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Emerging roles of p53 and other tumour-suppressor genes in immune regulation

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Abstract

Tumour-suppressor genes are indispensable for the maintenance of genomic integrity. Recently, several of these genes, including *p53*, *PTEN*, *RBI* and *ARF*, have been implicated in immune responses and inflammatory diseases. In particular, the p53 tumour-suppressor pathway is involved in crucial aspects of tumour immunology and in homeostatic regulation of immune responses. Other studies have identified roles for p53 in various cellular processes, including metabolism and stem cell maintenance. Here, we discuss the emerging roles of p53 and other tumour-suppressor genes in tumour immunology as well as in additional immunological settings, such as virus infection. This relatively unexplored area could yield important insights into the homeostatic control of immune cells in health and disease, and facilitate the development of more effective immunotherapies. Consequently, tumour-suppressor genes are emerging as potential guardians of immune integrity.

Introduction

Tumour-suppressor genes are activated by cellular stressors — such as DNA damage, heteroploidy or oncogenes — and govern core stress responses in cells, including cell-cycle arrest and apoptosis. These same genes are commonly mutated leading to a loss of, or reduction in, their functions; in combination with other genetic alterations, this can facilitate cellular progression to a cancerous state^{1–3}. Mutations in tumour-suppressor genes, or in components of the pathways that activate them, enable continued cell proliferation but dysregulate DNA replication and repair, ultimately resulting in genome instability and the

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inexorable selection of an ever more aggressive malignancy^{1, 3}. Host recognition of cancer cells via the immune system constitutes an independent line of defence based on the ability to identify and destroy tumour cells, which is defined as cancer immunosurveillance^{4–8}. Recently, a number of studies have indicated that the immune system has a critical role in regulating tumour development in non virally induced tumours in addition to the long established role of the immune system in controlling tumours initiated by viruses^{9, 10}. Accumulating evidence indicates that tumour-suppressor genes, and p53 (also known as TP53) in particular, may act in response to a variety of cellular homeostatic stresses ranging from ribosomal to metabolic^{11–22}. It now appears that tumour-suppressor genes, such as *p53*, retinoblastoma-associated gene 1 (*RBI*), phosphatase and tensin homologue (*PTEN*), and *ARF* (also known as *CDKN2A*), can influence immune responses as part of their tumour-suppressor activities^{23–32}. In recent years, p53 has been implicated in immune responses and inflammatory diseases^{26, 29, 30, 33–51}. Moreover, a novel connection between p53 tumour suppression and enhanced immune response has been proposed recently; p53 was shown to influence the innate immune system by modulating macrophage function via a non-cell-autonomous mechanism to suppress tumorigenesis^{52–54}. In this Review, we discuss the latest insights into the role of tumour-suppressor genes in the control of immune responses to infection, autoimmunity and cancer.

The role of p53 in immunity

The p53 tumour suppressor is a master regulatory transcription factor activated in response to various cellular stresses and governs multiple core programmes in cells, including cell-cycle arrest, apoptosis, senescence, fertility, and metabolism^{11–15, 17–21, 55}. Accumulating evidence strongly indicates that p53 also plays a broader role in immune responses and inflammation^{26, 29, 30}, as we discuss below.

Regulation of immune signalling by p53

p53 contributes to immune responses by directly transactivating key regulators of immune signalling pathways. Several p53 target genes have been identified within pathways involved in pathogen sensing, cytokine production, and inflammation^{33, 34, 37–38, 42, 47}. In addition, transcription of the p53 gene is induced by interferon α/β receptor (IFNAR) signalling^{43, 45}, suggesting a positive feedback loop involving p53-mediated enrichment of type I IFN signals to improve anti-viral immune responses (Figure 1). Upon viral infection, the major defensive strategy employed by the host immune system is the activation of the IFN-mediated immune responses. Cells that conserve wild-type p53 functions show an increase in p53-dependent apoptosis in response to viral infection in primary human cells and p53-deficient mice are more permissive to viral infection, likely due to the lack of a p53-dependent apoptotic response^{56, 57}. In addition, lack of p53 in mice impaired both innate and adaptive immunity to influenza A virus⁵⁸. It is also known that p53 directly activates expression of the immunity-responsive genes, including CC-chemokine ligand 2 (CCL2, also known as MCP1), IFN regulatory factor 5 (IRF5), IRF9, protein kinase RNA-activated (PKR), Toll-like receptor 3 (TLR3) and ISG15 that are central in initiation of antiviral responses^{42, 46, 59, 60}. In fact, many viruses, including SV40, human papillomavirus,

Kaposi's sarcoma herpesvirus and adenovirus as well as RNA viruses, such as polioviruses, have evolved mechanisms that abrogate p53-mediated responses^{61, 62}.

