

# p53, cancer and the immune response

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## ABSTRACT

The importance of cancer-cell-autonomous functions of the tumour suppressor p53 (encoded by *TP53*) has been established in many studies, but it is now clear that the p53 status of the cancer cell also has a profound impact on the immune response. Loss or mutation of p53 in cancers can affect the recruitment and activity of myeloid and T cells, allowing immune evasion and promoting cancer progression. p53 can also function in immune cells, resulting in various outcomes that can impede or support tumour development. Understanding the role of p53 in tumour and immune cells will help in the development of therapeutic approaches that can harness the differential p53 status of cancers compared with most normal tissue.

**KEY WORDS:** p53, Cancer, Immune response

## Introduction

The most common genetic lesion in human cancer is loss or mutation of the tumour suppressor gene *TP53*, and inheritance of a germline *TP53* mutation results in a strongly increased risk of cancer development (Baker et al., 1989; Le Beau et al., 1985; Li and Fraumeni, 1969; Nigro et al., 1989). p53 is activated in response to stress and can promote the permanent removal of nascent cancer cells through the induction of various forms of cell death or senescence, responses that contribute to the ability of p53 to limit tumour development (Kaiser and Attardi, 2018; Kastenhuber and Lowe, 2017; Vogelstein et al., 2000; Vousden and Prives, 2009). Indeed, tumour cells that lack p53 can tolerate the genomic instability and enhanced oncogenic signalling that are the hallmarks of malignant transformation. p53 can also induce a reversible cell cycle arrest, allowing cells to resume proliferation once the damage or stress has been resolved (Agarwal et al., 1995; Kruijswijk et al., 2015; Linke et al., 1996). Accompanying this function of p53 are various activities that contribute to damage resolution or help cells adapt to non-genotoxic stress, such as nutrient starvation. In this context, the loss of p53 function in tumour cells can make these cells more vulnerable to certain types of metabolic stress (Labuschagne et al., 2018; Lacroix et al., 2019). Many cancers express high levels of point-mutated versions of p53 that generally lose the ability to inhibit cell growth, but in some cases retain survival functions and acquire neomorphic oncogenic activity (Freed-Pastor and Prives, 2012; Humpton et al., 2018; Kim and Lozano, 2018; Tran et al., 2017).

Overall, the numerous activities that have been described for p53 indicate an ability to regulate a diverse array of biological pathways (Kastenhuber and Lowe, 2017). As a disease of ageing, cancer

generally has a limited impact on reproduction, suggesting that these functions of p53 did not evolve solely for tumour suppression. Roles for p53 in development, the maintenance of stem cell and tissue homeostasis (Jain and Barton, 2018) and protection of germ cell integrity (Gebel et al., 2017) have been described, while p53 can also contribute to non-cancer pathologies such as neurodegenerative disease and ischaemia (Gudkov and Komarova, 2010). Nevertheless, the most obvious consequence of loss or mutation of p53 in mice and humans is a profound acceleration of cancer development.

The hypothesis that the immune system can keep neoplastic growth in check was first postulated by Paul Ehrlich in 1909 and later termed ‘immune surveillance’ by Thomas and Burnet in the mid-twentieth century (Burnet, 1971; Ehrlich, 1913; Thomas, 1982). Both innate and adaptive immune responses play a role in immune surveillance, and CD4<sup>+</sup> T helper (Th) cells, CD8<sup>+</sup> cells, natural killer (NK) cells and, in some cases, neutrophils are involved (Girardi et al., 2001; Ponzetta et al., 2019; Shankaran et al., 2001; Smyth et al., 2000). Other immune subsets are reported to support tumour progression, such as regulatory T cells (Tregs) and cells from myeloid-derived lineages. Tregs permit tumour growth by suppressing CD4<sup>+</sup> and CD8<sup>+</sup> T cell activity (Arce Vargas et al., 2018; DiLillo et al., 2010; Togashi et al., 2019), and macrophages and other polymorphonuclear cells (PMNs) can promote angiogenesis, metastasis and immune suppression through modulation of suppressive cytokines and surface ligands (Cassetta and Pollard, 2018; Kitamura et al., 2017). Several oncogenic events, such as Kras mutation or Myc activation, have been shown to result in the suppression or evasion of anti-tumour immune responses (Coelho et al., 2017; Kortlever et al., 2017), and there is evidence suggesting that p53 also plays a role in controlling tumour-immune system crosstalk. As with other functions of p53, the ability to regulate immune responses is likely to reflect the selection for roles in normal or non-cancer disease pathologies, such as wound healing, damage repair and resolution or the control of viral infection (Levine, 2020; Miciak and Bunz, 2016). Nevertheless, it is clear that a major function of p53 in humans is to protect against malignant progression. In this Review, we consider the role of p53 in modulating the immune response during cancer development, focusing on functions of p53 in both the tumour and immune cells.

## Regulation of the p53 response

p53 can be activated by numerous stress signals, including genotoxic damage, oncogene activation, nutrient starvation and hypoxia (Efeyan et al., 2006; Graeber et al., 1996, 1994; Jones et al., 2005; Leszczynska et al., 2015; Maddocks et al., 2013; Tajan et al., 2018). In the context of an immune response, p53 has also been shown to be regulated by cytokine signalling, consistent with the observation that persistent inflammation causes stress that can also contribute to both cancer initiation and progression (Grivennikov et al., 2010). For example, type I interferons (IFNs) and CCL5 promote the tumour-suppressive functions of p53, such as cell cycle arrest and apoptosis. By contrast, interleukin-6 (IL-6) and

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macrophage migration inhibitory factor inhibit p53 as a mechanism to escape cell death and senescence (Fingerle-Rowson et al., 2003; Hodge et al., 2005; Hudson et al., 1999; Mañes et al., 2003; Niu et al., 2005; Takaoka et al., 2003; Yonish-Rouach et al., 1991).

Components of the immune response can also control the tumour suppressor function of p53 by promoting the acquisition of p53 mutations. For example, *Helicobacter pylori*, a cause of gastric carcinomas, expresses the virulence factor cytotoxin-associated gene A (CagA), which activates nuclear factor- $\kappa$ B (NF- $\kappa$ B)-induced inflammation in gastric epithelial cells (Keates et al., 1997; Uemura et al., 2001). In turn, CagA-dependent NF- $\kappa$ B transcriptional activity upregulates the expression of the DNA editing enzyme activation-induced cytidine deaminase (AID, also known as AICDA), which increases cancer risk by incorporating mutations into *TP53* (Matsumoto et al., 2007). Similarly, a hallmark of inflammatory bowel disease (IBD) is infiltration by PMNs, which are sources of free radicals that promote replication errors. The consequential increase in *TP53* mutations can further contribute to IBD and eventual malignant progression (Brazil et al., 2013; Butin-Israeli et al., 2019; Campregher et al., 2008; Hofseth et al., 2003; Hussain et al., 2000).

