PERSPECTIVE

When viral oncoprotein meets tumor suppressor: a structural view

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In 1898, Friedrich Loeffler and Paul Frosch reported on the identification of a filterable agent that was the cause of foot and mouth disease in livestock (Levine 2001). This was the first identification of a vertebrate virus, shortly after the isolation of the tobacco mosaic virus by Dimitrii Ivanovsky in 1892 (Horzinek 1997). Since these initial discoveries, we have come to appreciate how these genetic entities that lie somewhere between the living and nonliving state survive, propagate, infect, and mediate disease. We know that in the absence of a host cell, these obligate parasites exist in a latent form containing a protein or membrane coat surrounding genetic material that encodes protein products that are essential for host infection and propagation of the virus. Upon contact with its host cell, the virus injects its genetic material to exploit the host cellular machinery to assemble more virus particles that eventually go on to infect other host cells. We also know that many viruses are the causative agents for human diseases such as smallpox, influenza, the common cold, AIDS, and cervical cancer. We know considerably less about the molecular mechanisms for how viral proteins subvert the host machinery to establish the disease state. A study in this issue of *Genes & Development* by Lilyestrom et al. (2006) reports on a crystal structure of the simian virus 40 (SV40) large T-antigen (LTag) bound to the human p53 protein, a target that is also inactivated in the majority of human cancers. The study provides the first molecular insights into the mode of viral inactivation of this “guardian of the genome” and suggests avenues for the structure-based design of viral inhibitors (Weinberg 1997; O’Shea 2005).

More about viruses

Based on genome type, viruses can be grouped into two major categories: RNA viruses and DNA viruses. Examples of RNA viruses are influenza virus, severe acute respiratory syndrome (SARS) virus, and human immunodeficiency virus (HIV); examples of DNA viruses are

SV40, human papillomavirus (HPV), and adenovirus (Ad). Owing to the lack of particular enzyme activities in host cells, it is essential for most RNA viruses to encode either viral RNA-dependent RNA polymerases or viral RNA-dependent DNA polymerases (also known as reverse transcriptase) to achieve viral genome replication via an RNA or a DNA intermediate, respectively (Temin and Baltimore 1972; Ramig 1997; Neumann et al. 2002; Ahlquist et al. 2003; Ahlquist 2006). In contrast to RNA viruses, DNA viruses utilize the DNA replication machinery of the host cell in order to propagate their respective viral genomes. SV40 from *Polyomaviridae*, HPV from *Papillomaviridae*, and *Adenoviridae* (Ad) are the most-studied types of DNA viruses that are also known as tumor viruses due to the cancer-causing proteins that they encode. In accordance with the central role of genome amplification in their viral life cycle (Doorbar 2005), viruses have evolved diverse and elegant strategies to create a favorable replication environment by usurping and manipulating host cellular factors to replicate their own genome. SV40 LTag, HPV E6 and E7 proteins, and Ad E1A and E1B proteins (Fig. 1) are oncogenic early genes encoded by DNA tumor viruses that are capable of subverting for viral replication the otherwise tightly controlled host cell cycle (Munger et al. 2004; Ahuja et al. 2005; Berk 2005).

Two tumor suppressors that rule all

The hallmark of cancer is uncontrolled cell division resulting in tumor formation. Thus, the molecular mechanisms that control cell division have been a major focus of basic cancer research. The fidelity of cell division is maintained in a process called the cell cycle that contains four distinct phases, G1, S, G2, and M. During the S phase, DNA replication takes place; the M phase is when cells divide during a process called mitosis; and G1 and G2 are two gaps that precede the S and M phases, respectively. Cell progression through these phases correlates with the activity of a family of protein kinases called cyclin-dependent kinases (CDKs), which become fully activated when they are phosphorylated at a particular threonine residue and bound to regulatory subunits called cyclins. CDK inhibitory proteins (CKIs) function to inactivate particular CDK/cyclin complexes. Intrinsic checkpoints function to protect cells from ab-

