Transformation and Carcinogenesis

6

Contents

It was acknowledged long ago that viruses may cause cancer in animals. In 1911, Peyton Rous described viruses as causing sarcomas in poultry. The tumour-inducing virus responsible was later named after him, Rous sarcoma virus. In the following decades, a large number of viruses were discovered that can cause various cancers in poultry and rodents, such as lymphomas, sarcomas and carcinomas. Many of them belong to the family *Retroviridae*, and were classified into the genera *Alpharetrovirus*, *Betaretrovirus* and *Gammaretrovirus*. Most of these pathogens were isolated from inbred strains of the respective species or from cell cultures; under natural conditions, these strains are likely irrelevant as a cause of cancer in the corresponding species. An exception is feline leukaemia virus (► Sect. 18.1). The tumorigenic potential of oncogenic retroviruses is based on transformationally active proteins. They are similar to cellular products which are ordinarily involved in the regulation of cell division. In contrast to the cellular products, viral oncogene proteins are altered by mutations in such a way that they are not subject to regulatory control, and are thus constitutively active. In fact, the discovery of viral oncogenes was pioneering and has paved the way for deciphering cellular oncogenes, and thus for understanding the molecular basis of carcinogenesis.

S. Modrow et al., *Molecular Virology*, DOI 10.1007/978-3-642-20718-1_6,

Evidence for the existence of retroviruses that cause cancer in humans was found only in 1982 when Robert Gallo discovered human T-lymphotropic virus (HTLV; ▶ Sect. 18.1).

Nevertheless, most viruses that are correlated with cancer in humans have a DNA genome. The most important prototypes are papillomaviruses, which cause carcinomas, especially in the genital mucosa, and various malignant skin tumours (▶ Sect. 19.3), hepatitis B virus, which is involved in the development of primary liver cancer in humans (▶ Sect. 19.1), and Epstein–Barr virus as well as human herpes virus 8, which have a close causal relationship to Burkitt's lymphoma and nasopharyngeal carcinomas and to Kaposi's sarcoma, respectively (▶ Sect. 19.5). Hepatitis C virus, a flavivirus (▶ Sect. 14.5) with a single-stranded RNA genome, is associated with liver cancer, like hepatitis B virus. Recently, Merkel cell polyomavirus has been identified as another pathogen that is causally associated with a tumour of humans, namely Merkel cell carcinoma (▶ Sect. 19.2). Aetiologically, it is estimated that approximately 15–20 % of all human cancers are induced by viral infections. Adenoviruses, whose infections in humans could not be clearly associated with malignant diseases, can induce tumours, however, in newborn rodents (▶ Sect. 19.4). Their study has significantly contributed to elucidation of the mechanisms that are involved in cell transformation and tumour development. These insights could be applied to a number of other human cancers. Similarly, this is true for the simian virus 40 (SV40), which infects monkeys under natural conditions, but causes malignant diseases in newborn hamsters and mice (▶ Sect. 19.2). The DNA tumour viruses and hepatitis C virus do not have classic *v-onc* genes such as those found in retroviruses. Today, we know that those viruses principally deactivate the function of cellular tumour suppressors by specific viral regulatory proteins, which induce and maintain the malignant transformation of cells.

6.1 What Characterizes Transformed Cells?

The malignant properties of various viruses are primarily manifested through their ability to generate tumours in vivo. Frequently, this process can also be induced in experimental animal systems, so in many cases proper animal models are available for investigating the underlying molecular mechanisms. However, in vitro systems were and are essential for unveiling the malignant effect; tumour viruses are able to immortalize certain tissue culture cells and transform them in vitro. This makes possible detailed experimental investigations to elucidate the molecular processes that are associated with tumour development. Whereas immortalized cells acquire the capability of infinite cell division by viral activities, transformed cells are additionally characterized by the capability of inducing tumours, when transmitted into appropriate animals. Apart from this fundamental difference, both cell systems share many common characteristics that clearly distinguish them from normal cells.