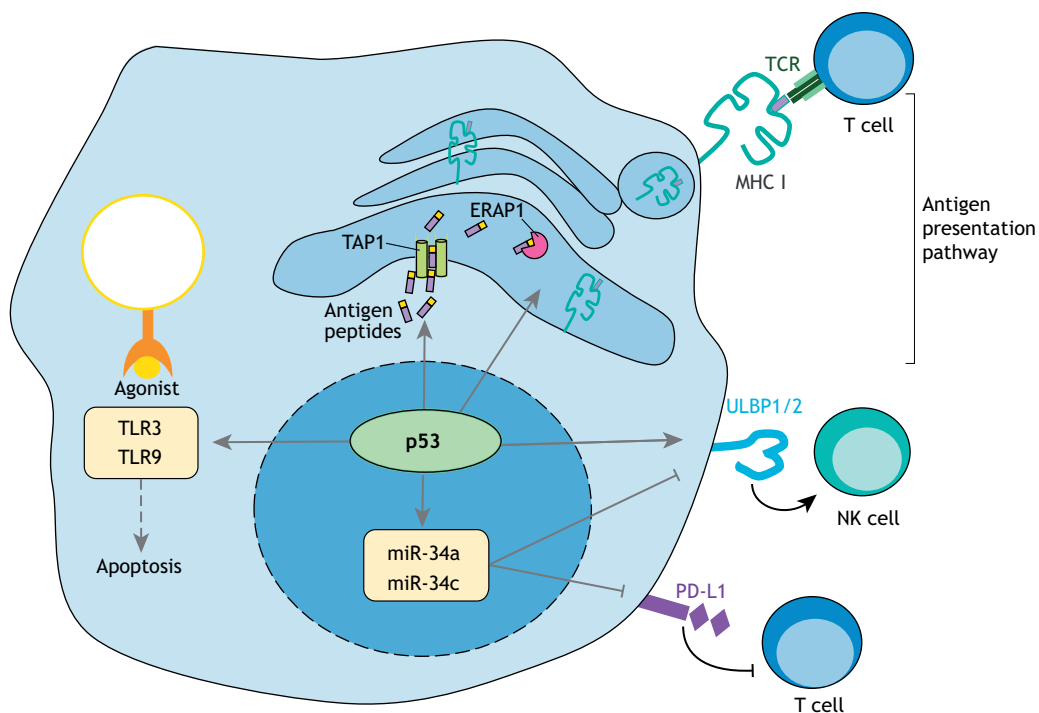
### Perturbation of p53 in cancer cells regulates immune escape

A great deal of recent interest has focused on the observation that some tumour cells can avoid immune clearance, allowing them to persist and grow in an immune-competent host. In some cases, genetic perturbations within the antigen presentation machinery (Rosenthal et al., 2019) reduces immunogenicity and promotes immune escape. Similarly, the downregulation of the activating ligands for the natural killer group membrane D (NKG2D) receptor can help cancer cells avoid immune detection (Smyth et al., 2005). While the major histocompatibility complex class I (MHC-I) and

NKG2D ligands are involved in immune recognition, cancer cells also engage in direct immune suppression by regulating expression of the immunosuppressive molecule programmed death ligand 1 (PD-L1, also known as CD274) (Sun et al., 2018). Furthermore, cancer cells modulate their environment through cytokine and chemokine secretion. Each of these immune responses is influenced by the p53 status of the tumour (Fig. 1).

### The MHC-I antigen processing pathway is targeted by wild-type p53

MHC-I-bound peptides can be generated by proteasome proteolysis of intracellular proteins and require transporter associated with antigen processing 1 and 2 (TAP1 and TAP2) for translocation into the endoplasmic reticulum (ER) and to form the peptide-loading complex with other components, including MHC-I subunits (e.g.  $\beta$ 2-microglobulin,  $\beta$ 2M) (Leone et al., 2013). Not all oligopeptides from the proteasome are the correct length for MHC-I loading and require endoplasmic reticulum aminopeptidase 1 (ERAP1) to further trim them into the appropriate length of 8–10 amino acids (Blum et al., 2013). While human leukocyte antigen B7 (HLA-B7), an allele of the MHC-I locus, can be transcriptionally repressed by p53 (Griffioen et al., 1998), other studies suggest that p53 induction promotes peptide processing and MHC-I surface expression (Wang et al., 2013; Zhu et al., 1999) (Fig. 1). TAP1 expression is enhanced through p53-mediated transcription in response to DNA damage or direct activation of p53, leading to increased surface MHC-I-peptide complexes in cancer cells. p53-dependent induction of ERAP1 expression (Wang et al., 2013) would also enhance the number of peptides available for MHC-I loading (Fig. 1). Both these aspects of antigen presentation are downregulated in p53-mutant and p53-null cell lines (Wang et al., 2013; Zhu et al., 1999). Intriguingly, deletion of key components of the MHC-I pathway (i.e.  $\beta$ 2M or TAP1) reduces p53 function, suggesting an interplay



**Fig. 1. Functions of p53 in tumour cells that regulate interactions with the immune system.** p53 regulates endogenous antigen presentation through transcriptional control of ERAP1 and TAP1. In addition, p53 regulates the expression of the NKG2D ligands ULBP1 and ULBP2, either positively as a transcriptional target or negatively through the upregulation of miR-34a. The miR34 family also represses PD-L1 expression, an inhibitor of T cell activity. TLR3 and TLR9 are transcriptional targets of p53 that promote agonist-induced cell death.

between the MHC-I presentation pathway and p53 activity in cancer cells that is not yet fully understood (Sabapathy and Nam, 2008).

### Regulation of immunomodulatory ligands by wild-type and mutant p53

NKG2D ligands bind to receptors on cytotoxic immune cells and alert them to damaged or transformed cells (López-Soto et al., 2015). Depending on the context, p53 can either upregulate or downregulate expression of UL16-binding protein 1 (ULBP1) and ULBP2 (two of the eight NKG2D ligands). Pharmacological activation of p53 with the small molecule ‘reactivation of p53 and induction of tumour cell apoptosis’ (RITA) or re-expression of p53 in otherwise unstressed cells induces ULBP1 and ULBP2 transcription and sensitizes them to NK-cell-mediated cytotoxicity (Li et al., 2011; Textor et al., 2011) (Fig. 1). By contrast, induction of miR-34a and miR-34c by wild-type p53 in melanoma cells leads to the repression of ULBP2 translation, potentially contributing to an escape from cytotoxic destruction (Fig. 1) (Heinemann et al., 2012).

