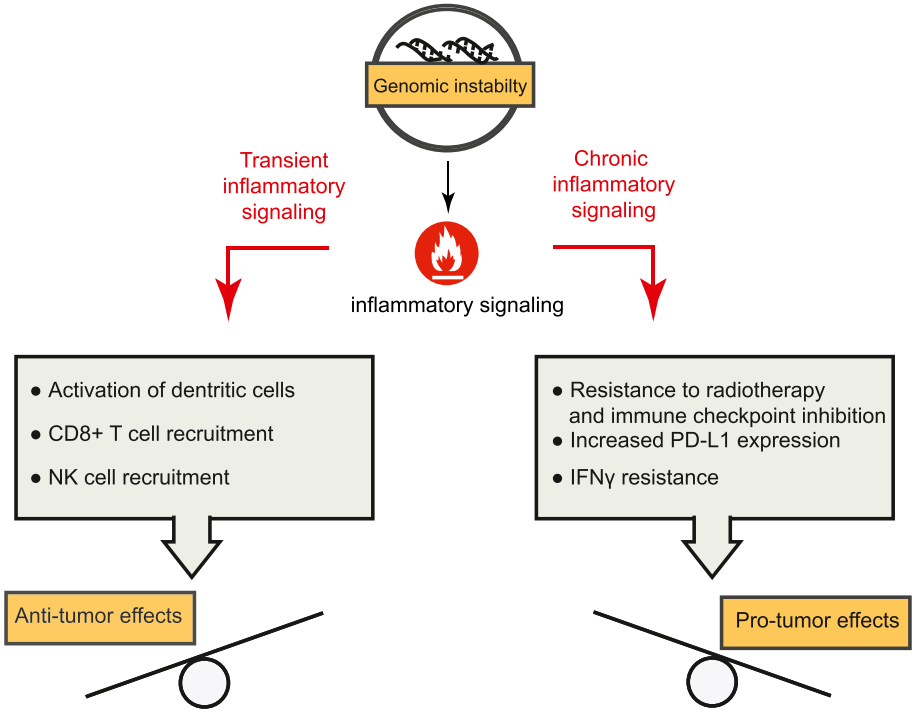

Fig. 3. The anti-tumor and pro-tumor effects of inflammatory signaling.
The transient activation of inflammatory signaling upon genomic instability promotes tumor clearance. These effects mainly result from a type I interferon response, which recruits $CD8^+$ T cells and NK cells to kill cancer cells. However, the chronic activation of inflammatory signaling may result in tumor-promoting activities.

signaling is related to the tumor microenvironment is becoming increasingly clear (Fig. 3). These mechanisms, along with adaptive mechanisms by which tumor cells evade immune clearance will be discussed below.

5.1. Anti-tumor effects of cGAS/STING signaling

The type I interferon response that is triggered by cGAS/STING or RIG-I/MAVS pathways in tumor cells, for instance due to genomic instability, can act in a paracrine fashion on neighboring tumor cells. Indeed, type I interferon can act directly on local tumor cells, where it induces the production of interferon-associated chemokines, including CXCL9, CXCL10 and CXCL11 [142]. In addition, type I interferon acts on immune cells, including tumor-infiltrating lymphocytes (TILs), in the tumor microenvironment and thereby activate anti-tumor immunity [93,134,143,144]. Additionally, type I interferon also promotes the activation of DCs and antigen cross-presentation to $CD8^+$ T cells (Fig. 3) [145]. In parallel, cGAMP production and excretion by cancer cells results in subsequent activation of STING and type I interferon signaling in immune cells, and stimulates the activation of tumor-associated DCs, NK cells and macrophages (Fig. 3) [100,146].

Through these mechanisms, type I interferon induced by DNA damaging agents or DNA repair defects may help to enhance immune clearance of cancer cells. Indeed, the recruitment of $CD8^+$ T cells that is induced by cancer cell-intrinsic activation of cGAS is associated with clinical responses to genotoxic treatments and immunotherapy [100]. Likewise, defects in HR genes *BRCA1* and *BRCA2* are strongly associated with changes in the tumor microenvironment [147,148]. However, the associated changes to the tumor microenvironment and clinical outcomes were not uniform [149]. Inactivation of BRCA1, but not BRCA2, was found to be associated with an immunoreactive tumor subtype in ovarian cancer [150]. Also, BRCA2-deficiency yielded a stronger induction of gene sets related to T cell cytotoxicity, interferon response and antigen presentation [149]. In line with these findings, *BRCA2* mutant cancers were reported to have stronger benefit from immune checkpoint inhibition treatment [151].

