Rb protein and transformation by DNA tumour viruses:

1. The central role of Rb in the regulation of cell proliferation is highlighted by the fact that a number of unrelated DNA tumour viruses have evolved mechanisms for disrupting Rb signalling.
2. These viruses hijack the host cell's DNA replication machinery in order to replicate their own genome.
3. They induce host cells to proliferate so that new viral DNA can be synthesised alongside replication of the host genome, and in order to achieve this, the **viruses must overcome Rb-dependent inhibition of E2F.**
4. The small tumour viruses are:
    - SV40 **T Ag**
    - Adenovirus **E1A**
    - Papilloma virus **E7**

5. To facilitate virus replication, viral proteins stimulate the host cell to **enter S phase.**
6. The transforming proteins of *three unrelated DNA tumour viruses* form complexes with the **hypo**phosphorylated form of Rb, displacing it from bound E2F.
7. This demonstrates how important overcoming Rb-dependent E2F inhibition is for enabling cell cycle progression.

Simian Virus 40 (SV40):

1. SV40 is a small circular dsDNA (double stranded DNA) genome encoding only 5-9 proteins.
2. The natural host of the SV40 is the monkey, but it is also capable of infecting humans and rodents – highly oncogenic in rodents.
3. In monkeys and humans, **T Ag recruits DNA polymerase** to the origin of replication on viral DNA, promoting new virion production.
4. New virus is packaged and ultimately released from the cell by lysis.
5. Conversely, in rodents, T Ag *cannot bind* DNA polymerase and the viral lifecycle cannot progress, leaving the **cells stuck in a proliferative, anti-apoptotic state.**

Uncontrolled proliferation → tumour formation

- Rb loss alone is **not sufficient enough** to result in cellular transformation as additional gene mutations are also required, i.e. disruption of the p53 pathway and possible oncogene activation.
- Retinoblasts seem to be acutely sensitive for the loss of Rb.

6. **Question:** "because there is no viral replication in the rodent, does this have any consequences that would be different from that of the monkey where viral replication does not occur?"