Journal of Cellular Biochemistry 53:329–335 (1993)

Adenovirus Genes That Modulate the Sensitivity of Virus-Infected Cells to Lysis by TNF

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Abstract TNF is a key inflammatory cytokine with antiviral properties. Human adenoviruses encode several intracellular proteins that mediate the effects of TNF. Expression of the adenovirus immediate early E1A proteins induces viral genes and a host of cellular genes, drives G_0 cells into S-phase, and induces apoptosis and susceptibility to TNF-induced apoptosis. The adenovirus E1B-19K protein inhibits both E1A- and TNF-induced apoptosis. The E3-14.7K protein and the E3-10.4K/14.5K complex of proteins inhibit TNF- but not E1A-induced apoptosis. The E3 14.7K and 10.4K/14.5K proteins inhibit TNF activation of cytosolic phospholipase A_2 ($cPLA_2$), which may explain how they inhibit TNF cytolysis. Since eicosinoids produced from arachidonic acid (the product of $cPLA_2$) are potent mediators of inflammation, the E3 proteins may block the inflammatory response to adenovirus infection. These adenovirus proteins should be novel tools to understand adenovirus pathogenesis, TNF signal transduction, and TNF cytolysis.

Key words: adenovirus, tumor necrosis factor, phospholipase A_2, inflammation

A new field of research has recently been emphasized in virology, termed *molecular pathogenicity*, which deals with the molecular basis of virus tissue specificity, persistent infections, disease, and the interaction between viruses and the immune system. In the past several years a variety of viral proteins have been identified that appear to allow viruses to evade the host antiviral defenses. In this article I will discuss novel human adenovirus proteins that counteract the antiviral effects of tumor necrosis factor (TNF).

There are 47 human adenovirus serotypes (Ad1–47) that form six subgroups (A–F). The subgroups are quite distinct, with only 10–20% hybridization among the DNA genomes. The serotypes and subgroups also differ in their pathogenicity and types of infections. Ad2 and Ad5 (subgroup C), the standard model for molecular biology and the topic of this article, tend to cause upper respiratory tract infections in infants and young children and to form persistent infections where the virus can be shed for weeks or even years following the initial infection. Lymphoid cells are thought to be the reservoir for these persistent infections.

Adenoviruses are nonenveloped viruses whose genome is a linear duplex DNA molecule of 36,000 base pairs (Fig. 1). The genes are expressed in the cell nucleus in two broad phases: "early," which precedes viral DNA replication, and "late" (see the legend to Fig. 1). Early genes encode about 25 proteins that function to usurp the infected cell and to counteract immunosurveillance. Late genes encode primarily viral structural proteins. Host cell DNA, mRNA, and protein synthesis are shut off at late stages of infection.

Many of the proteins that counteract immunosurveillance are derived from the E3 transcription unit (Fig. 2). E3 mRNAs are alternatively spliced, and they encode seven known proteins. None of the E3 genes is required for adenovirus replication in cultured cells; this has allowed the construction of a large number of viral E3 mutants which have proved to be valuable in understanding the functions of the E3 proteins. Interestingly, none of the E3 genes is required for adenovirus replication in cotton rats [1]. Thus, although the E3 proteins undoubtedly are important for long-term adenovirus survival, they are not essential for short-term replication.

I will concentrate on the E3-coded 10.4K (10,400 MW), 14.5K, and 14.7K proteins, all of

Received May 19, 1993; accepted June 29, 1993.