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Figure 1. Gallery of viral oncoprotein–tumor suppressor interactions. The tumor suppressors p53 and pRb, and oncoproteins from the small DNA tumor viruses SV40 LTag, HPV E7 and E6, and Ad E1A and E1B are shown as domain structures (adapted from the domain definitions of Pfam [<http://www.sanger.ac.uk/Software/Pfam>] and not drawn to scale). Cartoon representations of the independently folded structures from these proteins are also shown. Dashed arrows pointing to protein domains indicate the locations of structurally confirmed interactions between the viral oncoproteins and tumor suppressors, and dashed arrows pointing to the protein names indicate biochemically defined interactions only. The small solid-black bars within SV40 LTag, HPV E7, and Ad E1A signify the LxCxE motif. Designation of letter symbols on the domains are as follows: (p53-TA) Transactivation domain; (p53-DB) DNA-binding domain; (p53-T) tetramerization domain; (p53-R) regulatory domain; (pRb-N/C) N/C-terminal domain; (pRb-A) A-box of the pocket domain; (pRb-B) B-box of the pocket domain; (SV40 Large T-antigen-J) DnaJ-like domain; (SV40 Large T-antigen-DB) DNA-binding domain (Origin); (SV40 Large T-antigen-H) Helicase domain; (E7/E1A-CR) conserved region; (E6/E1B-N/C) N/C-terminal domain. Structure coordinates that are used for making images in PyMOL (<http://www.pymol.org>) were obtained from the Protein Data Bank (<http://www.pdb.org>).

errant proliferation along cell cycle procession, and loss of checkpoint control is the cause of many human cancers (Hartwell and Weinert 1989; Lowe et al. 2004). The p53 and retinoblastoma protein (pRb) play key roles in controlling progression through the cell cycle, whereby p53 exerts its effect on the G2–M and G1–S transition and pRb exerts its effect on the G1–S transition. Mutations that inactivate p53 or pRb function result in uncontrolled cell division leading to cancer, and so these proteins are called tumor suppressors (Hollingsworth et al. 1993; Weinberg 1995; Levine 1997). Not surprisingly, mutations of both tumor suppressors are observed frequently in human cancers of various types (Sherr 2004), and p53, also called “guardian of the genome” (Lane 1992), is mutated in the majority of human cancers.

p53 is a transcription factor that responds to cellular stresses such as DNA damage by binding to DNA and regulating the transcription of genes involved in cell cycle arrest, apoptosis, or senescence (Coutts and La Thangue 2006). Human p53 is 293 residues long, com-

prising four functionally distinct domains: an N-terminal transcriptional activation domain, a central core DNA-binding domain, a tetramerization domain, and a C-terminal regulatory domain (Fig. 1). The less structured N- and C-terminal domains (Bell et al. 2002; Dyson and Wright 2005) harbor sites for reversible and dynamic post-transcriptional modifications with phosphate, acetyl, and ubiquitin groups, which have been implicated in the regulation of p53 transcriptional activities (Steegenga et al. 1996; Waterman et al. 1998; Barlev et al. 2001; Li et al. 2002; Smith 2002; Brooks and Gu 2006). The more structured central DNA-binding core domain and tetramerization domain have been subjected to extensive crystallographic, nuclear magnetic resonance (NMR), and other biophysical studies, generating a plethora of information and hypotheses on the mode of DNA binding and p53 oligomerization for the regulation of various p53 functions (Cho et al. 1994; Lee et al. 1994; Jeffrey et al. 1995; Zhao et al. 2001; Ho et al. 2006). Structures of p53 bound to other host proteins, such as the MDM2 ubiquitin ligase, have also led to mechanistic insights into p53 regulation (Kussie et al. 1996).

