A series of chimeric pockets and pocket subsegments were tested for binding to cyclin A. The p107 pocket containing an RB spacer in place of its own spacer segment failed to bind cyclin A. In contrast, the RB pocket containing a p107 spacer did bind cyclin A, and T peptide did not inhibit binding. Both chimeric pockets did bind to T and E1A (*1, 25*), indicating that switching the spacer elements did not affect viral protein binding to the pocket. Thus, the p107 pocket and, in particular, its spacer can bind directly or indirectly to cyclin A. The following results (Fig. 3) further indicate that cyclin A binding is independent of cellular or viral protein binding: (i) GST-p107 (Cys^{713}→Phe), which does not bind T or E1A still bound cyclin A. (ii) Peptides from T and E7 did not compete with cyclin A for pocket binding. (iii) The spacer alone conferred cyclin A binding to RB.

The transcription factor E2F (DRTF1) can form a complex with RB and cyclin A (*16–21*). As defined by peptide competition and genetics, the pocket-binding proteins of p107 and RB appear to be the same (Fig. 2). E2F has been shown to be a pocket-binding protein (*19*), and would be predicted to form a complex with p107. Because cyclin A specifically binds to the p107 spacer, while other known pocket binding proteins likely interact with A and B domain sequences, E2F and cyclin A might be able to interact simultaneously with the p107 pocket (*28*).

If cyclin A operates by modulating the function of a bound cdc2 or cdk2 (cyclin-dependent kinase 2) kinase, at least three possibilities might be envisioned to explain how cyclin A complex formation could be linked to p107 function. (i) The target of a kinase–cyclin A complex might be p107, which, by analogy with RB (*7–12*), might be functionally altered by specific phosphorylation. (ii) The target of the bound cyclin A–kinase complex could be one or more p107 pocket-binding proteins such as E2F, which can be activated by phosphorylation (*29*) and binds cyclin A at a specific time in the cell cycle (*21*). (iii) The p107 protein might act as a transducer, sending a signal from a protein specifically bound in its pocket to the cyclin-kinase complex also bound on the pocket surface. Such a signal might regulate the kinase such that one or more proteins are or are not phosphorylated at a particular time in the cycle. These three models are not mutually exclusive. Finally, p107-bound cyclin A might, in theory, have functions other than regulating kinase activity of cdc2 or cdk2.

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Interaction Between Human Cyclin A and Adenovirus E1A-Associated p107 Protein

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The products of the adenovirus early region 1A (E1A) gene are potent oncoproteins when tested in standard transformation and immortalization assays. Many of the changes induced by E1A may be due to its interaction with cellular proteins. Four of these cellular proteins are the retinoblastoma protein (pRB), p107, cyclin A, and $p33^{cdk2}$. The pRB and p107 proteins are structurally related and have several characteristics in common, including that they both bind to the SV40 large T oncoprotein as well as to E1A. Cyclin A and $p33^{cdk2}$ are thought to function in the control of the cell cycle. They bind to one another, forming a kinase that closely resembles the cell cycle–regulating complexes containing $p34^{cdc2}$. Cyclin A is now shown to bind to p107 in the absence of E1A. The association of p107 with cyclin A suggests a direct link between cell cycle control and the function of p107.

CYCLIN A PARTICIPATES IN THE REGulation of the cell cycle (*1–5*), apparently by acting as a regulatory protein that associates with either the $p34^{cdc2}$ or $p33^{cdk2}$ kinase (*1, 6–8*). Cyclin A is also present in a protein complex that contains transcription factors such as E2F and DRTF1 (*9–11*). The biochemical significance of the interaction of cyclin A with both kinases and transcription factors is not clear at present.

We identified a 60-kD polypeptide, which was later shown to be cyclin A (*1*), as an E1A-associated protein. We have immunoprecipitated cyclin A and its associated proteins with two cyclin A–specific monoclonal antibodies, BF683 and C160 (*6, 8*). Proteins in lysates of [^{35}S]methionine-labeled 293 cells, which constitutively express E1A, or ML-1 myeloid leukemia cells were immunoprecipitated with these or control antibodies. Proteins from the 293 cell lysates were also precipitated with the E1A-specific antibody M73 (*12*). Both BF683 and C160 efficiently recognized cyclin A from ML-1 and 293 cells (Fig. 1, A and B). Each antibody precipitated several proteins, but our primary interest was in proteins that were detected with both antibodies to cyclin A.