6.1.1 Morphological Changes

During transformation, the cells change their form: they lose their normal epithelioid or fibroblast-like character and adopt mainly a spherical form. The transformation-associated change of the cytoskeleton is responsible for this effect, and confers on the eukaryotic cells their shape and is involved in cell division, cell motility and cell polarity. The breakdown of intracellular microfilaments is a prevailing process. In non-muscle cells, these microfilaments consist of the globular components β-actin and γ-actin, which are usually organized in long cables with a diameter of 7 nm and are cross-linked by the protein fimbrin. Actin cables form network structures beneath the cytoplasmic membrane, stabilize the shape of the cell and are also involved in the correct positioning of membrane proteins, where they are associated with other proteins such as myosin and tropomyosin, which tense the actin filaments. They are responsible for the short intracellular transport, for example, of vesicles to the plasma membrane. At the sites of the cytoplasmic membrane where the cables end, the cells form contacts with neighbouring cells, or are rooted in the surface of the base (in vitro, on the bottom of the cell culture flask). These regions are referred to as focal contacts. In the cells, there is a dynamic equilibrium of monomeric and polymeric actin. In the presence of Mg^{2+} and K^{+} ions and under ATP binding, globular actin monomers associate to filaments that are stabilized with the polypeptides α-actinin, filamin and fimbrin. During transformation, the cable-like arrangement of filaments is lost, and the actin monomers are diffusely distributed over the entire cell. This facilitates cell motility, which is necessary for tumour formation. Binding of the protein components profilin, gelsolin, vinculin and vilin has a destabilizing effect on the polymerization degree; the actin-bound ATP is hydrolysed during this process. It is unclear what regulates the changes of microfilaments at the molecular level. It is believed that increased phosphorylation of actin and vinculin is involved as it occurs in transformed cells.

Simultaneously with the alteration of actin filaments, a redistribution of transmembrane proteins is observed on the surfaces of transformed cells. They are connected with actin cables at the inner side of the cytoplasmic membrane and lose their position in defined groups, as a result of the collapse of actin cables. This changes, among other things, the concentration of integrins and their distribution. Integrins are membrane-anchored proteins which are connected to the actin cables by their cytoplasmic moiety. Their extracellular domains are associated with fibronectin, which in turn interacts with collagen and laminin. They make up the extracellular matrix, which mediates the interactions between different cells and is responsible for their organization and growth in cell aggregates; it ensures that cells grow as a monolayer in vitro and facilitates adhesion to the base, e.g., the cell culture dish. Owing to their low levels of integrins, transformed cells have significantly lower amounts of fibronectin on their surface and grow in cell clusters (foci). The concentrations of various ions, sugars and amino acid transporting proteins are increased on the surfaces of transformed cells. This is associated with up to tenfold increased metabolic activity in comparison with normal cells. The concentration of

other membrane proteins is also altered: for example, the levels of MHC class I proteins are usually reduced, whereas the levels of proteinases (metalloproteases, cysteine and serine proteases) and collagenases (type IV collagenases, transin/stromelin) are elevated on the cell surface. These proteins are also released into the surrounding region, which augments the potential of transformed cells to invade lymphatic vessels and capillaries and the formation of metastases. As a prerequisite for metastasis, primary tumour cells have to leave the tumour to overcome the basement membrane and to penetrate into the local stroma, e.g., in metastasis of cervical carcinoma that is induced by papillomaviruses (▶ Sect. 19.3). To find access to the circulatory system, to immigrate as a secondary colony into the new target organ and to proliferate there, tumour cells must induce angiogenesis, i.e. the de novo generation of blood vessels that supply the tumour with blood and all the nutrients contained therein.

6.1.2 Cell Growth Changes

In vitro transformed cells differ from normal cells in regard to their growth behaviour. Fibroblasts or epithelial cells which are placed in a cell culture bottle commonly attach to the plastic or glass surface. Subsequently, they divide continuously until a confluent monolayer is formed and the cells have used the entire available area completely. Then, cell division stops. In contrast to normal cells, transformed cells grow in multilayered, three-dimensional aggregates and reach cell concentrations that are five to ten times higher (foci). They are not subject to the so-called contact inhibition. If they are further cultivated in the culture bottle, an equilibrium is established between death of a subset of the cells and continuous division of the remaining subpopulation. Transformed cells grow in culture regardless of contact with plastic or glass surfaces, which is usually necessary for the proliferation of fibroblasts or epithelial cells. This property is an important feature of transformed cells. Therefore, some of these cells may also grow into larger aggregates, so-called cell clones, in a semiliquid medium such as soft agar. The ability to growth in soft agar correlates very well with the ability of transformed cells to form tumours in animal test systems. This behaviour is presumably based on the higher levels of transforming growth factor (TGF)-β, which is synthesized in such cells. TGF-β is a growth factor that stimulates, inter alia, the synthesis of fibronectin and collagen (▶ Chap. 8). The cells are thus provided with a locally limited extracellular matrix, which enables them to adhere together and to grow in grape-like aggregates.