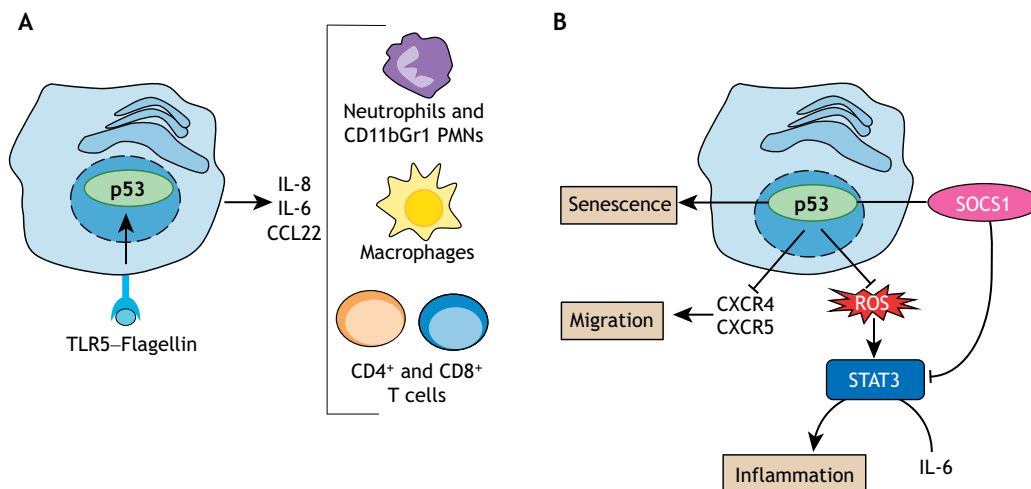
MHC-I peptide recognition by the T cell receptor (TCR) is the first step to T cell activation; once fully activated, effector T cells upregulate co-inhibitory receptors, such as programmed cell death protein 1 (PD-1, also known as PDCD1), to keep protective immunity in check (Sharpe and Pauken, 2018). Cancer cells can co-opt this equilibrium-maintaining pathway by overexpressing co-inhibitory ligands (such as PD-L1) to constrain T cell activity (Freeman et al., 2000). Targeting PD-L1 can release this inhibitory signal to T cells and can lead to tumour regression. miR-34a, a transcriptional target of p53, is a repressor of PD-L1 expression, and loss of p53 activity increases PD-L1 surface expression, which can suppress T cell function (Fig. 1) (Cortez et al., 2016). Consistent with this, the expression of mutant p53 in human lung cancers correlates with increased PD-L1 expression, which may help to identify patients responsive to checkpoint inhibitors targeting PD-L1 (Biton et al., 2018; Cha et al., 2016; Chamoto et al., 2020; Cortez et al., 2016; Dong et al., 2017).

Other immune-related receptors that can be modulated in cancer cells are those sensing pathogen-associated molecular patterns (PAMPs), including the Toll-like receptors (TLRs). TLRs are a family of evolutionarily conserved receptors involved in sampling

the environment both within and outside the cell. Signalling through surface TLRs (TLR1, TLR2, TLR4, TLR5 and TLR6) alerts the immune system to many bacterial and fungal species, while intracellular TLRs (TLR3, TLR7, TLR8 and TLR9) detect nucleic acids, predominantly of viral or bacterial origin (Blasius and Beutler, 2010). In cancer cells, TLR signalling can result in a wide range of responses, rendering tumour cells vulnerable to cell death or contributing to inflammation-induced proliferation, depending on the type of TLR stimulus (Rakoff-Nahoum and Medzhitov, 2008). Intracellular TLR3 and, to a lesser extent, TLR9, are transcriptional targets of wild-type p53. Increased expression of these receptors through p53 can trigger agonist-induced apoptotic cell death, a response that is lost in most cancer cells expressing mutant p53 (Menendez et al., 2016; Shatz et al., 2012) (Fig. 1). However, not all TLRs are deleterious to cancer cells expressing wild-type p53. The p53-mediated response to TLR5 ligands (i.e. bacterial flagellin) promotes IL-6, IL-8 and CCL22 secretion, cytokines that could attract pro-tumorigenic immune subsets to the tumour site and support tumorigenesis (Shatz et al., 2015) (Fig. 2). Hence, the type of TLR stimulus and p53 status within cancer cells may help shape the outcome of tumour growth within the host.

### The role of wild-type and mutant p53 in pro-inflammatory cytokine signalling

As discussed above, cytokines can both inhibit or induce p53 function. p53, in turn, modulates pathways that are activated in response to cytokine signalling. Wild-type p53 regulates inflammation through signal transducer and activator of transcription 3 (STAT3), which acts downstream of the inflammatory cytokine IL-6 (Fig. 2). Loss of p53 in mouse models of pancreatic and prostate cancers results in increased STAT3 phosphorylation, which is mediated, in part, through enhanced autocrine/paracrine IL-6 signalling (Nowak et al., 2015; Wörmann et al., 2016). p53 deficiency in pancreatic cancer cells increases reactive oxygen species (ROS), which inhibits Src homology region 2 (SH2) phosphatases and drives STAT3 activity (Wörmann et al., 2016). In addition, p53 ablation in PTEN-null mouse embryonic fibroblasts (MEFs) leads to enhanced STAT3–Myc pro-growth signalling (Lin et al., 2002; Nowak et al., 2015). STAT3 activation is regulated through a negative feedback



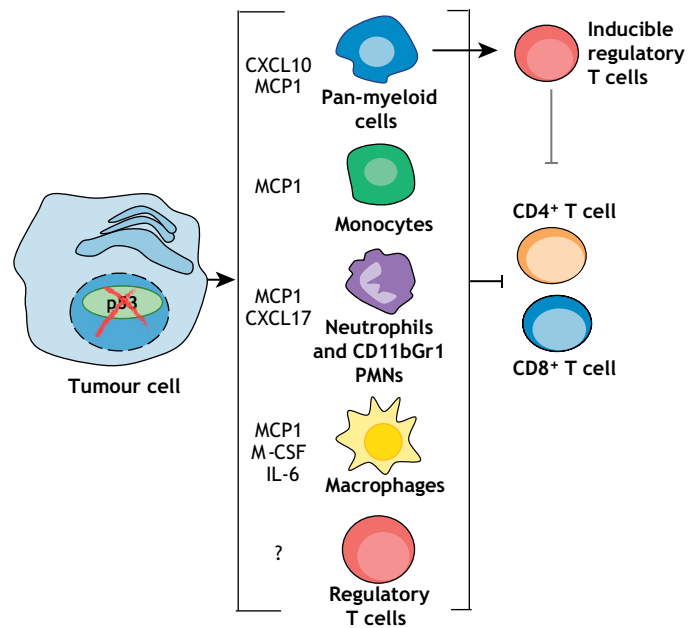
**Fig. 2. Functions of p53 in response to immune signalling.** (A) Activation of p53 downstream of TLR5 ligation by bacterial flagellin increases the secretion of IL-6, IL-8 and CCL22, which can regulate the recruitment of leukocytes including macrophages, neutrophils and T cells. (B) p53 suppresses STAT3 signalling (which drives inflammation) by downregulating ROS. SOCS1, a modulator of STAT3 activity, interacts with p53 to induce senescence. Migration-mediated chemokine signalling is also regulated by p53 through its inhibition of the chemokine receptors CXCR4 and CXCR5.