Two groups of differently sized proteins were immunoprecipitated with either BF683 or C160. A set of proteins that migrate with molecular sizes of approxi-

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mately 30 to 36 kD have been characterized (*1, 6, 7, 13*). These proteins are $p34^{cdc2}$ and $p33^{cdk2}$, both members of the cyclin-dependent kinase (cdk) family. They are seen more easily in the immunoprecipitates from ML-1 cells (Fig. 1B) but were also detected after longer exposure of autoradiograms of immunoprecipitated proteins from 293 cells (Fig. 1A) (*14*).

The other major group of proteins that were associated with cyclin A had molecular sizes of approximately 107, 120, and 130 kD. Although the 120-kD band was seen as a predominant band in all BF683 immunoprecipitations, in the C160 immunoprecipitations it varied in intensity from cell to cell. Also, when the 120-kD bands from BF683 and C160 immunoprecipitations were compared by proteolytic analyses, these proteins were not identical (*14*). The 130-kD protein was detected in various low amounts in different cell lines, making its analysis difficult. Although we do not know its identity, the 130-kD protein comigrated with the E1A-associated p130 protein during SDS–polyacrylamide gel electrophoresis (SDS-PAGE).

The 107-kD polypeptide comigrated during SDS-PAGE with the E1A-associated p107 immunoprecipitated with M73 (Fig. 1A). To determine if the 107-kD bands associated with cyclin A were indeed authentic p107, the proteins were partially digested with *Staphylococcus aureus* V8 protease (*15*). Gel slices containing the [^{35}S]methionine-labeled proteins were excised and treated with various amounts of V8 protease (Fig. 1C). The partial digestion products of these proteins were identical. Because V8 protease cleaves after acidic residues, this result indicates that the distribution and accessibility of these residues were the same, strongly suggesting that the 107-kD protein associated with cyclin A was p107.

Because complexes immunoprecipitated with antibodies to E1A contain both p107 and cyclin A, the appearance of p107 in complexes immunoprecipitated with antibodies to cyclin A might be explained by association of both p107 and cyclin A with the same molecule of E1A. However, when lysates from ML-1 cells, which do not contain E1A, were immunoprecipitated with the two monoclonal antibodies to cyclin A, p107 was still associated with cyclin A (Fig. 1B). Similar results were also found with other cell lines (*16*). This indicates that the detection of p107 in immunoprecipitates containing cyclin A does not require E1A.

The precipitation of p107 with the antibodies to cyclin A could be due to two possibilities: p107 might be precipitated through association with cyclin A, or it might be recognized directly by the BF683 and C160 antibodies. Two immunochemical experiments suggested that p107 was precipitated through a physical interaction with cyclin A: (i) In an immunoblot neither of the antibodies to cyclin A recognized p107 directly under conditions in which they both recognized cyclin A (Fig. 2A). (ii) BF683 and C160 antibodies appear to recognize different epitopes on cyclin A. BF683 and C160 antibodies precipitated a different subset of proteins from labeled cell lysates (Fig. 1). Also, the BF683 antibody still recognized its epitope on cyclin A when proteins in cell lysates were denatured with SDS, whereas the C160 antibody did not (Fig. 2B). Thus, either p107 has two epitopes in common with cyclin A or it is precipitated through interaction with cyclin A.