The pRb transcriptional repressor is a member of the “pocket protein” family, which also includes p130 and p107 (Cobrinik 2005), and binds and represses transcriptional activation by the E2F/DP family of DNA-binding proteins (Harbour and Dean 2000; Stevaux and Dyson 2002). Sequential phosphorylation by cyclin-dependent kinases at the end of the G1 phase leads to dissociation of pRb/E2F/DP complexes, which in turn activates the expression of cellular factors required for S-phase entry (Knudsen and Wang 1997; Harbour et al. 1999). Human pRb is 928 residues long and contains an oligomerization-mediating N-terminal domain (Hensey et al. 1994), a central pocket domain harboring the binding interface for the E2F transactivation domain (Lee et al. 2002; Xiao et al. 2003), and a C-terminal domain harboring a cluster of phosphorylation sites (Fig. 1; Adams et al. 1999). Structural studies on the pRb pocket domain in complex with the E2F transactivation domain and the pRb C-terminal domain in complex with another region of the E2F/DP heterodimer have revealed the molecular determinants of E2F/DP repression mediated by pRb and regulation of pRb by phosphorylation (Lee et al. 2002; Xiao et al. 2003; Rubin et al. 2005).

Attack of viruses—part I

Maximizing the genome replication of many viruses, in particular small DNA viruses, necessitates a substantial S-phase supply of host cell enzyme activities from proteins such as DNA polymerase and several nucleotide biosynthetic enzymes. These enzymes are under control of the universal host E2F/DP transcription factor family (Nevins 2001). Viruses have developed an efficient way to inactivate the pRb checkpoint, by stimulating the disassembly of the pRb/E2F/DP complex during the G1–S cell cycle transition, leading to the production of host enzymes required for replication of the virus genome. The SV40 LTag, HPV E7, and Ad E1A viral oncoproteins

employ a strictly conserved LxCxE motif to mediate high-affinity binding to a shallow groove within the pRb pocket domain (Fig. 1; Lee et al. 1998). However, the binding site for the LxCxE motif of the viral oncoproteins within the pRb pocket domain is ~ 30 Å away from the pRb-binding site for the E2F transactivation domain, leading to speculative models of how additional domains from these viral oncoproteins lead to the displacement of E2F/DP from pRb (Xiao et al. 2003; Rubin et al. 2005). The N-terminal J domain-like region of SV40 LTag, the conserved region 1 (CR1) of Ad E1A, and the homodimeric conserved region 3 (CR3) of HPV E7 have each been implicated in promoting E2F/DP release from pRb, although the mechanisms they employ for release are still unclear. Given the limited sequence conservation and dissimilar relative location with respect to the LxCxE motif of these domains, these viral oncoproteins probably exploit disparate mechanisms for pRb/E2F/DP complex disruption (Lee and Cho 2002). For SV40 LTag, biochemical and structural data suggest a pRb/E2F/DP displacement mechanism involving the T-antigen J domain that resembles the DnaJ–DnaK chaperone system (Kim et al. 2001). For HPV E7, the CR3 region has been shown to have direct interactions with both the C-terminal regions of E2F and pRb, relieving interactions between these regions and somehow leading to dissociation of the pRb/E2F/DP complex (Patrick et al. 1994; Hwang et al. 2002; Rubin et al. 2005; Liu et al. 2006). There are no available structures of Ad E1A, either alone or bound to pRb. Together, structures of pRb, HPV E7, and SV40 T-antigen and their respective complexes have provided important clues about viral inactivation of pRb function, although further studies are still required to derive more detailed mechanistic information.