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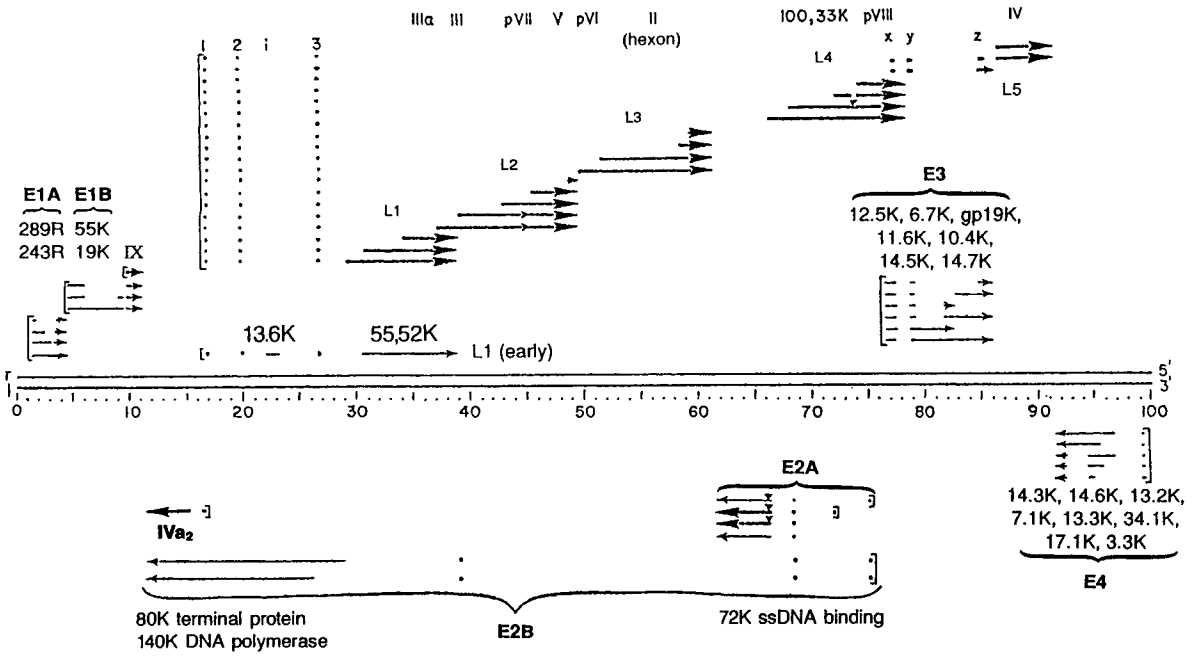

Fig. 1. Schematic representation of the adenovirus 2 genome. The parallel lines indicate the linear duplex DNA genome, divided into 100 map units of 360 base pairs per map unit. Rightward and leftward transcription are indicated by r and l, respectively. The split arrows indicate the spliced structures of the mRNAs. Designations such as 289R, IIIa, 12.5K, etc., refer to proteins. The immediate early E1A genes are expressed initially; then they induce expression of the delayed early genes in the E1B, E2 (A and B), E3, E4, and L1 (early) transcription units. Viral DNA replication occurs at 7 h postinfection, then the infection moves into late phase. Most late genes lie in the "major late transcription unit" whose promoter is at map position 16. The major late mRNAs form five families (L1–L5) that arise by alternative slicing of the major late pre-mRNA. All major late mRNAs have a tripartite leader consisting of exons 1, 2, and 3 spliced to their 5' termini.

which inhibit TNF cytolysis. Gp19K is another E3 protein that counteracts immunosurveillance. Gp19K is an abundant glycoprotein, localized in the endoplasmic reticulum (ER), which forms a complex with class I antigens of the major histocompatibility complex and thereby retains the class I antigens in the ER. As a result, gp19K prevents cells from being killed by cytotoxic T-lymphocytes (CTL). The functions of the E3 12.5K, 6.7K, and 11.6K proteins are unknown.

E1A PROTEINS SENSITIZE CELLS TO LYSIS BY TNF, AND THE E3 14.7K PROTEIN, THE E3 10.4K/14.5K COMPLEX OF PROTEINS, AND THE E1B-19K PROTEIN PREVENT CELL LYSIS BY TNF

CTL are a major mechanism by which viruses are eliminated in acute infections. However, macrophages and cytokines are also important. TNF, a cytokine secreted primarily by activated macrophages, regulates the inflammatory and immune responses. TNF is cytotoxic to many tumor cells, and it inhibits the replication of a number of DNA and RNA viruses in cultured