To demonstrate the association between cyclin A and p107 by an independent method, we tested whether cyclin A could bind to p107 in vitro. Coding regions of cyclin A or p107 were expressed in bacteria as fusion proteins with glutathione S-transferase (GST-CycA or GST-p107, respectively). The fusion proteins were bound to glutathione–agarose beads and used as adsorbants to bind to proteins from cell lysates. The p107 protein from ML-1 cell lysates bound GST-CycA (Fig. 3A). For comparison, p107 was immunoprecipitated with C160 or with XZ37, an antibody to pRB that cross-reacts with p107 (*17*). Proteins immunoprecipitated with antibodies to cyclin A have an associated kinase activity (*1, 13*), and this kinase activity was used to ^{32}P-label p107 and the other proteins associated with GST-CycA. The C160 and XZ37 antibodies and GST-CycA all precipitated a kinase activity that phosphorylated p107, whereas fusion proteins containing two deletion mutants of cyclin A, GST-CycAΔ211 and GST-CycAΔ369, did not. In the GST-CycAΔ211 protein, the NH_2-terminal 210 amino acids of cyclin A were deleted and GST-CycAΔ369 is missing the COOH-terminal sequences beyond amino acid 369. The identity of p107 in these experiments was confirmed by V8 mapping (*18*).

The GST-p107 fusion protein contains amino acids 252 to 816 of p107, the region that shows the most similarity to pRB and contains the sequences needed to bind E1A and the SV40 large T antigen (*19–22*). The GST-p107 fusion protein was bound to

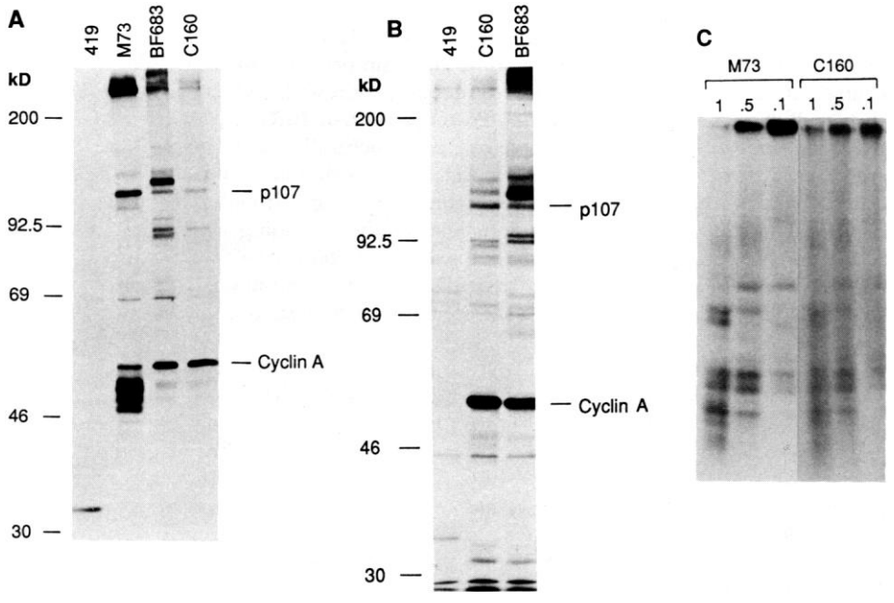

Fig. 1. Immunoprecipitation with antibodies to cyclin A. (**A**) Coprecipitation of a protein that comigrates with adenovirus E1A-associated p107. Proteins from lysates of [^{35}S]methionine-labeled 293 cells, an E1A-containing cell line, were immunoprecipitated a monoclonal antibody to E1A, M73 (*12*) (lane 2); two monoclonal antibodies to cyclin A, BF683 (lane 3) and C160 (*8*) (lane 4); and a control antibody that recognizes simian virus 40 large T antigen, PAb419 (*26*) (lane 1). Protein complexes were separated by SDS-PAGE (8% gel) (*27*) and detected by fluorography (*28*). (**B**) Coprecipitation of the 107-kD protein and cyclin A with antibodies to cyclin A in the absence of E1A. Lysates of [^{35}S]methionine-labeled ML-1 cells, a myeloid leukemia cell line, were immunoprecipitated with C160 (lane 2), BF683 (lane 3), and PAb419 (lane 1) as described above. (**C**) Partial proteolysis of E1A-associated p107 and the cyclin A associated protein with V8 protease from *S. aureus*. Proteins from lysates of [^{35}S]methionine-labeled 293 cells (lanes 1 to 3) and ML-1 cells (lanes 4 to 6) were immunoprecipitated with M73 and C160, respectively. The p107 protein from each immunoprecipitation was treated with the indicated amounts (in micrograms) of V8 protease (*15*).