Genes of the TLR family have been identified as direct p53 targets in humans but not in rodents^{44, 46}. TLRs are expressed in several types of human immune cells including splenocytes, T and B lymphocytes, dendritic cells (DCs) and macrophages^{44, 46}. The TLRs are membrane glycoproteins that recognize a variety of distinct pathogen-associated molecules^{63–65}. Deregulated expression and activity of TLRs are associated with autoimmune and chronic inflammatory diseases, including systematic lupus erythematosus (SLE), inflammatory bowel disease, type I diabetes, multiple sclerosis, and rheumatoid arthritis^{64, 65}. Therefore, p53-dependent upregulation of TLR expression may contribute to enhanced innate immune responses, although such functional links still remain to be further investigated.

p53 can also activate an anti-tumour immune response via direct transcriptional regulation of the natural killer (NK) cell ligands ULBP1 and ULBP2 in human cancer cells⁶⁶, leading to enhanced killing of tumour cells by NK cells. CD43 (also known as leukosialin) is a cell surface antigen expressed by most haematopoietic cells that is an important regulator of immune cell function and is involved in regulation of cell adhesion and proliferation^{67, 68}. In humans, overexpression of CD43 in non-haematopoietic cells activates the ARF—p53 tumour suppressor pathway [G] and leads to apoptosis^{69, 70}. However, p53 specifically downregulates the expression of CD43 at the mRNA and protein level in non-haematopoietic cells, suggesting a negative feedback loop between p53 and CD43^{69, 70}.

p53 in autoimmunity

Autoimmune diseases are broadly characterized by increased levels of autoreactive T and B cells and appear to involve adaptive immune responses targeting self-antigens. In recent years, evidence has emerged that dysfunction of the tumour-suppressor p53 is associated with the development of autoimmune diseases, strongly suggesting that p53 plays a protective role by suppressing inappropriate expression of pro-inflammatory factors^{51, 71–75}. Elevated levels of p53 and missense *p53* mutations (codons 213 and 239) have been reported in samples from patients with rheumatoid arthritis and are associated with increased production of IL-6⁷⁶. Defective p53 functions also have been linked to the development of SLE⁷⁷. Serum antibodies to p53 have been reported in patients with SLE, Graves disease, granulomatosis and autoimmune hepatitis^{77–81}. In addition, a number of studies have shown that p53 deficiency is associated with the development of autoimmune and inflammatory diseases in mice^{65–69}. Furthermore, mice deficient for *p21* or *Gadd45*, which are two major target genes of p53, develop autoimmune disorders such as SLE^{82–84}.

In other studies, p53 has been reported to inhibit signal transducer and activator of transcription 1 (STAT1), a transcription factor that drives the expression of IFN-inducible genes and pro-inflammatory cytokines^{85–87}. p53 can also directly repress the activation of the *IL6* promoter and nuclear factor- κ B (NF- κ B)-dependent promoters, and inhibit the transcription of a set of tumour necrosis factor (TNF)-inducible genes^{88–90}. p53 deficiency in macrophages enhances the production of pro-inflammatory cytokines such as IL-1, IL-6, IL-12 and TNF^{91, 92}, that are targets of NF- κ B and have been implicated in the development

of autoimmune diseases^{51, 74, 93, 94}. Therefore, it is conceivable that impaired p53 expression contributes to autoimmunity through the excessive production of these cytokines by immune cells.

A potential distinctive mechanism through which p53 suppresses autoimmunity may involve p53-mediated transcription of the *Foxp3* gene in Treg cells. It was reported that T cell receptor (TCR) signalling induces p53 expression and subsequently p53 activates the transcription of *Foxp3* by directly binding to its promoter, which contributes to p53-mediated Treg cell induction in mice^{48, 50, 93}. Thus, proper expression of p53 in T cells could be critical in the control of autoimmunity. If so, p53-targeted therapeutics involving small molecule p53 activators such as Nutlin-3a may be a potential strategy for intervening in autoimmune diseases.

Dead cell clearance and p53

Programed cell death/apoptosis occurs throughout life in all tissues of the body, and more than a billion cells die everyday as part of normal processes. Thus, rapid and efficient clearance of cell corpses is a vital prerequisite for homeostatic maintenance of tissue health^{95–99}. Failure to clear dying cells can lead to the accumulation of autoantigens in tissues that foster diseases such as chronic inflammatory diseases, cancer, autoimmune diseases and developmental abnormalities^{95–102}.