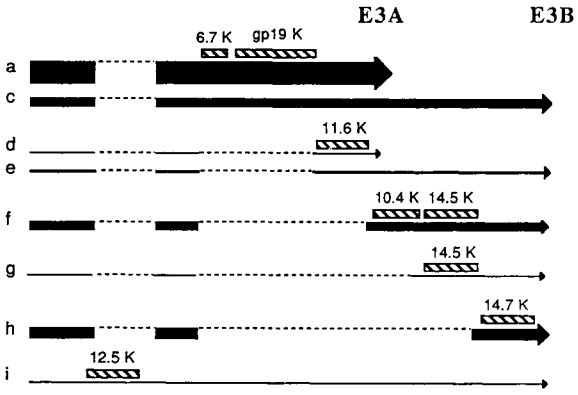

Fig. 2. Schematic representation of the E3 transcription unit. The split arrows depict the spliced structures of the mRNAs (a–i). The thickness of the arrow implies the relative abundance of the mRNAs. The dashes indicate introns. The mRNAs are coterminal at their 5' ends (at the left), and they form 3' ends at one of two polyadenylation sites termed E3A and E3B. The bars above the arrows indicate coding positions for proteins.

cells and lyses cells infected by certain viruses. TNF is released during infections by respiratory viruses such as influenza and respiratory syncytial virus, and virus infection induces TNF synthesis in some cells. Many workers believe that a

major function for TNF is the inhibition of virus replication.

There are two TNF receptors, termed p60 and p80, whose extracellular domains are part of a superfamily that includes the nerve growth factor receptor. The intracellular domains of p60 and p80 are different, indicating that signal transduction by the two receptors occurs by different mechanisms. TNF induces many genes by mechanisms that involve, depending on the cell type, a phosphatidyl choline/sphingomyelinase/ceramide pathway, protein kinase C, protein kinase A, or heterotrimeric G-proteins [reviewed in 2]. TNF induction of genes involves multiple transcription factors, mainly NFκB, c-fos, and c-jun.

The mechanism of TNF cytolysis is largely unknown, but it appears to occur via the p60 receptor. The TNF signal transduction pathway leading to cytolysis is controversial: studies using inhibitors have implicated arachidonic acid metabolism, protein kinase C, and protein kinase A. Most cells are resistant to TNF cytolysis, but they die when treated with TNF in the presence of cycloheximide (CHI). Thus, TNF cytolysis does not require protein synthesis, indicating that a pre-existing latent mechanism becomes activated. Cells are not killed when they are treated with TNF and then challenged by TNF + CHI; thus, TNF induces genes that prevent TNF cytolysis. There are two ways to interpret the observation that cells are killed by TNF + CHI. First, cells are constitutively susceptible to TNF, but TNF induces the protecting proteins before the cytolytic machinery becomes activated; CHI blocks TNF induction of the protecting proteins, so the cells die. Second, cells are constitutively resistant to TNF because of the action of a constitutive labile protein(s); this labile protein is degraded in the presence of TNF + CHI, so the cells die.

Figure 3 shows the response of adenovirus-infected mouse cells to TNF. Mouse cells are not permissive for human adenovirus replication, but adenovirus early proteins are expressed efficiently. Neither uninfected cells nor cells infected by wild-type Ad5 are lysed by TNF, but cells infected with a mutant that lacks region E3 are efficiently lysed [3]. This result has two implications. First, adenovirus infection must sensitize the cells to lysis by TNF. Second, a product of E3 must prevent lysis by TNF.

Studies using mutants deleted in region E3 as well as other early transcription units indicated

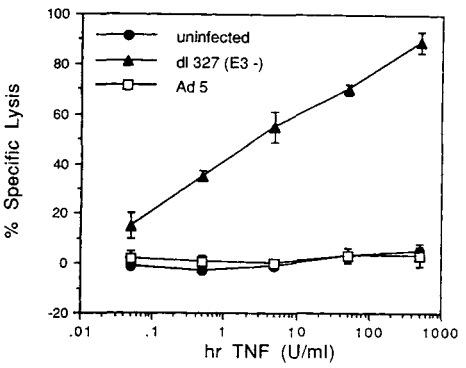

Fig. 3. TNF lysis of adenovirus-infected cells. Mouse C3HA cells were infected with adenovirus, labeled with $Na_2{}^{51}CrO_4$, washed, and treated with human recombinant TNF. After 18 h, cell lysis was measured by release of $^{51}CrO_4$ into the culture supernatant.

that the E1A 289 residue (289R) and 243R proteins sensitize cells to lysis by TNF [4]. The 289R and 243R proteins are synthesized from alternatively spliced mRNAs (Fig. 1), and they are identical except that 289R has a 46 amino acid domain that is lacking in 243R.