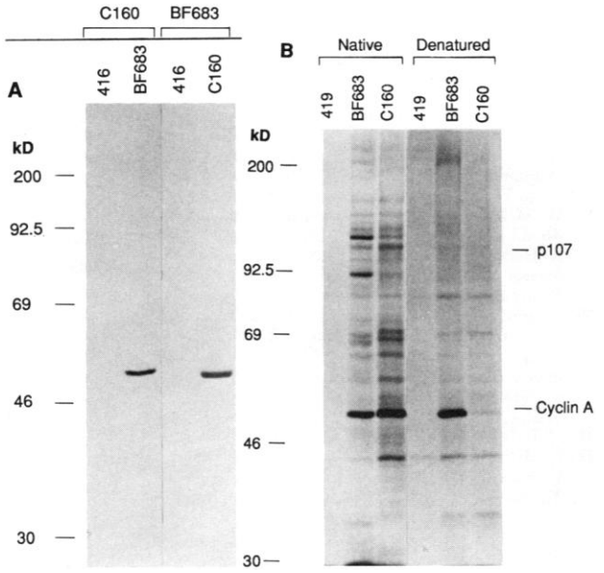

Fig. 2. Antibody characterization. (**A**) Specificity of antibodies to cyclin A. BF683, C160, and PAb416 (*26*), an antibody to SV40 large T antigen, were cross-linked to protein A–Sepharose by treatment with dimethylpimelimidate (*29*). Proteins from lysates of ML-1 cells, a myeloid leukemia cell line, were immunoprecipitated with the antibody beads. Immune complexes were separated by SDS-PAGE (8% gel), transferred to nitrocellulose, and probed with either C160 (lanes 1 and 2) or BF683 (lanes 3 and 4). The nitrocellulose was probed with rabbit antibody to mouse immunoglobulin G conjugated to alkaline phosphatase and proteins were visualized as described (*29*). (**B**) Specificity of antibodies after treatment of cell lysates with SDS. Lysates of [^{35}S]methionine-labeled ML-1 cells were either untreated (lanes 1 to 3) or treated with SDS and boiled (lanes 4 to 6) (*30*) as described (*12*). Proteins from the lysates were then immunoprecipitated with BF683 (lanes 2 and 5), C160 (lanes 3 and 6), or PAb419 (lanes 1 and 4).

glutathione agarose and incubated with cell lysates from the cell line WERI-Rb27, which lacks RB. Bound proteins were resolved by SDS-PAGE, transferred to nitrocellulose, and tested for the presence of cyclin A by immunoblotting with the C160 antibody (Fig. 3B). GST-p107 bound cyclin A in the absence or presence of peptides that block the interaction between p107 and E1A or T antigen (*22*).

The demonstration of a complex between p107 and cyclin A raises questions regarding the cellular targets for E1A-mediated transformation. Studies of peptide competition and peptide binding (*23*) have indicated that E1A binds directly to p107. While both p107 and cyclin A are found in complexes with E1A, they are also able to associate in the absence of E1A. Because the binding of cyclin A and p107 is not inhibited by a peptide that blocks interaction of E1A with p107, it appears that p107 binds cyclin A in a different manner than it binds E1A. Together these data suggest that the proteins form a multimeric complex with E1A binding to p107 and p107 binding directly or indirectly to cyclin A. Cyclin A appears not to be a direct target for E1A action but is more likely to be associated through its interaction with p107.

The interaction of cyclin A or other cyclins with proteins such as pRB or p130 is also possible. In the absence of E1A, pRB associates with a cell cycle–regulated kinase that appears to contain cyclin A (*24*). This may be another example of cyclins interacting with E1A-associated proteins. However, the interaction between cyclin A and pRB must be at a lower affinity or lower stoichiometry than that between cyclin A and p107, because we did not detect pRB in complexes immunoprecipitated with antibodies to cyclin A or binding of pRB to GST-CycA.