In addition to DNA repair defects, treatment with genotoxic drugs is also clearly associated with activation of the innate and adaptive immune system. For instance, DNA topoisomerase II inhibition leads to activation of NF-κB signaling and a STING-dependent type I interferon, boosting T cell responses [152]. Likewise, PARP inhibition in HR-deficient cells enhances cGAS/STING signaling, leads to production of type I IFNs [98,108,153–155], and promotes tumor cell clearance [117,118]. The anti-tumor effects of interferon signaling were also demonstrated in genome-wide CRISPR screens, in which inactivation of type I interferon pathway genes in tumor cells prevented clearance by immune cells in the context of immune checkpoint inhibition [156,157].

Also in the context of aneuploidy, signaling via NF-κB was intrumental in inducing anti-tumor activity, which occurred via NK cells [158]. In fact, inactivation of either canonical or non-canonical NF-κB signaling prevented NK cell-mediated killing of aneuploid cells [158]. Taken together, tumor-cell intrinsic type I interferon responses clearly promote anti-tumor immune responses (Fig. 3).

5.2. Tumor-promoting effects of cGAS/STING signaling

Despite its reported anti-tumor effects, interferon signaling may also promote immunosuppression and mediate resistance to radiotherapy or immune checkpoint inhibition (Fig. 3). Specifically, it was demonstrated that STING/ type I interferon signaling exerts immunosuppressive effect upon local ablative radiotherapy, though recruitment of myeloid-derived suppressor cells (MDSC) via the CCR2 pathway [159]. In line with this notion, a pan-cancer study showed that higher cGAS/STING signaling predicted a poor prognosis in a subset of cancer patients [160]. Chronic type I interferon signaling and its adverse effects could by induced by defective DNA repair, as for instance caused by mutations in *BRCA1/2*. A recent study showed a more active tumor microenvironment in sporadic breast and ovarian cancers when compared to hereditary cancers with germline *BRCA1/2* mutations [161]. Indeed, mutations in *BRCA1* were associated with immune-suppressive immune cells in the tumor micro-environment [162]. In BRCA1-deficient cells, prolonged or 'chronic' immune signaling was associated with higher basal expression of inflammatory chemokines CXCL10 and CXCL11 and IFI16, accompanied with a high basal STAT1 activation status [163]. Of note, a chronic high level of active STAT1 conferred resistance to the cytotoxic effects of IFNγ in BRCA1-deficient cells (Fig. 3) [163]. In line with these observations, chronic cGAS activation in *BRCA2* defective tumor cells promoted their survival when cell cycle progression was restored [98]. Inflammatory signaling in tumor cells also triggers the upregulation of immune checkpoint components. Upregulation of the T cell inhibitory protein PD-L1 was shown to be interferon-mediated and dependent on STING [99,164,165], and may contribute to STING-mediated immune escape.

In parallel, non-canonical NF-κB signaling has been demonstrated to exert pro-tumorigenic effects. Non-canonical NF-κB signaling negatively regulates IR-induced type I interferon production, through the recruitment of RelA to the type I interferon promotor, without affecting binding of IRF3 [106]. Conversely, inhibition of non-canonical NF-κB signaling was shown to promote IR-induced anti-tumor immunity [106]. These observations matched analyses in chromosomally unstable cancer cells, where non-canonical NF-κB was shown to promote cancer metastasis [134]. These observations underscore the delicate balance between pro-tumorigenic and anti-tumorigenic effects in cancer cells and their environment. Whereas signaling via the cGAS/STING pathway and its downstream components is widely associated with anti-tumor immunity, parallel pro-tumorigenic effects are clearly induced as well.

5.3. Adaptation mechanisms to escape clearance by the immune system

Transient activation of inflammatory signaling appears to promote clearance of tumor cells by the immune system. Genomically and chromosomally unstable tumors have apparently developed mechanisms to escape clearance by the immune system (Fig. 4). Such adaptive mechanisms that these tumors need to adopt to escape immune clearance during tumor development may also explain why genomically unstable cancers often poorly respond to immunotherapy, despite the fact that genomic instability is associated with increased immunogenicity [97,166,167].