Cells grow normally in vitro only if sufficient amounts of growth factors are available in the culture solution. For this reason, the medium is supplemented with approximately 10–15 % fetal calf serum, which ensures that all essential components are available. Important for cell proliferation are primarily epidermal growth factor, platelet-derived growth factor, various fibroblast growth factors and some hormones. These factors bind to their respective receptors on the cell surface and induce the activation of protein kinases by different signal transduction pathways,

which in a tightly regulated, cascade-like process phosphorylate various cellular proteins, including transactivators. Transactivators bind to the serum response elements in the promoter region of growth-factor-dependent genes and induce their expression. The newly formed gene products initiate cell division. By contrast, transformed cells divide independently of the presence of growth factors in the culture medium. They are able to grow in media containing no or very little serum. Transformed cells produce many of the necessary factors themselves, thus stimulating their autocrine proliferation. Moreover, they often secrete tumour growth factors (TGF-α and TGF-β), which also stimulate autocrine cell growth (▶ Chap. 8). In some transformed cells, the growth factor receptors are altered in such a way that they stimulate an active state even in the absence of the respective factor, incessantly transmitting signals into the cell.

6.1.3 Autocrine Cell Growth Stimulation by Viruses

Autocrine stimulation mechanisms are probably involved in the origin of HTLV-mediated T-cell leukaemia in humans. HTLV encodes a Tax protein that indirectly affects transactivation by interacting with nuclear factor κB (NFκB) and factors of the cyclic AMP response element binding (CREB) protein family, whereby they are activated, bind sequence-specifically to Tax response elements in the viral long terminal repeat promoter and induce transcription of the integrated viral genome (▶ Sect. 18.1). Furthermore, cellular genes are also expressed whose promoters contain CREB- or NFκB-dependent DNA regulatory elements. These include the genes encoding granulocyte–macrophage colony-stimulating factor, interleukin-2 and the α chain of interleukin-2 receptor (▶ Chap. 8). The increased expression of these cytokines and their corresponding receptors induces cell proliferation in an autocrine stimulation loop. It is the first stage in the development of HTLV-mediated T-cell leukaemia.

Even Epstein–Barr virus, which latently infects and immortalizes B lymphocytes, can stimulate autocrine proliferation of these cells (▶ Sect. 19.5). Latent Epstein-Barr virus nuclear antigen 2 (EBNA2) transactivates the promoters, which control the expression of latent viral genes. In addition, EBNA2 induces the synthesis of various cellular proteins, including that of CD23. Latent membrane protein 1 (LMP1), another viral polypeptide that is synthesized during latency, is also able to do so. The CD23 protein is found in two versions: the membrane-bound CD23 is a low-affinity IgE receptor; on the other hand, the secreted form of the protein serves as B-cell growth factor and promotes proliferation of infected B lymphocytes. The Epstein–Barr-virus-specific LMP1 gene product has also a number of other functions that are essential for transformation of latently infected cells. There is evidence that this envelope protein acts similarly to some of the classic oncogenes of retroviruses, and is a constitutively active growth factor receptor, which continuously triggers and maintains a signalling cascade. Apparently, it is similar to members of the nerve growth factor receptor family, which includes the TNF receptor. They constantly

transmit signals into the infected cells, resulting in induction of the expression of NFκB-dependent genes, among other things. As a result, apoptosis is inhibited, and increased concentrations of adhesion molecules, transferrin receptor, and CD23 proteins are induced.