Attack of viruses—part II

p53 is equipped to sense the abnormal activation of oncogenes including E2F through the p19ARF/MDM2 pathway to either arrest cell cycle progression or commit cells to apoptosis. In addition to targeting the pRb tumor suppressor protein for inactivation as described above, viral oncoproteins also target p53 activity (Sherr and McCormick 2002; Harris and Levine 2005). Correspondingly, the SV40 LTag, HPV E6, and Ad E1B viral oncoproteins mediate p53 inactivation, either by directly binding to p53 to sequester the protein in an inert form, as is the case for large SV40 LTag and Ad E1B, or by promoting ubiquitination-mediated p53 degradation, as is the case with HPV E6 (Scheffner et al. 1993; Collot-Teixeira et al. 2004). In contrast to the situation with pRb, considerably less is known about the mechanism of viral oncoprotein inactivation of p53, as there have been no structures reported of p53 bound to a viral oncoprotein.

In this issue of *Genes & Development*, Lilyestrom et al. (2006) report on the first structure of p53 bound to a viral oncoprotein. The X-ray crystal structure contains the p53 core DNA-binding domain in complex with the helicase domain of the SV40 LTag. The structure reveals a circular T-antigen helicase domain hexamer with a p53 DNA-binding domain bound to the outside surface of each subunit of the hexamer, forming a pinwheel-like structure (Fig. 2A). The LTag helicase domain, a member of the SF3 helicase superfamily, is an integral and indispensable component of the initiation complex of SV40 viral genome replication. Its structure and function have been well studied and reviewed elsewhere (Gai et al. 2004; Hickman and Dyda 2005). The T-antigen/p53 complex reveals extensive interactions between the outer

Figure 2. Structure of the SV40 LTag/p53 complex. (A) Overall structure of the complex. The p53 DNA-binding core domain is shown in magenta and the SV40 LTag helicase domain is shown in cyan. Yellow and gray solid spheres represent zinc ions coordinated by p53 and SV40 LTag, respectively. (B) The SV40 T-antigen/p53 interface. Regions of the p53 DNA-binding core domain that have interactions with the SV40 LTag helicase domain (H1 and H2 helices and L3 loop with the L2 loop omitted for clarity) are highlighted in magenta with other regions of p53 colored in gray. The two tumor-derived mutation hotspots of p53, R248, and R273 are shown in the stick model. The large SV40 LTag is shown in transparent surface representation, with regions located within a 5 Å radius of p53 highlighted in cyan.

surface of the LTag helicase domain and the H1 and H2 helices and L2 and L3 loops of p53 (Fig. 2B). Most interestingly, each of these elements of p53 has been shown to participate in DNA binding by p53 (Cho et al. 1994; Zhao et al. 2001). In particular, the H2 helix of p53 sits in the DNA major groove to mediate base-specific contacts (Cho et al. 1994), the H1 helix participates in cooperative p53 dimer contacts on DNA (Ho et al. 2006), and the L1 and L3 loops also have direct DNA contacts. Strikingly, LTag has direct interactions with Arg 248 and Arg 273 of p53, two of the most frequently mutated residues in human cancer. The participation of common p53 elements in both DNA and T-antigen association clearly shows that T-antigen subverts p53 function by preventing it from binding DNA for the appropriate regulation of p53 genes. Interestingly, the charge and contour of the LTag surface that contacts p53 resemble those of duplex DNA, suggesting that LTag adopts a scheme of “DNA mimicry” to abrogate p53 activity. Another interesting finding to come out of the structure is that while other reported structures of the p53 core domain—either alone or bound to DNA—do not show significant structural changes within the p53 core domain (Zhao et al. 2001), the p53 core domain structure bound to the LTag helicase domain does show more substantial structural rearrangement of the p53 core domain. In particular, a methionine residue (M246) within the L3 loop is positioned within the interior core of the p53 core domain, either alone or in complex with DNA, but when bound to the helicase domain of LTag, this residue flips out of the p53 core and into a hydrophobic pocket on the surface of LTag. Lilyestrom et al. (2006) call this a “methionine switch.” Together, the T-antigen/p53 structure, along with corresponding mutational analysis that is also presented in the study (Lilyestrom et al. 2006), reveals that T-antigen uses DNA mimicry and antigen-induced structural changes in the p53 core domain to subvert its cellular function.