loop by suppressors of cytokine signalling (SOCS) proteins. SOCS1, an inhibitor of STAT3, binds to the N-terminal transactivation domain of p53 to induce cell cycle arrest and senescence (with consequential induction of cytokine expression as further discussed below) (Fig. 2). Taken together, these studies indicate that loss of p53 function maintains STAT3 signalling and bypasses proliferation inhibition (Calabrese et al., 2009). Intriguingly, STAT3 can inhibit p53 expression in a reciprocal negative regulatory network (Niu et al., 2005). One consequence of p53 loss in activating the IL-6–STAT3 axis is the modification of the tumour microenvironment, as loss of STAT3 in p53-null pancreatic cancers reduces PMN infiltration (Wörmann et al., 2016). p53 can also indirectly suppress the expression of certain chemokine receptors, including CXCR4 and CXCR5, thereby reducing cancer cell migration (Mehta et al., 2007; Mitkin et al., 2015) (Fig. 2).

Beyond loss of wild-type p53 function, certain p53 mutants can gain new activities that influence cytokine signalling. NF- $\kappa$ B is a transcription factor that responds to pro-inflammatory signals. Classical activation of NF- $\kappa$ B involves the cytoplasmic release of the heterodimer between the NF- $\kappa$ B subunits p50 and p65 (p50 is encoded by *NFKB1* and p65 by *RELA*) from inhibitor of  $\kappa$ B (I $\kappa$ B), allowing transcriptional upregulation of tumour necrosis factor (TNF), IL-1 $\beta$ , IL-6 and other pro-inflammatory mediators (Hayden and Ghosh, 2014). Wild-type p53 and NF- $\kappa$ B take part in a complex crosstalk by transcriptionally co-regulating each other (Komarova et al., 2005; Ravi et al., 1998; Webster and Perkins, 1999). By contrast, expression of the p53 R175H mutant can potentiate NF- $\kappa$ B signalling and increase p65 nuclear localisation (Cooks et al., 2013; Weisz et al., 2007). Some mutant p53 proteins interact with p65, forming a complex that increases NF- $\kappa$ B transcriptional activity (Rahnamoun et al., 2017). Challenging mice with the inflammatory agent dextran sulphate sodium (DSS), a model of IBD and IBD-associated colorectal cancer, promotes inflammation-induced NF- $\kappa$ B and renders mice bearing germline p53 R172H mutations (the mouse equivalent of human R175H mutations) susceptible to colorectal adenomas (Cooks et al., 2013). The p53 R273H mutant can also sustain IL-1 $\beta$  signalling by transcriptionally repressing IL-1 receptor antagonist (IL-1RA) (Ubertini et al., 2015).

### The p53 status of tumours shapes the immune landscape by regulating myeloid and T cell populations

Loss of p53 function in cancers results in profound changes in chemokine/cytokine secretion, leading to important effects on the immune environment (Bezzi et al., 2018; Walton et al., 2016; Wellenstein et al., 2019; Wörmann et al., 2016) (Fig. 3). Tumour-infiltrating myeloid populations range from PMNs, including neutrophils, to monocytes and macrophages (Bronte et al., 2016). In prostate, breast and ovarian cancers, p53 loss promotes the recruitment of tumour-supporting myeloid cells (Bezzi et al., 2018; Walton et al., 2016; Wellenstein et al., 2019), while in breast cancer models, p53 loss within the tumour promotes dysregulated WNT signalling and consequently increases circulating neutrophils involved in supporting tumour growth and metastasis (Wellenstein et al., 2019). Monocytes home to the ascites of p53-null orthotopic ovarian cancers, potentially through tumorigenic production of CCL2 (Walton et al., 2016). Furthermore, the combination of PTEN and p53 loss in prostate cancer models increases the secretion of CXCL17, leading to the recruitment of tumour-associated PMNs. In this model, inhibition of PMN infiltration by CXCR2 receptor blockade attenuates tumour growth (Bezzi et al., 2018). Similarly, PMN recruitment has been shown to be supported by STAT3 signalling in p53-null pancreatic



**Fig. 3. Loss of p53 in cancer cells modifies the immune environment.** Loss of p53 in cancer cells modulates their cytokine production, which influences various tumour-associated immune populations (myeloid cells, neutrophils, macrophages, monocytes and regulatory T cells). MCP1 recruits all myeloid cells – neutrophils, macrophages and monocytes – while CXCL17 attracts PMNs (CD11bGr1), and CXCL10 is a general myeloid chemoattractant. M-CSF promotes the homeostasis and differentiation of macrophages. Regulatory T cells are enriched in p53-null tumours, a response that is in part mediated through *de novo* generation of Tregs by PMNs. Overall, the recruitment of these immune populations reduces T cell responses to favour tumour growth.

tumours, although the role, if any, of p53 loss in this response is not clear (Wörmann et al., 2016).

Tumour-associated macrophages (TAMs) also increase in response to loss of p53 in ovarian, lung, pancreatic and 7,12-dimethylbenz[*a*]anthracene (DMBA)-induced skin cancers (Ruddell et al., 2008; Walton et al., 2016). Pharmacological inhibition or neutralization of colony-stimulating factor 1 receptor (CSF1R), impedes macrophage differentiation and survival, reduces TAMs in both p53-null and mutant-p53-expressing pancreatic tumours and can modestly retard tumour growth in some models (Candido et al., 2018; Zhu et al., 2014). Overall, it seems likely that simultaneously targeting several immune-modulating aspects of p53 loss in cancers will provide the most effective and durable tumour-limiting responses.