6.2 What Is the Effect of Inactivation of Tumour-Suppressor Proteins?

Tumour suppressors, also called antioncogenes, are regulatory proteins that control cell division. They regulate the transition of proliferating cells from the G_1 phase, or in resting cells from the G_0 phase, to the S phase, in which the genome is replicated, and many other synthesis processes are performed (Fig. 6.1). The timing of the cell cycle is determined by synthesis and degradation of cyclins, whose concentration increases in a phase of the cell cycle, and then decreases during the following stages. Cyclins regulate, in turn, the activity of cyclin-dependent protein kinases (CDKs), which influence the phosphorylation status and thus the activity of various cell-cycle-specific transcription factors.

Many viruses can replicate only in dividing cells, where they perform productive infections that are associated with the generation of progeny viruses. Whereas some viruses – such as the autonomous parvoviruses (► Sect. 20.1) – have developed a strong tropism for dividing cells, others are able to accelerate the cell cycle in infected cells by inducing the S phase. They encode proteins which inhibit cellular factors that regulate, prevent or impede the entry of the cell into the S phase. All viruses that induce cancer in humans have such qualities and express the corresponding genes early during the infection cycle. They inactivate cell division regulators, and induce the transition from the G_1 or G_0 phase to the S phase. In DNA tumour viruses, viral replication is generally associated with cell death, which is induced by apoptosis mechanisms during the late phase of the infection cycle. If the lytic infection is interrupted, the viral gene expression is arrested at an early stage, and viral replication does not occur. Generally, the cellular milieu is responsible for these abortive infections. Thus, the lytic infection cycle of papillomaviruses (► Sect. 19.3) occurs only in skin keratinocytes, but not in the poorly differentiated cells of the basal layers. Cellular proteins, which are produced only in a specific stage of differentiation, facilitate the entry into the late viral replication phase. In other viruses, such as the oncogenic adenoviruses and SV40, an abortive infection occurs when the pathogen infect cells of non-natural hosts, in this case rodents (► Sects. 19.2 and ► 19.4). In addition, the viral genome is occasionally integrated completely or partially into the host-cell DNA, as may occur in hepatitis B virus and papillomavirus infections. This process disrupts the continuity of individual viral genes; as a result, there is often uncontrolled overexpression of viral genes, whose products interact with cellular tumour suppressors and induce continuous cell division, since the lytic replication cycle is blocked at the same time. This can eventually lead to carcinogenesis. Even if a growing number of tumour-suppressor