The E1A proteins are well-studied multifunctional proteins with a modular structure; specific functions are embodied in specific domains [5]. There are three domains that are highly conserved among serotypes in different subgroups; these domains are CR1 (conserved region 1), CR2, and CR3. CR1 (residues 40–80) is responsible for inducing sensitivity to TNF cytolysis, as indicated by studies with virus mutants [5]. In E1A stably transfected cells, both CR1 and CR2 are necessary to sensitize cells to TNF [6]. Other functions of the E1A proteins include induction of DNA synthesis in quiescent cells, immortalization of primary cells in cooperation with activated *ras* or with the E1B proteins, *trans*-activation of delayed early adenovirus genes, induction or repression of a variety of cellular genes, and induction of apoptosis (programmed cell death) [7,8]. Interestingly, CR1 is necessary for E1A-induced apoptosis.

The mechanism by which CR1 of E1A induces apoptosis, or induces susceptibility to TNF cytolysis, which occurs in most cells by apoptosis, is not known. E1A upregulates p53, a tumor suppressor protein, by extending the half-life of p53 [9]. p53 is a DNA sequence-specific transcription factor that may induce differentiation and that causes cell cycle arrest in response to DNA damage. p53 also induces apoptosis under certain conditions [8]. It has not been shown that

CR1 is required to upregulate p53, but given that CR1 is required to induce DNA synthesis and apoptosis, it is reasonable to postulate that CR1 induces apoptosis by upregulating p53 [8]. It may be that forced cellular DNA synthesis as well as deregulation of the cell cycle by E1A is incompatible with high levels of p53, and this leads to cell suicide [8]. It is not clear how susceptibility to TNF cytolysis fits into this picture, but it seems possible that some of the same genes or mechanisms may be involved in E1A- and TNF-induced cytolysis.

It is also possible that other transcription factors are involved in E1A- and TNF-induced cytolysis. The E1A 243R and 289R proteins differentially regulate AP-1–responsive genes: *they repress* collagenase and stromolysin and they induce *c-jun* and *junB* [10]. Induction or repression appears to result from different combinations of transcription factors, c-jun and c-fos heterodimers for repression and c-jun and ATF-2(–like) heterodimers for activation [10]. These effects are mediated via CR1 of E1A [10]. The E1A 243R and 289R proteins are reported to bind directly to members of the ATF/CREB and AP-1 (c-fos, c-jun) families of transcription factors [11], which may allow these transcription factors plus E1A to assemble with other transcription factors on the promoter and thereby stimulate or repress transcription.

Deletion of CR1 but not other regions of E1A abrogates the induction of TNF susceptibility in adenovirus-infected cells [5]. However, in E1A stably transfected rat cells, deletion of either CR1 or CR2 abrogates induction of TNF susceptibility [6]. It is not known why infected cells differ from E1A-transfected cells in this respect. CR2, and to a lesser extent CR1, are essential for E1A to liberate the transcription factor E2F from an E2F●RB complex and from an E2F●p107●cyclin A●cdk2 complex [reviewed in 12]. (RB is the retinoblastoma tumor suppressor protein, p107 is a protein of unknown function that is related to RB, and cdk2 is a cyclin dependent serine/threonine protein kinase). E2F is essential for activation of the adenovirus E2A promoter which drives expression of proteins that are essential for adenovirus DNA replication. E2F is also thought to induce genes in S-phase that are important for DNA synthesis (e.g., DNA polymerase α, ribonucleotide reductase, thymidine kinase, and others).