Supporting the association of p53 loss with macrophage infiltration seen in mouse models of cancer, human breast cancer datasets show positive correlations between CSF1 response signatures and p53 mutations (Beck et al., 2009). In addition to modifying CSF1 signalling, several other p53-associated pathways influence macrophage recruitment and function. For example, myeloid cells within p53-null tumours are recruited and reprogrammed through the secretome of p53-deficient cancer cells towards tumour-promoting macrophages (Blagih et al., 2020). Furthermore, some mutant forms of p53 gain the ability to influence macrophage behaviour. For example, the ability of the p53 R248W mutant to accelerate tumour growth reflects, in part, exosome secretion of miR-1246 and its macrophage-instructing function (Cooks et al., 2018). Either through loss of p53 or the selection of mutant gain-of-function forms of p53, cancer cells can repurpose macrophages and other myeloid subsets to help support tumour development.



p53 deficiency in some tumours also modulates Treg cell populations, which are involved in suppressing effector T cells found in the tumour and in the periphery (Togashi et al., 2019). Loss of p53 in prostate, ovarian and subcutaneous pancreatic cancers can increase peripheral and intratumoural Tregs, which in prostate cancers reflects *de novo* differentiation of Tregs elicited by p53-null tumour-educated PMNs (Bezzi et al., 2018) (Fig. 3). In addition to acquiring more Tregs, p53-null tumour-bearing mice develop highly suppressive Treg populations in comparison to wild-type controls (Blagih et al., 2020). Another consequence of p53 loss within tumours is a reduction of activated inflammatory cytokine-producing T cells, which are involved in tumour regression. This ability of p53-null cancer cells to promote immune suppression can be overcome by Treg depletion and CSF1R neutralization (Blagih et al., 2020), highlighting a complex interplay of both suppressive myeloid and Treg populations in dampening T cell effector function.

### **p53-mediated senescence in cancer cells regulates leukocyte recruitment through SASP**

Various forms of oncogenic or genotoxic stress can trigger a stable cell cycle arrest in cells, termed senescence (Chen et al., 2005; Nelson and Kastan, 1994). p53 is an important mediator of senescence, which can prevent the further proliferation of nascent tumour cells and therefore represents a tumour-suppressing function of p53 (Rufini et al., 2013; Zambetti et al., 1992). In addition to growth arrest, senescence is accompanied by the production of an array of angiogenic and growth factor cytokines known as the senescence-associated secretory phenotype (SASP) (Hernandez-Segura et al., 2018). The SASP molecules can attract both anti- and pro-tumorigenic immune populations, depending on the cancer type and mechanism of senescence (Coppé et al., 2008; Herranz and Gil, 2018).

Re-expression of wild-type p53 in established hepatocellular carcinomas (HCCs) and transplantable lung adenocarcinomas (LUADs) induces senescence, resulting in the production of SASP-related chemokines and cytokines. In response, the recruitment of NK, T and myeloid cells contribute to the clearing of the cancers (Iannello et al., 2013; Stokes et al., 2019; Xue et al., 2007). Modulating leukocyte trafficking, either through CCL2 antibody blockade or by using lymphocyte-deficient hosts, prevents SASP-mediated immune clearance of cancer cells and supports tumorigenesis (Iannello et al., 2013). Similarly, loss of PTEN in prostate epithelial cells promotes p53 stabilization and senescence, which impedes tumour development (Chen et al., 2005). However, SASP induction can also promote the infiltration of immune cells that aid escape from senescence, allowing cancer cell progression. For example, IL-1 production by senescent cells can reinforce senescence (Acosta et al., 2013), and the secretion of IL-1RA by infiltrating PMNs in benign prostate lesions leads to the suppression of IL-1 signaling and the downregulation of p53 expression. As a consequence, some tumour cells bypass proliferation arrest and progress to prostate cancer (Di Mitri et al., 2014).

### **Functions of p53 in stromal populations during tumour development and progression**

The tumour–stromal network is a heterogeneous population of cells, originating from mesenchymal or lymphoid origins, that directly or indirectly interact with tumour cells (Mahadevan and Von Hoff, 2007; Pietras and Östman, 2010). While there has been a focus on how alterations of p53 in the tumour cells contribute to cancer progression, tumour cells expressing wild-type p53 show accelerated growth when transplanted into p53-null hosts (Guo

et al., 2013), demonstrating a role for p53 in the non-cancer-associated stromal cells in modulating tumorigenesis.

### **p53 within the mesenchymal stromal compartment restricts tumour growth**

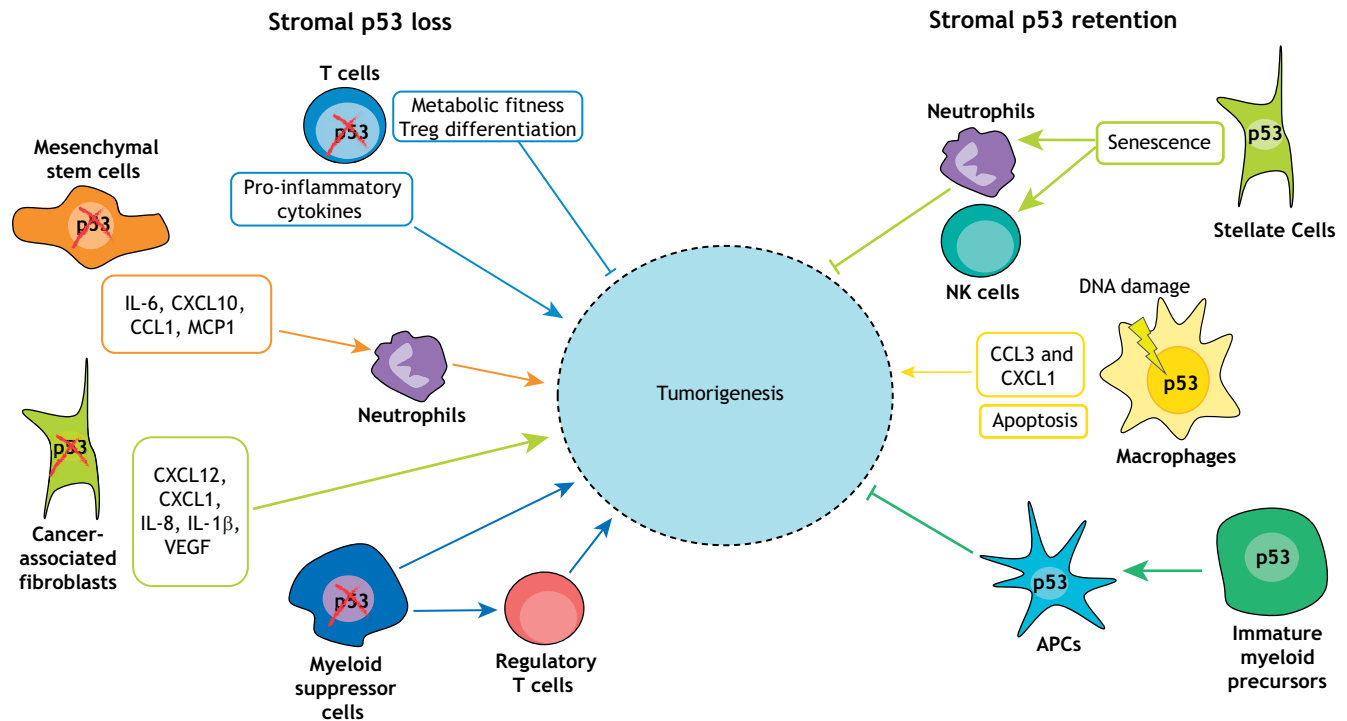
A consideration of the activities of p53 in the mesenchymal stroma becomes important in two broad contexts. Firstly, many systemic chemotherapy or radiation therapy regimes function to activate p53 in both stroma and tumour cells, so understanding the consequences of this response in the normal cells surrounding a tumour may help to improve these therapies. Secondly, recent studies show that many apparently normal somatic cells harbour alterations such as p53 mutation (Kennedy et al., 2019), and that positive selection for clones harbouring these mutations occurs as a normal part of ageing. Some studies have suggested the presence of p53 mutations in cancer-associated fibroblasts (CAFs) (Hill et al., 2005; Kurose et al., 2002; Patocs et al., 2007), raising the possibility that the tumour microenvironment may also be mutated. It has been suggested that Li Fraumeni patients, who carry a mutant p53 allele in all tissues, are cancer prone, in part, because changes in p53 function in normal tissue support the development of malignant cancer (Pantziarka, 2015).