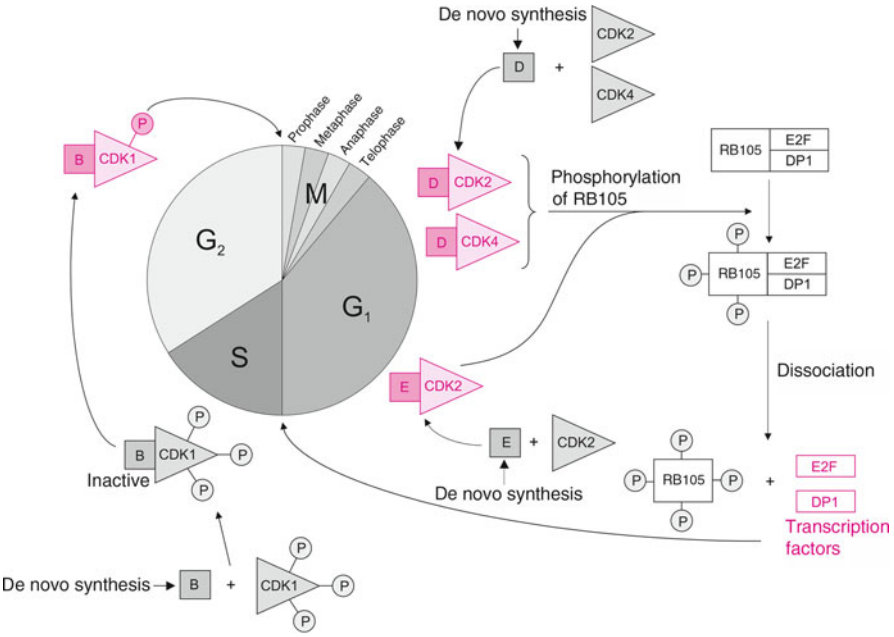

Fig. 6.1 Cell cycle phases (*M* mitosis, G_1 presynthesis phase, *S* synthesis phase, G_2 postsynthesis phase) and the factors involved in regulating the transitions. Cyclin D is synthesized in the early G_1 phase, binds to cyclin-dependent kinase 2 (*CDK2*) and cyclin-dependent kinase 4 (*CDK4*) and activates them. These kinases phosphorylate, among other proteins, retinoblastoma protein RB105, which is present in a complex with transcription factors E2F and DP1. In the later G_1 phase, cyclin E is synthesized, and interacts with CDK2, which performs the complete phosphorylation of RB105. E2F and DP1 are released from the complex, and act as transactivators of various cellular genes. These genes encode proteins which in turn regulate the transition from the G_1 to the S phase of the cell cycle. At the beginning of the S phase, cyclin B is synthesized, and interacts with the phosphorylated form of cyclin-dependent kinase 1 (*CDK1*). During the S and G_2 phases, CDK1 is dephosphorylated and regulates, in its monophosphorylated form, in complex with cyclin B, the entry of the cells into mitosis. *Squares* cyclins, *triangles* different cyclin kinases, *red* active components, *grey* inactive components

genes are known, viral gene products influence the activity principally of two groups of these protein families. On the one hand, tumour suppressor p53; on the other hand, the family of retinoblastoma proteins (RB105/RB107). The following sections provide a brief overview of the functions of these two protein classes.

6.2.1 Protein p53

The p53 gene is highly conserved among mammalian species. In humans, the p53 gene is located on the short arm of chromosome 17. It encodes a protein of about 393 amino acids residues. Normally, p53 has a short half-life of 6–15 min, it is

phosphorylated and is localized in the nucleus, where it assembles into tetrameric complexes. Increased concentrations of p53 are found in cells which were exposed to UV radiation or γ-radiation or were incubated with radioactive substances, chemotherapeutic drugs or DNA-damaging agents. All these compounds can cause mutations, i.e. changes in the DNA sequence.

The protein p53 can be functionally divided into four principal domains: the transcriptional transactivation domain resides in the amino-terminal region, which predominantly contains acidic amino acids. It is followed by a proline-rich region. The central DNA-binding core domain consists of a variety of structural motifs that are evolutionarily conserved; this important region is responsible for the sequence-specific DNA-binding activity and the correct folding of p53, thus essentially contributing to its tumour-suppressor activity, as demonstrated by the fact that it is the target of more than 90 % of p53 mutations found in human cancers. The carboxy-terminal region contains several functional motifs, including the tetramerization domain, three nuclear localization signals, which flank the oligomerization domain, a single putative nuclear export signal located within the tetramerization domain and a basic negative regulatory domain.

The protein p53 interacts with specific promoters containing p53 consensus sequences or with transcription factors that bind to p53-responsive promoters, and transactivates them. This induces the synthesis of proteins, which arrest the cell in the G_1 phase and delay the transition to the S phase. For example, the protein p21 is strongly induced, and interacts with the CDK2 and CDK4, and inhibits them. CDK2 and CDK4 have the function to phosphorylate various proteins, such as RB105. If RB105 is not phosphorylated, it remains associated with the E2F and DP1 transcription factors, which thus cannot exert their transactivation functions. This prevents the cell from entering the S phase of the cell cycle and provides more time to repair DNA damage (Fig. 6.1). If DNA repair is not successful, p53 induces apoptosis in eukaryotic cells (programmed cell death), and thus also prevents tumour formation. To a certain degree, the function of p53 is comparable to the SOS response, which is induced under similar DNA-damaging conditions in bacteria. This regulatory mechanism delays replication of the bacterial chromosome, so more time is available for the repair systems to correct the DNA damage before it can be manifested as mutations in DNA daughter molecules after subsequent replication rounds.