In the normal immune system, phagocytic engulfment of apoptotic cells is accompanied by a certain degree of immune tolerance through the activation of immune checkpoint pathways [G] in order to prevent self-antigen recognition^{95–99}. Engulfment of apoptotic cells is an active process coordinated by receptors on phagocytes and ligands on apoptotic cells^{100–105}. Therefore, a better understanding of the homeostatic removal of apoptotic cells could have significant implications concerning the basic physiology of cell fate, immunotolerance and host response to infection.

It is well established that p53 is an important regulator of apoptosis, and numerous p53 pro-apoptotic target genes have been identified and implicated in apoptosis cascades^{17, 20, 106–108}. However, the involvement of p53 in post-apoptosis has only lately been identified^{109, 110}. We recently reported that p53 controls phagocytosis-mediated clearance of dead cells by inducing the expression of the immunoglobulin superfamily member DD1α¹⁰⁹ (also known as VISTA, PD-1H or Gi24^{111–114}). This suggests that p53 promotes both pro-apoptotic pathway and post-apoptotic events that are important for the removal of damaged host cell. Three immunologically relevant cell types — namely dying cells, macrophages, and T cells — express DD1α. The p53-mediated induction and maintenance of DD1α expression in apoptotic cells and its subsequent functional intercellular homotypic interactions between apoptotic cells and macrophages are required for engulfment of apoptotic cells¹⁰⁹. DD1α-deficient mice show impaired clearance of apoptotic cells¹⁰⁹. Such mice are indistinguishable in appearance from wild-type littermates at an early age. However, by ~10 months or later, DD1α-deficiency results in the development of immune infiltrates in the skin, lung, and kidney, implying immune dysregulation and failure of self-tolerance. These findings suggest that p53-mediated induction of DD1α promotes efficient clearance of apoptotic cells and guards against

systemic autoimmune diseases, including ulcerative dermatitis, seizures, otitis, eye lesions, and glomerulonephritis ^{109, 110}.

The classical and most well-studied ‘eat-me’ signal [G] for clearance of apoptotic cells is the phosphatidylserine pathway ^{100, 103, 104}. Phosphatidylserine, which is sequestered on the inner leaflet of the plasma membrane, becomes exposed on the outer leaflet of the plasma membrane during apoptosis, where it can interact with phosphatidylserine receptors on phagocytes and enable the engulfment of the dying cells ^{100, 103, 104, 108}. Unlike typical phosphatidylserine scavenger receptors such as brain angiogenesis inhibitor 1 (BAI1), T cell immunoglobulin and mucin domain-containing protein 4 (TIM4) and tyrosine-protein kinase MER (MERTK), DD1α on the surface of dying cells as well as on macrophages can engage in homophilic interactions, which facilitate the recognition, engulfment, and clearance of dying cells by macrophages ¹⁰⁹. Thus, p53-dependent stress-mediated activation of DD1α promotes the phagocytic engulfment of dead cells and may assist in the step-wise priming of immune surveillance.

Immune checkpoint regulation and p53

With the exception of virus-induced tumours, cancer cells originate from normal host cells that have acquired genetic alterations that prompt their malignant transformation. Therefore, cancer cells have been thought to be essentially viewed as ‘self’ by the host immune system. However, recent evidence indicates that cancer cells may become immunogenic owing to the accumulation of genetically altered proteins termed ‘neo-antigens’. Cancer cells exploit various immune escape mechanisms to persist despite chemotherapy and radiotherapy. In fact, tumours can upregulate inhibitory receptors (known as immune-checkpoint molecules), such as cytotoxic T lymphocyte antigen 4 (CTLA-4) and programmed cell death ligand 1 (PD-L1) ^{116–121}. These immune checkpoint molecules are important for the induction and maintenance of T cell tolerance ^{116–123}. Recent preclinical and clinical studies have indicated that combining chemotherapy or radiotherapy with immune-checkpoint inhibitors, such as anti-PD-L1, leads to synergistically enhanced anti-tumour immune responses that are associated with positive immunomodulatory effects, such as reduced numbers of Treg cells and enhanced frequencies of circulating monocytes and dendritic cells ¹¹⁵. Several newer immune checkpoint proteins, such as B and T lymphocyte attenuator (BTLA) ¹²², TIM3 ¹²⁴, DD1α ^{109–111, 114} and lymphocyte activation gene 3 protein (LAG3) ^{125, 126}, have also been identified.