In summary, CR1 of E1A may induce apoptosis and susceptibility to TNF-induced cytolysis by upregulating p53. In addition, or alternatively, CR1 of E1A may exert these effects by activation or repression of transcription via members of the AP-1 or ATF/CREB families. In the case of E1A-transfected cells, activation of E2F may also be important.

With regard to the proteins in region E3 that prevent TNF cytolysis, studies with virus mutants indicate that there are two sets of proteins that function independently to prevent TNF cytolysis [3,13]. The 14.7K protein prevented TNF lysis in 13 of 15 mouse cell lines analyzed [3,13]. The 10.4K and 14.5K proteins, functioning as a complex, prevented TNF lysis in 11 of 15 mouse cell lines [13]. In adenovirus-infected human cells, E1A also sensitizes cells to TNF lysis [7,14]. E3 proteins, very likely 14.7K and/or the 10.4K/14.5K complex, prevent TNF lysis of human cells [14]. Interestingly, yet a third adenovirus protein, the 19K protein encoded by the E1B transcription unit, also can prevent TNF lysis of human cells [14], and it can do so independently of 14.7K and 10.4K/14.5K. For unknown reasons, E1B-19K does not prevent TNF lysis of mouse cells.

As mentioned, E1A induces apoptosis. E1B-19K inhibits apoptosis induced by E1A [7]. Thus, E1B-19K can inhibit apoptosis induced by two agents, E1A and TNF. The E3 proteins inhibit TNF-induced apoptosis but not E1A-induced apoptosis. It seems likely that a major role for E1B-19K, E3-14.7K, and E3-10.4K/14.5K is to keep the virus-infected cell alive in the context of the cytotoxic effects associated with E1A expression or with TNF action on the infected cells. It is remarkable that four of the approximately 25 adenovirus early proteins prevent TNF cytolysis; such a large expenditure of genes implies that TNF is an important antiviral defense of the host.

The mechanisms by which these adenovirus TNF protecting proteins function are not known. E3-14.7K is a hydrophilic protein of 128 amino acids (in Ad2 or Ad5), localized in the nucleus and cytoplasm as indicated by immunofluorescence and cell fractionation. The 14.7K gene is conserved in serotypes in subgroups A through F, and the 14.7K protein from these subgroups appears to prevent TNF cytolysis [15]. Cells can be sensitized to TNF by expression of E1A, by inhibition of protein synthesis, and by treatment with cytochalasin E (an agent that disrupts microfilaments), and some cells are spontaneously sensitive to TNF; the 14.7K protein

prevents TNF cytolysis under all these conditions, suggesting that 14.7K is a general inhibitor of TNF cytolysis [16]. The 14.7K protein prevents TNF cytolysis when expressed in stably transfected mouse cells, establishing that 14.7K functions independently of other adenovirus proteins [17]. Studies with virus mutants having in-frame deletions as well as cysteine-to-serine mutations in the 14.7K protein suggest that 14.7K functions as a single functional unit [18].

The E3-10.4K and 14.5K proteins exist as a complex of integral membrane proteins localized on the cell surface [19; R. Steward, A. Tollefson, and P. Krajcsi, unpublished results]. The 14.5K protein has an N-terminal signal sequence that is cleaved, and the protein has an N_{exo}-C_{cyt} orientation in the membrane [20]. The 14.5K protein is phosphorylated on serine residues, probably at a single site near the C-terminus, and it is O-glycosylated with mucin type oligosaccharides. The 10.4K protein exists as two forms. One form has a cleaved N-terminal signal sequence and an N_{exo}-C_{cyt} orientation on the membrane [21]. With the other form, the N-terminal signal is not cleaved, but rather functions as a transmembrane domain [19,21]. The two forms of 10.4K are joined by a disulfide bond between the cysteine residues at position 31 [19].