A generic mechanism by which genomic instable tumors escape immune clearance is their genomic instability itself. The elevated frequency by which (fragments of) chromosomes are lost and gained accelerates the shaping of tumor cell karyotypes in which genes that promote clearance by the immune system are lost, and genes that suppress immunogenic features are gained [9,168].

A first specific mechanism of immune evasion involves the suppression of the amounts of cytoplasmic DNA. This could be achieved when the cause of genomic instability or chromosomal instability is reversed. In the case defective DNA repair, reversion mutations that restore *BRCA1/2* reading frames will reinstate HR repair [169]. Alternatively, upregulation of alternative DNA repair pathways and cell cycle checkpoints can compensate for DDR defects. For instance, HR-deficient cancers show upregulation of alternative end-joining repair [119], DNA tethering mechanisms to prevent cytoplasmic DNA [170,171], and increasingly rely on cell cycle checkpoint kinases [172]. Inactivation of these upregulated alternative repair pathways yields upregulated inflammatory responses, and is currently investigated as a therapeutic means to potentiate immune checkpoint treatments [108].

Alternatively, the amount of cytosolic DNA fragments can be suppressed by cytoplasmic nucleases. Upregulation of the cytoplasmic DNA exonuclease TREX1 prevents the activation of cGAS and thereby abrogates the immunogenicity of irradiated cancer cells [173,174]. Likewise, micronuclei can be cleared by autophagy, as was demonstrated in RNase

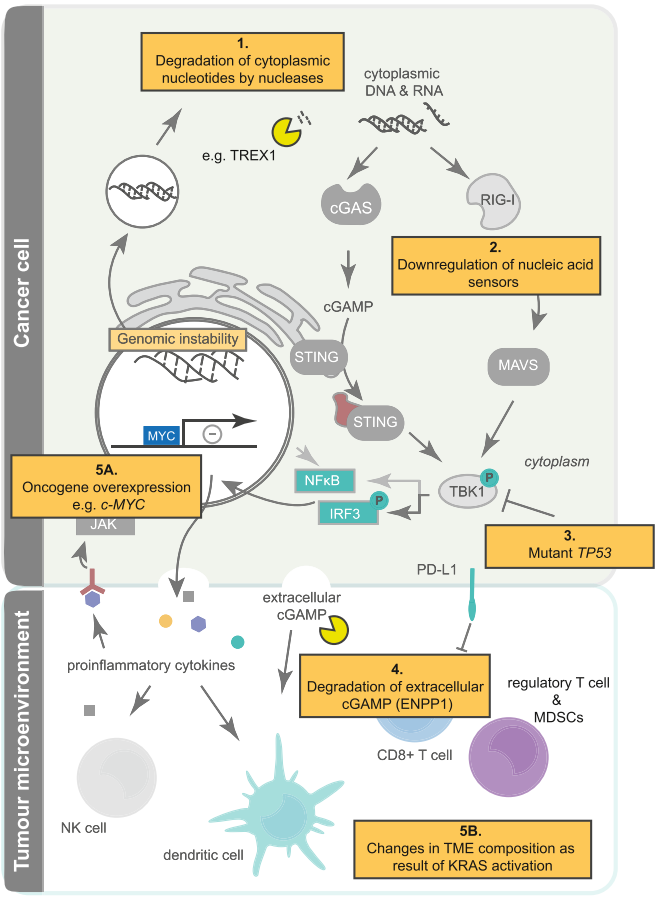

Fig. 4. Adaptation mechanisms to evade clearance by the immune system Downregulation of inflammatory signaling genes will potentially aid cancer cells to evade immune clearance. This immune evasion is mediated trough several mechanisms: 1) The degradation of cytosolic dsDNA by nucleases (e.g. TREX1). 2) Downregulation of nucleic acid sensors, including RIG-I 3) The inhibition of TBK1 by mutant *TP53*, which inhibits IRF3 activation and nuclear translocation. 4) Degradation of extracellular cGAMP by ectonucleotidase ENPP1. 5) Activation or amplification of oncogenes (e.g. *c-MYC or KRAS)* (5A) c-MYC overexpression results in downregulation of STAT1 signaling (c-MYC), resulting in decreased recruitment of T and NK cells. (5B) Overexpression of KRAS is associated with recruitment of myeloid-derived suppressor cells (MDSCs).