Several studies have shown that p53 in mesenchymal stromal cells can function to restrain tumour development (Fig. 4). Loss of p53 in CAFs, mesenchymal stem cells (MSCs) or hepatic stellate cells (HSCs) promotes the growth of many cancer cell types including breast, prostate, ovarian and liver cancers (Addadi et al., 2010; Huang et al., 2014; Narendran et al., 2003; Ren et al., 2012; Schauer et al., 2013). Deletion or suppression of p53 in CAFs relieves the repression of pro-inflammatory chemokine and cytokine production, including CXCL1, CXCL12, IL-8, IL-1 $\beta$  and vascular endothelial growth factor (VEGF), thereby regulating leukocyte and cancer cell migration and angiogenesis (Addadi et al., 2010; Narendran et al., 2003; Schauer et al., 2013) (Fig. 4). In MSCs, which can function to support neoplastic growth, loss of p53 leads to the secretion of chemokines that drive the recruitment of tumour-promoting neutrophils that suppress T cell responses (Huang et al., 2014; Ren et al., 2012). Blocking the receptor for CCL2, C-C chemokine receptor type 2 (CCR2), is sufficient to counteract the tumour-promoting effect of p53-null MSCs (Ren et al., 2012).

Fibrosis-associated liver damage has been shown to induce p53-dependent senescence and SASP production in hepatic stellate cells (HSCs). This response attracts NK and myeloid cells that can function to remove damaged hepatocytes and so limit fibrosis, cirrhosis and HCC development (Krizhanovsky et al., 2008; Lujambio et al., 2013) (Fig. 4).

### **Alterations of p53 in leukocytes affect tumour growth**

The function of immune cells can also be regulated by p53 (Komarova et al., 2005; Li et al., 2015). In some studies, p53-null mice show increased susceptibility to inflammation and autoimmunity, responses that could contribute to tumour growth (Donehower et al., 1992; Guo et al., 2013; Okuda et al., 2003; Zheng et al., 2005). Indeed, enhanced growth of tumours in p53-null hosts is likely to reflect, to some extent, the consequences of loss of p53 in the immune cells. Therefore, in order to dissect the role of p53 in various immune compartments, genetic alterations of p53 in monocytes, pan myeloid lineages and T cells have been investigated (Banerjee et al., 2016; He et al., 2015; Sharma et al., 2018) (Fig. 4).



**Fig. 4. Functions of p53 in stromal cells.** The consequences of loss (left) or retention (right) of p53 in stromal cells are shown. Right: immature myeloid precursors recruited to the tumour depend on p53 for their differentiation into antigen presenting cells (APCs). Activation of wild-type p53 in stellate cells promotes a senescence response that recruits leukocytes (neutrophils and NK cells) that function to clear tumour cells. Both of these responses are tumour suppressive. However, damage-induced p53 in macrophages either eliminates these cells through apoptosis or drives the expression of the proinflammatory cytokines CCL3 and CXCL1. These responses may contribute to tumour progression. Left: loss of p53 in cancer-associated fibroblasts or mesenchymal stem cells increases cytokine secretion, which drives tumour growth and the recruitment of tumour-promoting neutrophils. In myeloid suppressor cells, loss of p53 directly or indirectly (through the recruitment of regulatory T cells) helps to promote tumorigenesis. The loss of p53 in T cells promotes the expression of potentially pro-tumorigenic inflammatory cytokines. However, p53-null T cells show increased metabolic fitness and a defect in Treg differentiation, both of which may limit cancer development.

Different studies have identified a complex role for p53 activity in myeloid cells, reflecting the abilities of these cells to either inhibit or promote cancer development. In most tumour models, p53 in the myeloid compartment regulates the fine balance between myeloid suppressor cells and antigen-presenting cells (APCs), the latter of which shape T cell-mediated anti-tumour immunity (Fu and Jiang, 2018). Loss of p53 from all stromal cells in subcutaneous tumour models and myeloid-specific deletion of p53 in a colorectal cancer model increase the number of tumour-promoting myeloid cells and tumour progression (Guo et al., 2013; He et al., 2015). In line with this, local stabilization of p53 reprograms suppressive myeloid populations towards effective APCs and induces tumour regression in some, but not all, subcutaneous cancer models (Guo et al., 2017) (Fig. 4). In this case, activation of p53 in myeloid cells limits the inflammatory response and reduces tumour development (Guo et al., 2013, 2017; He et al., 2015). In some models, intratumoral APCs derived from immature myeloid precursors (IMPs) have been shown to rely on p53 to upregulate the expression of transcription factors associated with differentiation. As a result, deletion of p53 in these IMPs accelerates subcutaneous tumour growth due to a lack of tumour-associated APCs and, consequently, reduces T cell activation (Sharma et al., 2018) (Fig. 4).

However, in some cases, p53 induction within the myeloid lineage can be tumour promoting. In a mouse model of diethylnitrosamine (DEN)-induced liver cancer, activation of p53 in hepatic macrophages results in macrophage depletion, leading to HCC development (Li et al., 2018) (Fig. 4). DNA-damaging agents

can also induce p53 and NF- $\kappa$ B co-regulated signalling in human macrophages to stimulate the secretion of the leukocyte-recruiting chemokines CXCL1, CCL3 and CCL20 – another response that may play a supportive role in tumorigenesis (Lowe et al., 2014) (Fig. 4). While these studies suggest that stress-induced p53 in myeloid cells can be tumour promoting, the experiments using genetic ablation of p53 in myeloid lineages in tumour-bearing mice point towards a tumour-suppressive role for p53 in the myeloid compartment.