A link between p53 and immune-checkpoint regulators has been identified in that cancer cells respond to genotoxic stress and DNA damage by upregulating PD-1 and its ligand PD-L1 in a p53-dependent manner ¹⁰⁹. Moreover, another immune-checkpoint regulator DD1α is a direct transcriptional target of p53 ^{109, 110, 114}. A number of p53-regulated microRNAs (miRNAs) have also been implicated in adaptive and innate immunity, including the miR-17-92 cluster ¹²⁷, miR-145 and let-7 ^{128, 129}. p53 regulates the expression of miR34, which directly binds to the 3′ untranslated region of the gene encoding PD-L1, suggesting that p53 specifically modulates the tumour immune response by regulating PD-L1 expression via miR-34 ¹³⁰.

p53 functions in innate and adaptive immunity

Role of p53 in DC function

The reported roles of p53 as an important modulator of TLR function, cytokine production and expression of T cell co-inhibitory molecules has prompted investigations on the role of this tumor suppressor in the DC-T cell immune synapsis. The nature of the interaction between DCs and T cells, involving MHC-peptide-TCR interactions as well as a myriad of other pathways regulating immunity and tolerance regulates T cell fate and is an important target for therapies aimed at harnessing immune responses. As we will show, p53 as well as other tumour suppressors play important roles controlling the microenvironment of the immune synapsis (Figure 2).

DCs are myeloid cells present in lymphoid as well as peripheral tissues with high capacity for pathogen detection. Importantly, DCs are the only antigen-presenting cells capable of transporting antigen from the periphery to the lymphoid tissues, where they encounter and activate cognate naive T cells ¹³¹. In order to prime T cells, DCs need to undergo a process termed 'maturation' or perhaps more accurately, 'activation' *in vivo*. This process involves cytoskeletal rearrangements, loss of phagocytic capacity, and increased surface expression of T cell co-stimulatory molecules, such as CD40, CD86, CD80 and MHC proteins ^{131, 132}.

Due to their unique role as linkers of innate and adaptive immunity, DCs play a chief role in host immune responses to viruses, especially to those that use epithelial and mucosal surfaces for entry. While no studies have directly addressed the role of p53 in DC functions, an important body of work indicates that p53 signalling is necessary for proper DC function. For example, p53-dependent cytokine production was shown to be necessary for recruitment of blood-borne inflammatory monocytes to the sites of influenza virus replication in mice ⁵⁸, where they differentiated into monocyte-derived DCs (moDCs). As moDCs are major depots of influenza virus-derived antigens in the respiratory tract ¹³³, these findings may have implications in antigen storage during influenza virus infection. Moreover, treatment with Nutlin-3 (which blocks the interaction between p53 and its negative regulator MDM2) enhanced the ability of DCs to induce T cell proliferation in a mixed leukocyte reaction, suggesting that p53 participates in the maturation and/or activation of DCs ¹³⁴.

Another link between p53 and DC function is the reported ability of p53 to enhance the expression of MHC class I molecules (Figure 2) ^{135, 136}. It is likely that this would enhance the induction of cytotoxic CD8+ T cells that are specific for viruses or other intracellular pathogens, and it will be interesting to assess whether p53 signalling plays a direct role in DC antigen presentation. Pointing in this direction, p53 has been shown to enhance exosome production and secretion ¹³⁷. Exosome production by activated DCs is a mechanism for exchange of MHC molecules between antigen presenting cells, presumably to enhance the antigen presentation capability of the host ^{138, 139}.

p53 regulation of cytokine production

Takaoka and colleagues identified p53 as a transcriptional target of type I IFN signalling⁴⁵. More recent studies identified a positive feed-back loop between p53 and IFN expression during the antiviral response, due to the ability of p53 to directly trans-activate IRF9, a key

component of the IFN signalling pathway⁴³. These studies, complemented previous evidence that p53 inhibited replication of some viruses *in vitro* due to its ability to induce apoptosis^{56–58, 140}, and strongly suggested that p53 helped to enforce antiviral responses independently of its functions as a tumour-suppressor gene. In fact, p53 drives the transcriptional activation of other antiviral genes, including TLR3 and IRF5^{42, 46}. This activation of innate immune signalling by p53 has been shown to lead to production of several cytokines and chemokines including IFN- α/β ^{43, 59}, CCL2, and CXC-chemokine ligand 10 (CXCL10, also known as IP-10)⁶⁰. Thus, p53 plays an important role in enforcing cytokine production in response to viral infection as well as in response to other types of cellular stress. p53-dependent expression of IL-15 and CCL2 has also been shown to be necessary to attract NK cells, macrophages and neutrophils, for elimination of senescent cells *in vivo*⁶⁰.