Cyclin A binds to a multimeric complex that contains the transcription factor E2F or DRTF1 (*9–11*). When E1A is added to these cyclin A–containing complexes, free and presumably active E2F (or DRTF1) is released (*25*). The addition of E1A to complexes containing E2F-pRB releases active E2F, apparently by the physical interaction of E1A with pRB (*10*). By analogy, some subunit in the cyclin A–containing complexes we observed should carry a binding site for E1A. The structural similarities of pRB and p107 suggest that p107 could be an E1A-binding subunit of the cyclin A complex. Perhaps many of the protein associations seen in immunoprecipitations of E1A represent the consequences of E1A stripping regulatory proteins, such as p107 and pRB, from transcription factors such as E2F.

By analogy with cyclin B, the interaction of cyclin A with its kinase partners, p33^{cdk2} and p34^{cdc2}, may regulate their kinase activity. It is not known whether the kinase subunits p34^{cdc2} or p33^{cdk2} are present in the p107 complex. The interaction of cyclin A with p107 may only mark p107 for later action by the kinase. Alternatively, cyclin A might act in an unexpected manner; its interaction with p107 might hint of a previously undescribed cyclin activity. Further analysis of the cyclin A-p107 interaction may clarify the links between cell cycle regulation and carcinogenesis.

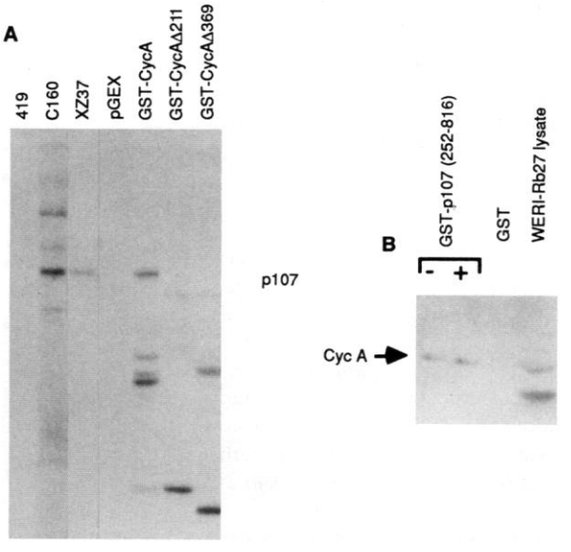

Fig. 3. In vitro association of cyclin A with p107. (**A**) Precipitation of p107 and a kinase activity that phosphorylates p107 with glutathione S-transferase–cyclin A fusion protein. Cyclin A was immunoprecipitated with C160 (lane 2). An antibody to RB that cross-reacts with p107 (*17*) was used to immunoprecipitate p107 (lane 3), and a glutathione S-transferase–cyclin A fusion protein was used to precipitate proteins that bound cyclin A (lane 5). PAb419 (lane 1), pGEX-2T (*31*) (vector alone, lane 4) and two deletion mutants of cyclin A fused to glutathione S-transferase (lanes 6 and 7) were used as negative controls. All proteins were precipitated from lysates of ML-1 cells and subjected to subsequent kinase assays (*32*). (**B**) Precipitation of cyclin A with glutathione S-transferase–p107 fusion protein. A glutathione S-transferase–p107 fusion protein was used to precipitate proteins that bound to p107 in the absence (lane 1) or presence (lane 2) of peptides that block the interaction of p107 and E1A or T antigen. The peptides include wild-type T antigen peptide (*33*) and a peptide containing the wild-type sequence of residues 16 to 32, of human papilloma virus–16 E7 protein (QPETTDLYCYEQLNDSS). The vector pGEX-2T alone (lane 3) was used as a negative control and whole cell lysate (lane 4) was a positive control. Cell lysates were made from the cell line WERI-Rb27, which lacks Rb. Abbreviations for the amino acid residues are: A, Ala; C, Cys; D, Asp; E, Glu; F, Phe; G, Gly; H, His; I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln; R, Arg; S, Ser; T, Thr; V, Val; W, Trp; and Y, Tyr.