Without TCR engagement, p53 functions to limit T cell proliferation (Watanabe et al., 2014), and deletion of p53 in T cells results in an inflammatory phenotype and spontaneous autoimmunity (Kawashima et al., 2013; Zhang et al., 2011), which could help to promote cancer development (Fig. 4). However, p53 also regulates CD4<sup>+</sup> T cell polarisation by transcriptionally upregulating FOXP3, the transcription factor responsible for Treg differentiation (Kawashima et al., 2013). Loss of this role of p53 in T cells would reduce Treg differentiation and would predict enhanced anti-tumour immunity in hosts with T-cell-specific ablation of p53 (Fig. 4). Furthermore, genetic deletion of p53 in antigen-specific T cells increases their metabolic fitness and reduces human melanoma growth in xenograft models (Banerjee et al., 2016) (Fig. 4). The concept that p53 activity in T cells can limit the anti-tumour immune response is interesting, but may be influenced by p53-dependent responses in other stromal compartments. Indeed, subcutaneous tumours grown in p53-null mice accumulate more Tregs compared with syngeneic wild-type controls, suggesting that other p53-null

stromal populations help to promote Treg polarisation (Guo et al., 2013).

### Immune recognition of p53 in cancers

While wild-type p53 levels are very low in normal cells, mutant p53 proteins tend to accumulate at high levels in cancer cells. These observations raise the possibility that the tumour-specific expression of p53 could stimulate a B cell (humoral) response, providing diagnostic value, as well as activating T cells that may be harnessed for vaccination (Fig. 5).

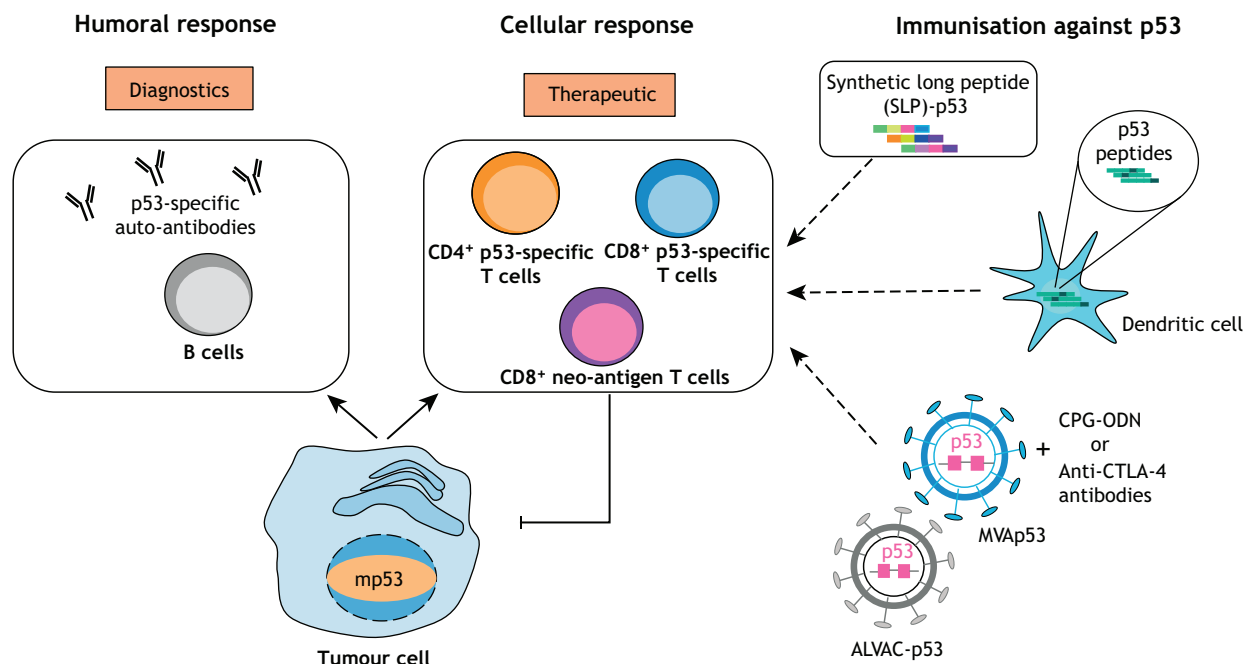
#### p53 accumulation in cancer increases circulating B cell autoantibodies

A strong correlation between p53 mutation and the presence of autoantibodies against p53 has been reported in ovarian, lung, colorectal, breast and liver cancer patients (Angelopoulou and Diamandis, 1997; Angelopoulou et al., 1997; Davidoff et al., 1992; Houbiers et al., 1995; Lubin et al., 1995; Volkmann et al., 1993) (Fig. 5). Antibodies raised against autologous p53 predominantly recognise epitopes found in the N- and C-termini of the protein, which generally excludes epitope recognition in hotspot regions affected by the mutations (Schlichtholz et al., 1992). These observations suggest that the production of anti-p53 antibodies is a consequence of protein accumulation rather than being the outcome of neo-epitopes generated from mutant p53. The presence of circulating anti-p53 autoantibodies could provide diagnostic value to some mutant p53 cancers, although not all cancers harbouring mutations in p53 develop an antibody response (Rainov et al., 1995; Weller et al., 1998). The prognostic significance of p53 autoantibodies is also unclear. While anti-p53 antibodies predict a poorer survival in colorectal cancer (CRC), potentially reflecting a

high tumour burden, ovarian cancer patients with autoantibodies against p53 show improved survival (Angelopoulou and Diamandis, 1997; Goodell et al., 2006; Houbiers et al., 1995). Unfortunately, beyond the scope of serum autoantibodies, little is known about the role of B-cell-mediated immunity in cancers with p53 perturbations.

#### T cell recognition of cancer-associated p53 and developing vaccine-based therapy

The clear importance of p53 in controlling the development of cancer has prompted numerous attempts to develop anti-p53 vaccines. While T cells are crucial to restricting tumour growth, raising a T cell response against self-proteins such as p53 may breach self-tolerance and result in autoimmunity. However, a number of studies have shown that inducing a T cell response against wild-type p53 does not cause autoimmunity in mice and that p53 might be a safe target for vaccination (Hernández et al., 2000; Lauwen et al., 2008; Vierboom et al., 1997; Zwaveling et al., 2002). Evidence of CD4<sup>+</sup> and CD8<sup>+</sup> T-cell-specific responses against p53 are seen in head and neck, ovarian and colorectal cancers (van der Burg et al., 2001) (Fig. 5). In both humans and mice, mutant p53 tumours can elicit T cell responses against wild-type p53 epitopes, and human head and neck cancers that harbour mutations in p53 are also associated with the development of dominant T cell clones against wild-type p53 peptides (Albers et al., 2018; Fedoseyeva et al., 2000; Lambeck et al., 2007; van der Burg et al., 2002). Furthermore, adoptive transfer of wild-type p53-specific T cell clones limits the growth of mutant p53 transformed MEFs *in vivo* (Hoffmann et al., 2002; Zwaveling et al., 2002). Taken together, these data indicate that the development of a T cell response against wild-type p53 epitopes could target both mutant and wild-type p53 cancer cells.



