**Introduction**

Since its discovery in 1979, many different roles for the tumor suppressor protein p53 in tumorigenesis have been described. Correct p53 function is required for proper regulation of cell division, apoptosis, senescence, and the responses to cellular stresses such as DNA damage and hypoxia. Indeed, mutations in p53 are observed in as many as 50% of human cancers. However, recent reports have highlighted an emerging role for p53 in anti-viral immunity. This chapter reviews the available literature on p53 and the body’s immune response, and how p53 may link immunity and cancer.

**Overview of the Immune System**

The immune system comprises an innate and an adaptive component. Upon exposure to pathogens or foreign molecules (antigens), the innate response is immediately triggered. If the innate component is unable to clear the pathogen and infection persists, the adaptive response is activated.

The innate immune system comprises structural barriers against infection, such as the skin, and phagocytic cells such as macrophages and neutrophils. The innate response has therefore been believed to be largely nonspecific. However, specialized cell surface receptors, toll-like receptors (TLRs), respond to particular pathogen-derived molecules, such as lipopolysaccharides, CpG deoxynucleotides and double-stranded (ds) RNA (reviewed in ref. 3). Viral dsRNA is also recognized by cytoplasmic receptors such as RIG-I. Overall, particular pathogen-associated molecular patterns (PAMPs) will generate particular patterns of signaling pathway activation. This leads to the production of Type I interferons and pro-inflammatory cytokines. Interestingly, p53 appears to be involved in the TLR response, as described later in this chapter.

The adaptive component is the “specific” response of the immune system. It comprises T and B lymphocytes, and antigen presenting cells (APCs). During development these lymphocytes undergo a series of gene rearrangements and selections, culminating in the expression of a unique cell surface receptor (T cell receptor or B cell receptor ('antibody')). APCs internalize antigenic molecules, process them and express antigens on their surface with molecules known as MHCs (major histocompatibility complex). T cells, through their specific T cell receptors, recognize these MHC-antigen complexes, and initiate the cell-mediated response. Activated T cells give rise to various T cell sub-groups having distinct functions, including cytotoxic T cells, which secrete toxic molecules to kill pathogens, and helper T cells, which secrete cytokines including IL-4 (Th2 cells) and Type II interferons (IFNγ, Th1 cells). B cells, through their B cell receptor recognize and bind to free antigens that are not usually presented by MHCs. The binding of a B cell to an antigen causes it to divide rapidly, generating clones secreting the same
specific antibody. T_{H} cells are required for this process. Adaptive immune cells which remain in
the bloodstream give the immune system a component of 'memory'.

Recently, it has become clear that the innate and adaptive immune systems are not entirely
distinct. For instance, TLRs link the two systems: TLRs are required both for activation of T_{H}
cells, and for B-cell activation.

**p53 in the Antiviral Response**

In addition to its role in ensuring genome stability as a key activator of the cells DNA
damage responses, the tumor suppressor protein p53 appears to play a role in the response to
viral infections. It is well-known that p53 is targeted by many oncogenic viruses. Examples of
this are human Papillomavirus protein E6 binding to and inactivating p53 and SV40 cellular
transformation where p53 is inactivated by large T-antigen, both mechanisms allow host cell
survival and proliferation, which correlates with tumorigenesis. However, interestingly, the
anti-viral role of p53 is not limited to tumor viruses and this is highlighted by the fact that
many viruses have evolved proteins that bind to and inactivate or degrade p53, highlighting the
role of p53 in general defense, in addition to protection against cancer.

**p53 Cooperation with IFNα/β**

The first link between p53 and the general antiviral response was demonstrated by Takaoka
et al. The authors showed that treating cells with Interferon (IFN) α and β caused an increase
in both p53 mRNA and protein levels. This induction was mediated by Interferon Stimulated
Gene Factor 3 (ISGF3), a heterotrimer comprising Stat1 (signal transducer and activator of
transcription factor), Stat2 and IRF-9 (interferon regulatory factor 9), binding to
interferon-stimulated response element (ISRE) consensus sequences in the p53 promoter.

Interestingly, this induction did not correlate with activating phosphorylations or produc-
tion of p53 target genes. Therefore, IFN induction of p53 may sensitize cells to subsequent
stresses, but may not by itself be sufficient to fully activate the p53 pathway. In addition to
direct activation by the Type 1 interferons p53 can also be indirectly activated by IFIXα-1 an
IFN-inducible protein which inhibits MDM2-dependent degradation of p53. Further, p53
has been shown to cooperate with a number of IFN-inducible proteins to regulate gene expres-
sion including STAT1, IRF-1 and PML.

**p53 Protects against Virus Infection**

In addition to a role in the response to DNA tumor viruses such as SV40, human
papillomavirus, Kaposi's sarcoma herpesvirus and adenovirus, p53 function is also activated by
nontransforming virus such as the DNA virus HHV-6B and RNA viruses such as influenza
virus, poliovirus and vesicular somatitis virus (VSV). One of the ways in which cells respond to
viral infection is by activating signaling pathways that initiate a protective programme leading
to cell death, thus limiting the spread of the viral infection. The role of p53 in viral infection
has been linked to this cell death arm of the anti-viral response. For example, using MEFs
(mouse embryonic fibroblasts) from 'super' p53 mice which exhibit enhanced cancer resis-
tance, a 10-fold decrease in virus yield is seen in VSV infected cells when compared to MEFs
from wild-type animal. This corresponds with enhanced apoptosis of infected super p53 MEFs,
which is likely to be p53-mediated: the proapoptotic p53 target gene Puma was upregulated in
these cells, while p21, a p53 cell cycle arrest target, was not. Studies on influenza virus also
supported the link between p53 status and virus induced cell death as dominant negative p53
inhibited cell death in influenza infected lung cell lines. More recently, it has been suggested
that p53 is activated at a much earlier stage in the infection process suggesting that p53-medi-
ated gene expression plays a role in the early as well as the later stages of viral infection. Thus,
influenza infection produces a bi-phasic p53 response with an early peak in protein levels 6-8
hours post infection that is not associated with viral replication and which also occurs in the
presence of UV-inactivated viral particles. At later time points a second p53 peak is observed
which has been shown to require live replication competent virus.