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The Updating of the Representation of Visual Space in Parietal Cortex by Intended Eye Movements

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Every eye movement produces a shift in the visual image on the retina. The receptive field, or retinal response area, of an individual visual neuron moves with the eyes so that after an eye movement it covers a new portion of visual space. For some parietal neurons, the location of the receptive field is shown to shift transiently before an eye movement. In addition, nearly all parietal neurons respond when an eye movement brings the site of a previously flashed stimulus into the receptive field. Parietal cortex both anticipates the retinal consequences of eye movements and updates the retinal coordinates of remembered stimuli to generate a continuously accurate representation of visual space.

AS WE MOVE OUR EYES, A STATIONary object excites successive locations on the retina. Despite this constantly shifting input, we perceive a stable visual world. This perception is presumably based on an internal representation derived from both visual and nonvisual information. Helmholtz proposed that the brain uses information about intended movement to interpret retinal displacements (*1*). We show that single neurons in monkey parietal cortex use information about intended eye movements to update the representation of visual space (*2*).

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The shift in the visual image on the retina produced by a saccade is determined by the size and direction of the eye movement. This predictability enables the representation of visual space in parietal cortex to be remapped in advance of the eye movement. At the single cell level, the intention to move the eyes evokes a transient shift in the retinal location at which a stimulus can excite the neuron.

Our results are summarized schematically in Fig. 1, in which an observer transfers fixation from the mountain top to the tree. During fixation, the representation of the visual scene in parietal cortex is stable. A given neuron encodes the stimulus at a certain retinal location (the cloud). Immediately before and during the saccade, the cortical representation shifts into the coordinates of the next intended fixation. The neuron now responds to the stimulus at a new retinal location (the sun) and stops responding to the stimulus at the initial location (the cloud). The neuron thus anticipates the retinal consequences of the intended eye movement: the cortical representation shifts first, and then the eye catches up. After the eye movement, the representation in parietal cortex matches the reafferent visual input and the neuron continues to respond to the stimulus (the sun). This process constitutes a remapping of the stimulus from the coordinates of the initial fixation to those of the intended fixation.

We demonstrated this remapping by studying the visual responsiveness of neurons in the lateral intraparietal area (LIP) of alert monkeys performing fixation and saccade tasks (*3*). Neurons in LIP have retinocentric receptive fields and carry visual and visual memory signals (*4*). An example is shown in Fig. 2. When the monkey fixates, this neuron responds to the onset of a visual stimulus in its receptive field at a latency of 70 ms (Fig. 2A). Receptive field borders were defined while the monkey maintained fixation, and, under these conditions, stimuli presented outside these borders never activated the neuron. In the saccade task, the fixation target jumps at the same time that a visual stimulus appears. The visual stimulus is positioned so that it will be in the receptive field when the monkey has completed the saccade. If there were no predictive remapping, the cell would be expected to begin discharging 70 ms after the eye movement brings the stimulus into

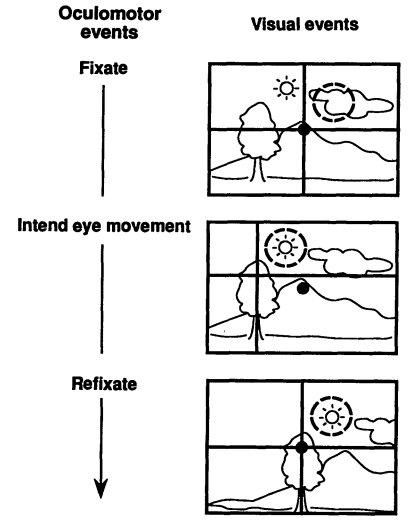

Fig. 1. Remapping of the visual representation in parietal cortex. Each panel represents the visual image at a point in time relative to a sequence of oculomotor events. Receptive field of a parietal neuron, dashed circle; center of current gaze location, solid circle; and coordinates of the cortical representation, cross hairs.