H2-deficient cells, which also prevents activation of downstream immune responses [175,176].

A second adaptation mechanism involves suppression of inflammatory signaling at the level of DNA sensing in the cytoplasm. Mutations in *CGAS*, *TMEM173* (encoding STING) or *RIG-I* genes have been reported in a variety of human tumors, preventing efficient cGAS/STING signaling and allowing immune escape [177]. However, these mutations are only observed in less than 1% of all tumors and rarely affect protein function [107,134]. Epigenetic silencing of the promotor regions of *CGAS* and *TMEM173* was observed across cancer subtypes, and may contribute to decreased expression of these genes [177–180]. In line with this notion, down-regulated STING expression was found in gastric cancer, and was associated with poor prognosis and defective type I interferon signaling [181]. When considering the balance between the pro-tumorigenic and anti-tumorigenic effects of STING, the observation that the majority of tumors retains functional cGAS and STING, supports the notion that other alterations in the cGAS/STING pathway are responsible for immune escape of these tumors [180,182].

A third mechanism of immune escape involves the degradation of cGAMP. Specifically, the upregulation of the ectonucleotide pyrophosphatase/phosphodiesterase ENPP1 promotes metastasis by selectively degrading extracellular cGAMP, thereby preventing the activation of STING in neighboring immune cells [183]. Interestingly, extracellular degradation of cGAMP leads to its conversion into adenosine, which promotes cancer cell migration and has immune suppressive effects. Moreover, by selectively degrading cGAMP in the extracellular environment, cancer cells retain high levels of intracellular cGAMP which may promote their metastatic progression, while suppressing the anti-tumor effects on immune cells in the tumor microenvironment [134].

A fourth adaptation mechanism that facilitates immune escape of genomically unstable cancers involves oncogene overexpression. Genomically unstable tumors, including TNBCs, were reported to have multiple recurring gene alterations affecting tumor suppressor genes and oncogenes [184]. Notably, tumors with a *BRCA1* mutation often carry amplifications in the *MYC* oncogene [185]. MYC is often referred to as a global immune regulator, and its overexpression or amplification is associated with changes in interferon responses and the tumor microenvironment in cancer (Fig. 4) [186]. For instance, MYC was described to be an important switch in the formation and deconstruction of the tumor microenvironment of pancreatic ductal adenocarcinoma (PDAC), contributing to the depletion of intra-tumoral CD3+ T cells, NK-cells and B-cells [187]. Specifically, MYC was shown to directly repress several genes belonging to the type I interferon response, including *IRF5*, *IRF7*, *STAT1* and *STAT2* [187,188]. This repression was mediated by binding of MYC to the MYC-interacting zinc finger protein MIZ1, thereby forming a transcriptional repressive complex [188]. Also, in Myc-driven lymphomas, type I interferon signaling was suppressed via transcriptional repression of STAT1/2 [189]. In addition, MYC can suppress immune responses via upregulation of immune inhibitory surface receptors PD-L1 and CD47, inhibiting T cell activation and phagocytosis

[190].

Moreover, MYC expression resulted in decreased expression of T cell markers, including CD3, CD4 and CD8, B cells and NK cells. The observed inhibition of the type I interferon pathway was mediated via cooperation of MYC and KRAS [188,191]. Of note, also mutant *KRAS* itself appeared to play an important role in immune evasion [188]. Firstly, KRAS promotes the development of regulatory T cells (T-regs), by promoting the secretion of cytokines and chemokines important for T-reg development, including IL-10 and TGF-β1 [192]. Moreover, KRAS affects the recruitment of immune-suppressive myeloid derived suppressor cells (MDSCs), which is mediated by direct targeting and downregulation of the type I interferon signaling pathway protein interferon regulatory factor 2 (IRF2) **(**Fig. 4**)** [193]. These results indicate that oncogene activation can mediate immune suppression broadly, and is not restricted to a single oncogene.