Mutations in the p53 gene in tumour cells lead to the synthesis of p53 variants which are not properly folded, no longer associate to form tetramers, and have thus lost the ability to function as sequence-specific DNA-binding transcription factors. Mutations in only one allele of the p53 gene are usually sufficient since wild-type and mutant proteins form inactive heterotetramers. In cells carrying p53 gene mutations, further mutations occur in the entire genome because of the impaired activity of p53, and these additionally contribute to malignant transformation in a multistep process. Viruses have developed diverse mechanisms to inactivate the cell-cycle-regulating effect of p53, and to create conditions that are necessary for their own reproduction. The T antigen of SV40 (▶ Sect. 19.2), the 55-kDa E1B protein of adenoviruses (▶ Sect. 19.4) and the X protein of hepatitis B virus (▶ Sect. 19.1) bind to p53 and prevent the formation of functionally

active tetramers. In papillomaviruses (▶ Sect. 19.3), the viral E6 protein induces complex formation between cellular E3-ubiquitin ligases and p53 and initiates its ubiquitin-dependent proteolytic degradation, thereby decreasing the intracellular concentration of p53.

6.2.2 Retinoblastoma Proteins

The retinoblastoma gene was first described in children with eye cancer. In these patients, both alleles of a gene are defective; the gene is located on the long arm of chromosome 13 and encodes a protein with a molecular mass of about 105 kDa (RB105). Later, mutated forms of this protein were also detected in osteosarcomas, soft tissue sarcomas and in breast, lung and bladder cancers. Phosphorylation of RB105 and the similar protein RB107 depends on the phase of the cell cycle. The aforementioned CDK2 and CDK4 are responsible for the phosphorylation of these proteins (Fig. 6.1). They are active, i.e. proliferation-inhibiting, in their dephosphorylated state. In this form, they bind to transcription factors E2F and DP1, which as free proteins interact with DNA elements in the promoters of specific genes in a sequence-specific fashion; such genes include the genes encoding the cellular enzymes thymidine kinase, dihydrofolate reductase, DNA polymerase-α and CDK2. All these proteins are required during the S phase of the cell cycle. The transactivation functions of transcription factors E2F and DP1 are inhibited in association with RB105. Therefore, the entry of cells into the S phase is blocked. If retinoblastoma proteins are phosphorylated, the complex with the transcription factors is dissolved. The latter can bind to the corresponding promoters and induce the expression of the genes that they regulate. Viruses that exclusively replicate in proliferating cells possess factors which influence the functions of retinoblastoma proteins. The papillomavirus E7 protein, the T antigen of SV40, the hepatitis C virus NS5B protein, and the E1A proteins of adenoviruses bind to RB105/RB107. These interactions abolish the complex formation with transcription factors E2F and DP1, which in turn become activated, and exert their transactivation activities (▶ Sects. 14.5 and ▶ 19.1–19.4).

6.2.3 Alternative Pathways to Induce Proliferation

Epstein–Barr virus has probably developed alternative ways to stimulate proliferation in latently infected cells. Epstein–Barr virus nuclear antigen leader protein is a gene product that is synthesized in B cells during the latent infection cycle. Although it can interact with the tumour-suppressor proteins p53 and RB105, it does not apparently influence their regulatory functions (▶ Sect. 19.5). However, Epstein–Barr virus nuclear antigen leader protein activates along with EBNA2 the expression of the cyclin D2 gene. The cooperative effect of the two latent viral proteins together with the antiapoptotic activity of Epstein–Barr-virus-encoded RNA induces the transition from G_0 into G_1 in resting B cells.

6.3 How Can Tumour Cells Evade the Immune Response?

Tumours can develop in vivo only if transformed cells are unrecognizable to the immune defence systems, and if they are able to evade the immune response. This applies also for tumours which are induced by viruses. Cells infected with adenoviruses or Epstein–Barr virus can elude the antiviral effect of interferon by synthesis of adenovirus-encoded virus-associated RNA molecules or Epstein–Barr-virus-encoded RNA molecules, respectively. Both virus types also reduce the concentration of MHC class I proteins on the cell surface. This prevents infected cells from being recognized and destroyed by cytotoxic T lymphocytes (▶ Chap. 7, ▶ Sects. 19.4 and ▶ 19.5). Epstein–Barr virus nuclear antigen 1 (EBNA1) also has an important function in this process: this protein is expressed in all latently infected cells; it acts as a transactivator and also increases its own expression. Concomitantly, it binds to the viral origin of replication oriP, at which the episomal replication of the viral genome is initiated during the latent state. Hence, EBNA1 is responsible for maintaining the immortalized state. Despite the long-lasting production of this viral protein, the cells are not recognized as foreign: a domain within EBNA1 which consists of repeated glycine–alanine residues prevents degradation by the proteasome, i.e. it inhibits the process that is essential for the formation of MHC antigen–peptide complexes (▶ Sect. 19.5).