A link between p53-induced cytokines and the clearance of virus-infected cells *in vivo* was identified with regards to influenza virus infection in the lung. Specifically, p53-deficient mice failed to produce early pro-inflammatory mediators, such as CXCL10 and CCL2, which resulted in defective DC migration and impaired recruitment of activated monocytes to infected lungs leading to poor influenza clearance⁶⁰. Perhaps counter-intuitively, p53 has also been shown to antagonize inflammation through inhibition of NF- κ B function^{92, 141}; this was shown to result in increased mortality of p53-deficient mice during experimental bacterial infection¹⁴². However, under other physiological conditions, p53 cooperates with NF- κ B, for example, in the transactivation of genes that contain both NF- κ B- and p53-binding sites in their promoters¹⁴³. Such genes include intracellular adhesion molecule 1 (ICAM1)¹⁴⁴, which is an important modulator of immunity. It is therefore plausible that the cell-fate decisions influenced by p53 in response to infection by different agents may depend on the cytokine context and/or microenvironment. Further studies are needed to dissect the mechanisms responsible for p53 activation by innate immunity stimuli, and to further define the role of p53 in response to intracellular and extracellular pathogens.

Immune roles of other tumour-suppressor pathways

A growing body of evidence indicates that tumour suppressors other than p53 also play key roles in the modulation of the innate immune system. A clear function in antiviral defence has been reported for the tumour suppressors RB1, ARF and PTEN^{43, 45, 145–147}. Activation of these tumour-suppressor genes has been described after IFN treatment, following the expression of viral proteins and during viral infection. Mice-deficient in several prominent tumour-suppressor genes, including p53, RB, ARF and PTEN, have been demonstrated to be more susceptible to chronic inflammatory responses triggered by pathogens and environmental stress^{43, 145–147}. Below, we discuss the immunological roles that have been described for tumour-suppressor proteins other than p53.

Role of RB1 in immune cell differentiation and immune evasion

RB1 was first identified as the gene, whose loss of function, was responsible for initiating congenital retinoblastoma [G]^{31, 148}. Subsequently, it became apparent that functional inactivation of the RB1 pathway is a common event in most human malignancies^{31, 148–152}.

RB1 directly binds to members of the E2F family of transcription factors^{31, 151}, which play a major role in the regulation of cell proliferation, and differentiation^{153, 154}. An increasing body of evidence indicates that the tumour suppressor RB1 is also involved in immune functions¹⁵⁵, and the expression of a large subset of immune genes is down-regulated upon RB1 loss^{150, 155}. These genes include those encoding immune cell surface receptors, complement components, and cytokines (Figure 2)^{150, 155}. RB1 deficiency in mice also results in increased susceptibility to viral infection, decreased TLR3 expression, reduced nuclear localization of the RELA/p65 subunit of NF- κ B, and diminished production of cytokines and chemokines, including IFN β and IL-8^{146, 150, 156}. Moreover, RB1 is frequently downregulated by oncogenic viral proteins during viral infection in mouse cells^{146, 157–159}.

PTEN tumor suppressor in T cell regulation

The PI3K-signalling pathway is one of the major pathways activated upon TCR, IL-2R, and CD28 stimulation, leading to T cell activation, proliferation, and cell survival^{160, 161}. This pathway is negatively regulated by the tumour suppressor PTEN, a lipid phosphatase²⁵ that is frequently inactivated in a variety of human cancers^{23, 25}. Mice with a T cell-specific deficiency in PTEN activation have defects in central and peripheral tolerance and show increased susceptibility to T cell lymphoma and leukaemia^{162–166}. Mice heterozygous for PTEN also develop lethal autoimmune diseases with splenomegaly, lymphadenopathy, inflammatory infiltration in many organs, and glomerulopathy resembling autoimmune-prone mouse strains^{166–168}.

In the context of T cell function, PTEN influences T cell differentiation and polarization towards T helper (Th) cell phenotypes in mice¹⁶⁹. Likely, this is partially due to important functions of PTEN in DC maturation (Figure 2). During Th cell induction, PTEN function is suppressed whereas the level of PTEN transcripts is increased during the formation of peripheral FOXP3⁺ Treg cells¹⁶⁹. In patients, loss of PTEN significantly correlates with diminished T cell infiltration at tumour sites, reduced chance of successful T cell growth from resected tumours, and a poorer responses to PD-1 blockade therapy. This suggests that combinatorial strategies that target the PI3K–AKT pathway may enhance the efficacy of immunotherapy¹⁷⁰. Although mechanistically not fully understood, these findings strongly suggest that PTEN is directly involved in T cell fate.