**Fig. 5. Immune responses to p53 expression in tumour cells.** p53 expression in cancer cells can provoke immune recognition, most commonly in response to the accumulation of high levels of mutant p53 protein. The presence of p53-specific autoantibodies can be detected in patients with a variety of cancers, such as colorectal, liver, ovarian, lung and breast cancers, and may have diagnostic value. p53 can also elicit T-cell-specific responses both in CD4<sup>+</sup> and CD8<sup>+</sup> T cells, including those recognising neo-antigens derived from point-mutated p53 proteins. Therapeutic approaches using p53 vaccines or synthetic long peptides of p53 drive T cell responses, and have shown some efficacy in early clinical trials. Vaccine-based therapies include use of ALVAC-p53 and MVAp53. Combination therapy with either CPG-ODN or anti-CTLA-4 antibodies and MVAp53 elicits T cell responses that might reduce tumour growth. SLP-p53 alone and dendritic cells (DCs) pulsed with mutant p53 peptides can also drive p53-specific T cell responses.



T cells generated to recognise neo-epitopes of p53 that contain hotspot mutations (and therefore would not be present in wild-type p53) have been detected in lung cancer patients and in mouse models (Fedoseyeva et al., 2000; Malekzadeh et al., 2019). Similarly, syngeneic growth of mutant p53 sarcoma cell lines in mice generated CD8<sup>+</sup> and CD4<sup>+</sup> T cells against a neo-antigen containing the mutated amino acid (Fedoseyeva et al., 2000; Noguchi et al., 1994) (Fig. 5). Therefore, it is evident that mutant p53 is effectively processed, presented and immunogenic (Couch et al., 2007; Malekzadeh et al., 2019), and may allow the generation of a cancer-specific immune response. Interestingly, different antigenic T cell clones against wild-type p53 and mutant sequences develop over the time-course of mutant p53 sarcoma growth in mice, highlighting a dynamic process of immune–tumour evolution (Fedoseyeva et al., 2000).

Various approaches aimed at developing vaccines to boost T cell responses against p53 are being explored (Fig. 5). One method of stimulating an immune response against p53 in mouse models of cancer is treatment with a modified vaccinia Ankara-expressing murine p53 (MVAp53) virus. Single-agent therapy of MVAp53 provide only moderate relief from tumour burden, despite the presence of a p53-specific T cell response. However, combining this therapy with the TLR9 agonists CpG deoxynucleotides (CPG-ODN) or CTLA-4 blockade successfully induces tumour rejection (Daftarian et al., 2004; Espenschied et al., 2003) (Fig. 5). Other methods of vaccination include priming dendritic cells (DCs) with mutant p53 peptides and adoptively transferring them into tumour-bearing hosts. This approach was shown to successfully promote T cell activation and tumour regression (Mayordomo et al., 1996) (Fig. 5).

Building on these preclinical models, several phase I and II trials have been organized globally using different delivery methods of p53. One vaccination approach utilises the synthetic long peptide of p53 (SLP-p53<sup>®</sup>), which has been primarily used in phase I/II trials in ovarian cancer patients post chemotherapy. Interestingly, only p53-specific CD4<sup>+</sup> T cell responses were observed and sustained after chemotherapy (Fig. 5). Unfortunately, however, no impact on overall survival was detected in any of the trials (Leffers et al., 2009, 2012; Vermeij et al., 2012). Other trials testing the effect of SLP-p53<sup>®</sup> in combination with therapies such as gemcitabine and Pegniron (IFN $\alpha$ ) are underway (Dijkgraaf et al., 2015). Another method of stimulating p53-specific responses is the use of the recombinant canary pox virus vaccine encoding wild-type human p53 (ALVAC), which has shown promise in preclinical models (Roth et al., 1996) (Fig. 5). Clinical trials of this vaccine in advanced CRC or small cell lung carcinoma patients did not show benefit, despite inducing a p53-specific T cell response (Antonia et al., 2006; Chiappori et al., 2019; van der Burg et al., 2002). However, one phase I trial using MVAp53 gene therapy in platinum-resistant ovarian cancers showed an increase in patient survival (Hardwick et al., 2018). The potential to combine this approach with checkpoint inhibitors remains to be explored.

### Concluding remarks

While the cell-autonomous tumour-suppressor functions of p53 have been studied extensively, we are just beginning to appreciate the impact of p53 on the immune response to the cancer cell. Perturbations in p53 contribute to the ability of tumour cells to escape from immune surveillance and thus promote an immunosuppressive environment. Loss or mutation of p53 in the tumour has been shown to modulate immune recognition through mechanisms such as decreased MHC-I presentation and increased

recruitment of suppressive myeloid cells and Tregs. However, p53 also has a crucial role in the stromal compartment, where it can play diverse roles in inhibiting or supporting tumour development. Functions of p53 in epithelial, mesenchymal or immune cells are unlikely to have been selected for tumour suppression and the role of p53 in normal development and in the control of other diseases is slowly being uncovered (Labuschagne et al., 2018; Vousden and Lane, 2007). For example, p53 activity in normal T cells is necessary to prevent inappropriate proliferation in the absence of TCR signalling, allowing tight regulation of antigen-specific T cell expansion (Watanabe et al., 2014). In terms of cancer therapy, however, the generation of tumour-limiting immune responses to mutant p53, whose expression is predominantly seen in premalignant and malignant cells, is an extremely attractive proposition. We hope that an increased understanding of how p53 modulates the immune response to cancer will allow for the development of targeted therapies and the promotion of long-lasting anti-tumour responses in patients.

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### Competing interests

K.H.V. is on the Board of Directors and shareholder of Bristol Myers Squibb, a shareholder of GRAIL, Inc. and on the Science Advisory Board of PMV Pharma, RAZE Therapeutics, Volestra Therapeutics and Ludwig Cancer. She is a co-founder and consultant of Faeth Therapeutics, funded by Khosla Ventures. She has been in receipt of research funding from Astex Pharmaceuticals and AstraZeneca and contributed to CRUK Cancer Research Technology filing of Patent Application WO/2017/144877.

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