Other human tumour viruses can also avoid immune defence systems. Papillomaviruses (▶ Sect. 19.3) evade most immune responses by infecting preferably the outer skin layers, and thus occupying an ecological niche, which is not accessible to many immunologically active components. Hepatitis B virus produces and secretes large amounts of the surface protein HBsAg, which intercepts virus-specific neutralizing immunoglobulins, which thus cannot exert their antiviral activity.

6.4 Are Viruses Capable of Suppressing Apoptosis?

Apoptotic processes are probably associated with the occasionally observed phenomenon of spontaneous tumour regression. Although little is known about these processes, there is a growing body of evidence that transformation and tumour formation can solely be successful if viruses induce not only cell proliferation and have mechanisms to evade the immune system, but also prevent the induction of apoptosis. These processes are best studied in Epstein–Barr virus, which has complex mechanisms for immortalization and transformation. The latent protein LMP1 induces the expression of the cellular proto-oncogene c-bcl-2 (Fig. 6.1), which in turn prevents the cell triggering apoptosis by inducing the Fas signalling pathway. The same effect is exerted by the adenovirus 19-kDa E1B protein and a protein of Epstein–Barr virus which is encoded in the BHRF1 open reading frame ORF. They have sequence and functional homology to the protein Bcl2 and also counteract the induction of apoptosis (▶ Sects. 19.4 and ▶ 19.5). Besides tumour viruses, several other viruses that can establish persistent infections have developed

mechanisms to suppress apoptosis; these include the poxviruses (▶ Sect. 19.6). On the other hand, viruses that induce acute infections also seem to have functions that suppress apoptosis in a tissue-specific manner, such as SARS virus (▶ Sect. 14.8).

Further Reading

Chiarugi V, Meguelli L, Cinelli M, Basi G (1994) Apoptosis and the cell cycle. Cell Mol Biol Res 40:603–612

Cuff S, Ruby J (1996) Evasion of apoptosis by DNA viruses. Immunol Cell Biol 74:527–537

Diller L, Kassel J, Nelson CE, Cryka MA, Litwak G, Gebhardt M, Bressac B, Ozturk M, Baker SJ, Vogelstein B (1990) p53 functions as a cell cycle control protein in osteosarcoma. Mol Cell Biol 10:5772–5781

Hinds PW, Weinberg RA (1994) Tumor suppressor genes. Curr Opin Genet Dev 4:135–141

Knudson AG (1993) Antioncogenes and human cancer. Proc Natl Acad Sci 90:10914–10921

Kouzarides T (1995) Transcriptional control by the retinoblastoma protein. Semin Cancer Biol 6:91–98

Liu X, Miller CW, Koeffler PH, Ber AJ (1993) The p53 activation domain binds the TATA box-binding polypeptide in holo-TFIID, a neighboring p53 domain inhibits transcription. Mol Cell Biol 13:3291–3300

Lowe SW (1999) Activation of p53 by oncogenes. Endocr Relat Cancer 6:45–48

Ludlow JW, Skuse GR (1995) Viral oncoprotein binding to pRB, p107, p130, p300. Virus Res 35:113–121

Mahr JA, Gooding LR (1999) Immunoevasion by adenoviruses. Immunol Rev 168:121–130

Marcel MM, Roy FM, van Bracke ME (1993) How and when do tumor cells metastasize? Crit Rev Oncog 4:559–594

Mercer WE (1992) Cell cycle regulation and the p53 tumor suppressor protein. Crit Rev Eukaryot Gene Expr 2:251–263

Truyen U, Löchelt M (2006) Review of viral oncogenesis in animals and relevant oncogenes in veterinary medicine. In: Dittmar T, Schmidt A, Zänker KS (eds) Infection and inflammation: impacts on oncogenesis. Contributions to microbiology, vol 13. Karger, Basel, pp 101–117