ARF tumour suppressor as a regulator of inflammation and macrophage activation

The alternative reading frame (ARF) is, together with p16, one of two tumour suppressors encoded by the INK4a–ARF locus, a frequently mutated locus in human cancer^{171, 172}. p16/INK4a and ARF, respectively, regulate the activity of RB1 and p53^{172–174}. ARF was initially discovered as an upregulated cellular protein after oncogenic stress, and was later linked to p53 stabilization^{63, 172, 173}. ARF also inhibits the cell cycle, promotes cellular senescence, and has been linked to cancer and aging^{171–175}. In addition, ARF acts a general sensor for cellular stress. ARF-deficiency in mice has been reported to aggravate atherosclerosis through the reduction of macrophage and vascular smooth muscle cell apoptosis^{176, 177}.

ARF is activated in response to the expression of viral proteins, viral infection, or type I IFN treatment in human cells ^{145, 178, 179}. ARF appears to serve as a critical modulator of the inflammatory response and macrophage activation. Mice lacking the ARF gene are resistant to LPS-induced endotoxic shock, and show a significant reduction of leukocyte recruitment ^{176, 180}. In addition, ARF-deficiency can lead to a more immunosuppressive tumour microenvironment in which there is increased production of the anti-inflammatory cytokine IL-10 and of chemokines, such as CCL2 and CCL22, that drive the recruitment of Treg cells..

Several reports describe the activation of ARF in response to the expression of oncogenic viral proteins ¹⁷⁸ type I IFN treatment ¹⁷⁹, or virus infection ¹⁴⁵. However, due to the well-known link between ARF and p53, it was only recently that ARF was hypothesized to drive p53-independent functions during virus infection. To date, ARF has been demonstrated to play an antiviral role against DNA viruses with oncogenic properties, such as human papilloma virus (HPV) and simian virus 40 (SV40), and similarly to p53 against non-oncogenic RNA viruses, such as VSV, Sindbis virus or an engineered IFN-sensitive recombinant vaccinia virus strain ¹⁴⁵. Again, resembling the antiviral functions of p53, ARF is activated via IRF3 response elements in its promoter ¹⁷⁹ and provides a positive feedback loop in the IFN-mediated antiviral response through direct activation of protein kinase R (PKR) ¹⁴⁵. Perhaps linked to its activation of PKR or other IFN-induced genes, a role of ARF in the regulation of cytokine production in mice in response to LPS and other pro-inflammatory stimuli has also been described ¹⁸⁰.

The role of BRCA1 and BRCA2 in the immune response

The *breast cancer type 1 susceptibility (BRCA1)* and *breast cancer type 2 susceptibility (BRCA2)* genes are associated with familial breast cancer and ovarian cancer ^{181–184}. Individuals who inherit germline mutations in these genes have a high lifetime risk of developing breast and ovarian cancers. The *BRCA* genes have been implicated in the regulation of a number of cellular functions, including DNA damage responses, DNA repair and replication, cell cycle regulation, ubiquitination, and transcriptional regulation ^{181, 184}. Recently, a panel of genes was identified that are regulated by BRCA1 in the presence of IFN γ , but not in the presence of IFN α or IFN β ¹⁸⁵. These genes included those involved in the induction of STAT1, STAT2 and type 1 IFNs in response to IFN γ , suggesting that BRCA1 and IFN γ cooperate to activate a subset of innate immune response genes. Moreover, combined treatment using a poly (ADP-ribose) polymerase 1 PARP inhibitor together with CTLA4 checkpoint blockade increased long-term survival in a BRCA1-deficient mouse ovarian tumour model ¹⁸⁶. A heterozygous germ-line *BRCA2* mutation was associated with immune dysfunction in mice, and mature naive T cell populations were highly susceptible to death caused by BRCA2 deficiency ¹⁸⁷. A large, population-based study with intermediate-risk ovarian cancer observed a significant association between intraepithelial tumour-infiltrating lymphocytes and *BRCA1* and/or *BRCA2* mutation or epigenetic loss ¹⁸⁸.

While the tumour-suppressor genes are clearly involved in crucial aspects of tumour immunology and in homeostatic regulation of immune responses, accumulating recent

evidence strongly suggest that differential activation of specific oncogene pathways, such as β -catenin and MYC, promotes immune exclusion in a subset of cancers^{189–191}. Thus, further understanding of the molecular mechanisms underlying the oncogenic signalling-mediated immune evasion may lead to the identification of new therapeutic targets/approaches for escalating efficacy of immunotherapies.