Besides oncogene activation, inactivation of tumor suppressor genes also contributes to immune evasion. Mutant *TP53* was shown to suppress cGAS/STING signaling to promote tumorigenesis **(**Fig. 4**)** [194]. Specifically, mutant *TP53* binds to TBK1, thereby preventing the formation of the trimeric complex between TBK1, STING and IRF3. Through this mechanism, mutant *TP53* prevents the activation, translocation and transcriptional activity of IRF3 [194].

In conclusion, inflammatory signaling and the ensuing immune response induced by genomic instability can be abrogated in various ways, including modulation of cytosolic dsDNA or cGAMP levels and overexpression of oncogenes and inactivation of tumor-suppressor genes (Fig. 4).

6. Genomic instability and immune checkpoint inhibitor (ICI) response

Antibodies that block the immune checkpoint components PD-1/PD-L1 and CTLA4, including pembrolizumab and nivolumab, have demonstrated efficacy across cancer subtypes [195,196]. However, some 'immunologically cold' tumors remain unresponsive to immunotherapy. The identification and development of biomarkers that can reliably identify ICI-sensitive patients is therefore critical for effectively using immune checkpoint inhibitors in clinical practice. For instance, MMR deficiency has become one of the indications of ICI treatment for patients with colorectal cancer [197]. Mutations in DNA repair genes and their consequent mutational burden in tumors cells have been coined as potential predictors of ICI response. Tumors carrying deletions and mutations in NER and HR pathways were shown to be more likely to benefit from ICI, independent of tumor mutation burden [198]. Indeed, among NSCLC patients, mutations in DNA repair genes were correlated with improved clinical outcomes in patients treated with ICI [199]. Of note, cancer-associated *POLE* mutation drives hypermutagenesis [200], whereas ICI treatment surprisingly increased proliferation of *POLE* mutant T cell lymphomas in mouse models [200].

DNA damaging agents have been shown to boost tumor response to ICI, and these combination therapies may become promising cancer treatments. For instance, cisplatin treatment upregulates PD-L1, MHC I and T-cell infiltration through cGAS-STING in ovarian cancer [201]. Combined inhibition of PD-1 and CTLA-4 combined with cisplatin significantly reduced growth of BRCA1-deficient TNBC models *in vivo* [201,202]. These results are not confined to conventional chemotherapeutics. *BRCA1/2* mutations significantly sensitize breast and ovarian cancer cells to DNA damaging agents and PARP inhibitors such as olaparib and niraparib. Interestingly, recent studies demonstrated that PARP inhibitor treatment induces cGAS/STING pathway activation and improved the efficacy of ICI [155,203]. Accordingly, increasing evidence indicates that HR-deficient tumors express higher levels of PD-L1, and may be sensitive to ICI treatment [204]. Combination of anti–PD-L1 and olaparib appears to be safe in a phase 1 study [205], and further clinical evaluation is ongoing.

Alternatively, cell cycle checkpoint inhibitors can lead to increased DNA damage and thereby potentiate ICI effects in cancer. ATM inhibition induces type I interferon through TBK1 and SRC, and sensitizes pancreatic cancers to PD-L1 blockade [206]. Accordingly, recent bioinformatics analysis predicted that patients with *ATM* mutant bladder cancer may benefited from ICIs, through the effects of ATM on the tumor immune microenvironment [207]. Likewise, ATR inhibition combined with radiotherapy and ICI showed synergistic antitumor effects mediated by cGAS/STING pathway activation in various cancer models [208–210]. Moreover, treatment with the CHK1 inhibitor prexasertib enhanced innate and adaptive immunity and improved clinical outcome in recurrent *BRCA1/2* wild-type high grade serous ovarian cancer (HGSOC) [211]. Specifically, combined CHK1 inhibition with gemcitabine treatment remarkably increased CD8+ T cells, DC and M1 macrophages in tumors [211]. In line with these effects, CHK1 inhibition also enhanced the efficacy of ICI in small cell lung cancer [212–214].

Finally, therapeutic activation of the interferon pathway is also considered to enhance ICI treatment in cancer. STING agonists were shown to upregulate PD-L1 and overcome resistance to PD-1 blockade [215]. In a preclinical model of hepatocellular carcinoma, STING agonist application significantly reduced tumor size [216]. Moreover, combined treatment with a STING agonist and ICI significantly improved the response to carboplatin in HGSOC models [142]. Likewise, a STING-activating nano vaccine was shown to boost anti-cancer immunity [217]. Besides STING agonist treatment, RIG-I agonists could also potentially enhance innate immunity against tumor cells through type I interferon activation [218]. Taken together, genomic instability induced by various factors may enhance anti-cancer immunity and response to ICI **(**Table 1**)**.