p53 inactivation and beyond

While the study by Lilyestrom et al. (2006) provides new and important insights into p53 inactivation by SV40 LTag, it also generates additional questions. One question is whether the crystallographically observed 1:1 stoichiometry of the complex between T-antigen and p53 has biological significance. Since intact p53 binds to DNA as a homotetramer, a 1:1 stoichiometry would require that at least two T-antigen hexamers bind to three p53 tetramers, generating a large, ~400-kDa complex. Alternatively, T-antigen binding might modify the oligomerization state of p53. An argument in favor of additional perturbation of the p53 oligomerization state upon T-antigen binding is the fact that the H1 helix and L3 loop of p53 that participates in T-antigen association also participate in p53 core domain dimerization on DNA (Ma et al. 2005; Ho et al. 2006; Lilyestrom et al. 2006). Indeed, alteration of the p53 oligomerization state has been implicated in the regulation of p53 activity (Pietenpol et al. 1994). Intriguingly, Lilyestrom et al. (2006)

also found that the binding of p53 to the T-antigen helicase domain inhibits the helicase activity of LTag *in vitro*. This seems counterintuitive, since it would not make sense for a virus to target a host protein by sacrificing an activity that is required for the replication of its own genome. However, if the level of LTag protein is higher than that of p53 protein, a pool of LTag may be used for p53 inactivation while another pool, not bound to p53, may be used for helicase-dependant replication of viral genes.

Does the proposed molecular mimicry mechanism for LTag inactivation of p53 extend to how other viral oncoproteins inhibit p53 and other tumor suppressor proteins such as pRb? For example, we know that pRb interacts with the LxCxE motifs of SV40 T-antigen, HPV E7, and Ad E1A, while pRb is also known to interact with other cellular targets, such as pRbBP1, that also contain LxCxE motifs (Singh et al. 2005). The simplest model is that the viral oncoproteins and the cellular LxCxE motif-containing proteins compete for binding to the same site on the pRb pocket region. However, we also know that some host proteins that interact with pRb, such as E2F, do not contain LxCxE motifs and that viral oncoprotein disruption of pRb/E2F complexes is more complicated. It is interesting to note that HPV E6 also disrupts p53 function through its interaction with the p53 core domain (Li and Coffino 1996), although the mechanism for this is unknown, even with the recent report of the NMR structure of the HPV E6 C-terminal zinc-binding domain (Nomine et al. 2006). It seems clear that viral oncoproteins use a variety of mechanisms to target host tumor suppressor proteins for inactivation.

Design for the cure

Given the disparate modes of tumor suppressor inactivation by viral oncoproteins, as highlighted by the structure of the SV40 LTag in complex with p53 reported by Lilyestrom et al. (2006), are we any closer to the structure-based design of antiviral inhibitors (De Clercq 2004)? In our view, the answer is yes. The recently determined structures of the CR3 domain of HPV E7 (Liu et al. 2006) and the C-terminal metal domain of HPV E6 (Nomine et al. 2006), two domains required for cell transformation, reveal novel zinc-binding folds that, at least in theory, could be targeted for inactivation with a small molecule compound or peptide without the complication of targeting structurally unrelated host proteins (Liu et al. 2006; Nomine et al. 2006; Ohlenschläger et al. 2006). Indeed, Baleja et al. (2006) recently reported on the use of information about HPV E6-binding proteins to generate an E6-binding pharmacophore that was used to screen a virtual chemical database, resulting in the identification of molecules that selectively inhibit the ability of HPV E6 to promote ubiquitin-mediated degradation of p53. Likewise, the design of peptides that mimic the ability of p53 to inhibit the helicase function of LTag may pave the way for small molecule inhibitors of SV40 LTag. At least two things are clear: There is still much to learn about how viral oncoproteins inactivate

host tumor suppressors and, like Achilles, viruses are well protected but not invulnerable.

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