Conclusion

The discovery of new tumour-suppressor genes and improved insight into the biology of these genes has led to a better understanding of the pathophysiological roles of tumour suppressors in both healthy and cancerous cells. The critical roles of these genes in suppressing malignancy have led to wide-ranging investigation into the mechanisms of their actions at the molecular, cellular and organismal levels. Most studies have focused on determining the pathways involved in cell cycle arrest, apoptosis or DNA-damage response signalling. More recently, ample evidence has pointed to a potential link between tumour suppressor genes, such as p53, and immune function, and tumour-suppressor genes have also been implicated in inflammatory diseases.

Accumulating evidence suggests that tumour suppressor genes may negatively regulate immune responses, as highlighted by the numerous alterations or phenotypic dysfunctions that have been observed in cells and mice deficient in these genes. It is not surprising that recently discovered physiological activities of p53 involve homeostatic stress responses involved in maintenance of key processes that help to prevent unnecessary inflammation and sustain self tolerance mechanisms. Therefore, p53 not only keeps cellular proliferation in check through the activation of cell-cycle checkpoint regulators, but also keeps immune responses in check through the activation of immune checkpoint inhibitors (Figure 3). Thus, the coordinate induction of multiple p53 immune checkpoint targets may explain why the absence of p53 predisposes mice to autoimmune diseases.

p53 has a well-established function as the ‘guardian of genome integrity’. However, it has also been implicated in a growing number of homeostatic stress responses, including in aspects of innate and adaptive immunity, as described above. While these studies are still at a relatively early stage, it is possible that p53 may eventually come to be regarded as a ‘guardian of immune integrity’. Notably, accumulating evidence indicates that other tumour-suppressor genes may have similar functions.

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Glossary

ARF-p53 tumor suppressor pathway

ARF regulates p53 activity through the direct binding to Mdm2 to neutralize its function and initiates transcription factor activity of p53. ARF/p53 axis plays essential role in the

detection and removal of damaged cells, and the inactivation of ARF and p53 occurs in a mutually exclusive manner in human cancers

immune checkpoint pathways

Immune checkpoint pathways. Immune checkpoints are utilized by the host to oblige immune responses and prevent immune hyperactivation from harming normal tissues

‘eat-me’ signal

The apoptotic cells expose specific “eat-me” signals (specific markers) on their surface that are recognized by phagocytes through specific engulfment receptors

Congenital retinoblastoma

Congenital retinoblastoma is the most common eye tumor in children and the third most common cancer overall affecting children, and is caused by the abnormality in the RB1 gene. This is known as a germline mutation

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Online Summary

- The role of tumour suppressors in immunity is strongly linked to maintenance of genomic integrity.
- Impaired expression of tumor suppressor genes such as p53, RB, PTEN and ARF results in susceptibility to chronic inflammatory responses triggered by pathogens and environmental stress.
- The tumour suppressor p53 and its transcriptional targets are involved in crucial aspects of tumour and pathogen immunology and in homeostatic regulation of immune responses. This pathway plays an important role in host immunity influencing both innate and adaptive immune responses.
- A link between the tumor suppressor p53 and immune-checkpoint regulators including PD-1, PD-L1 and DD1 α /VISTA has been identified in that cancer cells.
- Several tumour suppressor genes including p53, ARF, Rb and PTEN influence T cell fate by modulating the immune synapsis through pattern recognition receptors, cytokine production, and expression of MHC and co-inhibitory molecules.
- Tumour suppressor gene function is emerging as a ‘potential guardian of immune integrity’.

Figure 1. Roles of tumour suppressor p53 in antiviral immunity

p53 is activated in response to type I IFN signalling due to the presence of IFN-stimulated response elements (ISRE) within the *p53* promoter sequence. Activation of p53 leads to the upregulation of genes that can promote cell cycle arrest, apoptosis and intracellular immunity. Several p53 target genes are in turn involved in driving IFN production and signalling, including TLR3, IRF5, ISG15 and IRF9. This provides a positive feedback loop on the type I IFN pathway with important implications in immune responses, in particular against viral infections.