7. Conclusions and outlook

Taken together, genomic instability as well as chromosomal instability induced by DNA repair defects or SAC defects respectively lead to cytosolic DNA and trigger activation of the cGAS/STING or RIG-I/MAVS pathway, which ultimately triggers type I interferon responses in cancer cells. The ensuing acute inflammatory signaling leads to anti-cancer immunity, while inflammatory signaling may result in potential protumorigenic activity when it becomes chronic. As a consequence, DNA repair gene mutations that are associated with genomic instability may become potential predictors of ICI sensitivity. In the context of MMR defects and their ensuing mutational load, associations with favorable responses to ICI have been reported [47] (although these associations have recently been challenged [219]). For other DNA repair mutations, these links are less well described.

Clinically, therapeutic approaches to enhance inflammatory signaling have been shown to sensitize cancers to immune checkpoint blockades **(**Table 1**)**. Importantly, we should pay attention to the downsides of therapeutic induction of type I interferon signaling, since chronic type I interferon signaling in the tumor microenvironment can promote aggressive tumor behavior.

Also the mechanisms by which tumor cells evade immune clearance need further investigation. Tumors can suppress inflammatory signaling in various ways, including through oncogene activation, PD-L1 expression and cytosolic dsDNA or cGAMP degradation. These mechanisms may potentially reflect therapeutic targets for ICI potentiation.

Some questions still remain unanswered. Firstly, it is critical to have a more comprehensive understanding of how the different types of genomic instability induce innate and adaptive immunity. In this context it is of interest to explore which other DNA/RNA sensing pathways are involved beyond cGAS/STING and RIG-I/MAVS signaling. Moreover, studies are needed that investigate how acute and chronic inflammation differ at the molecular level and how this affects downstream consequences. In this context, the potentially adverse effects of chronic inflammatory signaling upon STING and RIG-I agonist treatment should be carefully investigated.

Secondly, it is incompletely clear how cancer cells avoid immune

Table 1
In vivo pre-clinical combination therapeutics in cancer.

Therapeutic	ICI	Cancer subtype	Effects	Reference
PARP inhibitor (Talazoparib)	anti-PD-L1	ovarian cancer	tumor growth inhibition and improved survival	[155]
PARP inhibitor (Niraparib)	anti-PD-1	multiple cancers	tumor growth inhibition	[203]
Cisplatin	anti-PD-1 and anti-CTLA4	*BRCA1*-mutant TNBC	tumor growth inhibition and improved survival	[202]
Cisplatin	anti-PD-L1	ovarian cancer	improved survival	[201]
ATM inhibitor	anti-PD-L1	pancreatic cancer	increased sensitivity to anti-PD-L1	[206]
ATR inhibitor and radiotherapy	anti-PD-L1	hepatocellular carcinoma; lung adenocarcinoma	stronger immunologic memory and longer antitumor immunity	[208,210]
CHK1 inhibitor and gemcitabine	anti-PD-L1	small cell lung cancer	tumor growth inhibition	[212]
CDK7 inhibitor	anti-PD-1	small cell lung cancer	improved survival	[213]
STING agonist and carboplatin	anti-PD-1	ovarian cancer	tumor growth inhibition and improved survival	[142]

evasion, while utilizing the pro-survival and pro-metastasizing traits of inflammatory signaling.

Research into the regulation of inflammatory signaling could lead to treatments that change immunologically "cold" tumors into "hot" tumors, to ultimately provide benefit of ICIs in a wider range of patients. Currently, ICI treatments of genomically unstable cancers has succeeded in pre-clinical models. However, due to the lack of consistent benefit of ICI in patients with HRD cancers, selection of patients for such trials remains of key importance.

Author contributions

Mengting Chen and Renske Linstra: writing manuscript; Marcel A.T. M. Van Vugt: writing-review and editing.

Funding statement

This work has been funded by a China Scholarship Council scholarship to M.C. (201906100046) and a European Research Council CoS grant to M.A.T.M.v.V. (682421).

Declaration of Competing Interest

The authors declare no competing interests.

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