Figure 2. Roles of tumour-suppressor genes at the immune synapse

The synapse between antigen-presenting cells such as DCs and T cells regulates T cell fate through multiple mechanisms. The tumour suppressor p53 influences many aspects of the immune synapse including activation through pattern recognition receptors, cytokine production, and expression of MHC and co-inhibitory molecules. In T cells, p53 regulates expression of Foxp3. Other tumor suppressors also modulate the immune synapse by influencing DC maturation and cytokine production among others.

Figure 3. p53 as a guardian of immune integrity

Owing to its roles in inducing cell cycle arrest and apoptosis in stressed cells, p53 has been referred to as the ‘guardian of the genome’. More recently, it has become apparent that p53 has important roles in promoting immune tolerance. p53 induces the expression of immune checkpoint molecules such as PD-1, PD-L1 and DD1α (also known as VISTA and PD-H1), which negatively regulate effector T cell responses. Furthermore, p53 enhances the detection and uptake of apoptotic cells by the immune system. As such, we suggest that p53 can also be considered as a guardian of immune integrity.

Table 1

Tumour suppressor genes involved in immune response

Tumour suppressor	Major roles in immunity	Open questions	Refs
p53	Induction of apoptosis. Removal of apoptotic cells. Antiviral defence. Induction of type I IFN Enhanced pathogen recognition. Cytokine production. Immune checkpoint regulation.	Knockout mice are sensitive to virus infections. Controls expression of hundreds of genes involved in immunity. The biological consequences of some transcriptional targets (e. g. Foxp3) remain to be elucidated.	9,16,17,26,37,43,44,45,48,56,59,109,110
RB1	Induction of NF- κ B. Induction of senescence-associated secretory phenotype. Recruitment of NKT cells.	Induced by type I IFN, RB1 and its family members may influence monocyte fate, in particular fate decisions towards formation of myeloid suppressor cells or inflammatory monocytes.	150,155,156
PTEN	Controls STAT3-dependent cytokine upregulation, DC maturation, T cell polarization.	PTEN is strongly involved in T cell fate but the mechanisms involved are not fully understood. In particular it has been difficult to dissect the functions of PTEN in DCs and in T cells. Functional experiments in available PTEN conditional knockout mice may help to define the involvement of PTEN in adaptive Immune responses.	166,168,169,170
ARF	Activated in response to viral proteins, viral infection or type I IFN treatment. Critical modulator of the inflammatory response and macrophage activation.	Linked to activation of protein kinase R (PKR) or IFN-I-induced genes. It has been suggested that ARF play an antiviral role against DNA viruses such as HPV and SV40, and also RNA viruses such as VSV and Sinbis virus.	176,177,179,180
BRCA1 and BRCA2	Familial breast and ovarian Cancer genes. BRCA1 and IFN γ cooperate to activate a subset of innate immune response genes. <i>BRCA2</i> mutation leads to T cell loss in mice.	Still not clear how BRCA1 and BRCA2 are involved in immune cell functions. Putative role on mature naïve T cell population.	181,182,185,187

Abbreviations: BRCA1, breast cancer type 1 susceptibility protein; BRCA2, breast cancer type 2 susceptibility protein; DC, dendritic cell; IFN, interferon; NF- κ B, nuclear factor κ B; NKT cells, natural killer T cells; PTEN, phosphatase and tensin homologue; RB1, retinoblastoma-associated gene 1; SASP, STAT3, signal transducer and activator of transcription 3;

Table 2

p53 target genes involved in immune responses

Target	Role in immunity	Diseases	Refs
IRF9	Induction of IFN-I-dependent genes Via formation of the ISGF3 complex with STAT1 and STAT2	SLE? Susceptibility to infections?	37,42,43,59,60
IRF5	Production of type I IFN	Inflammatory bowel disease, SLE	34,37,42,47
TLR3	Pathogen recognition via binding to dsRNA in endosomes	Susceptibility to HIV-1 infection	44,46
ISG15	Ubiquitin-like modification of hundreds of IFN-I target genes	Immunodeficiency with basal ganglia calcification	39,40,41
Foxp3	T cell polarization towards Regulatory T cell phenotype	Diabetes, polyendocrinopathy, Wiskott-Aldrich Syndrome (in mice)	48,49
PD-1	T cell checkpoint co-inhibitor T cell homeostasis T cell exhaustion	Cancer, SLE (mice)	116,118,121
PD-L1	PD-1 ligand T cell checkpoint co-inhibitor	Cancer, Lupus	116,118,121
DD1 α /VISTA/PD-1H	T cell checkpoint co-inhibitor T cell exhaustion Dead cell clearance/post-apoptotic receptor	Cancer, Autoimmune (mice) EAE, Graft-versus-host disease	109,110,112,114,