The 10.4/14.5K protein complex also has another function: it downregulates the cell surface expression of the epidermal growth factor receptor (EGF-R) in adenovirus-infected cells [22,23]. The insulin receptor (I-R) and the insulin growth factor I receptor (IGF1-R) are also downregulated, a process that requires 10.4K [24] and probably also 14.5K. EGF-R, I-R, and IGF1-R are members of the protein tyrosine kinase class of receptors. The natural ligands bind to these receptors, stimulate the receptor protein tyrosine kinase activity, and then cause the receptors to be down-regulated. It is not known whether the adenovirus proteins mimic the natural ligands in their ability to stimulate the protein tyrosine kinase activities of the receptors. This would be a useful property for the adenovirus proteins, because this would help activate the infected cell and make it more efficient for adenovirus replication. Studies with virus mutants having in-frame deletions in the 10.4K gene indicate that the ability of the adenovirus proteins to affect the cell surface expression of these receptors is not related to their ability to prevent TNF cytolysis [unpublished].

The E1B-19K protein localizes to the nuclear membrane, and in transformed cells it binds to and disrupts vimentin-containing intermediate filaments and the nuclear lamina. E1B-19K can also transform cells in cooperation with E1A. Studies with E1B-19K mutants suggest that the ability of E1B-19K to inhibit apoptosis explains its ability to cooperation with E1A in cell transformation (E1A transforms the cells but induces apoptosis: E1B-19K inhibits apoptosis and keeps the transformed cell alive) [7].

One possible mechanism by which the E3-14.7K, E3-10.4K/14.5K, and E1B-19K proteins could function is to downregulate one or both of the TNF receptors. However, in stably transfected mouse cells that express 14.7K, there is no reduction in the number of TNF receptors per cell nor in the affinity of these receptors for TNF [17]. A possible effect of 10.4K/14.5K or E1B-19K on the TNF receptors has not yet been investigated.

Perhaps the most promising insight into how these TNF protecting proteins may function was provided by Zilli et al. [25], who showed that 14.7K inhibits the TNF-induced release of arachidonic acid (AA) in mouse cells stably transfected with the 14.7K gene. AA is released from the *sn*-2 position of membrane phospholipids by phospholipase A_2 (PLA_2). Zilli et al. [25] found that AA is not released when cells were treated with TNF alone, but it is released by TNF + CHI. This is highly significant because TNF kills most cells in the presence of CHI and because activation of PLA_2 seems to be a critical step in TNF lysis of at least some cell types [25]. Recent studies with virus mutants lacking 14.7K and either 10.4K or 14.5K show that not only does 14.7K inhibit TNF-induced release of AA, but the 10.5K/14.5K complex does so as well [P. Krajcsi, A. Scaria, S. Laster, and W. Wold, unpublished results]. When in-frame deletion and cysteine-to-serine mutants within the 14.7K gene were analyzed, there was a strict correlation between inhibition of TNF cytolysis and inhibition of TNF-induced release of AA. In the virus infection experiments, it is not necessary to treat the cells with CHI to sensitize them to TNF-induced release of AA; it is likely that this is achieved by expression of E1A, as E1A sensitizes cells to TNF cytolysis.

The PLA_2 that is activated by TNF in these experiments is very likely a unique cytosolic

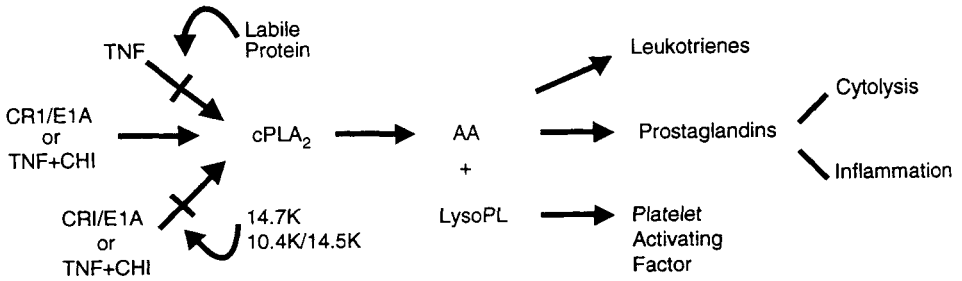

Fig. 4. Summary and implications of the ability of the adenovirus 14.7K and 10.4K/14.5K proteins to block TNF-activation of $cPLA_2$. See text for details.

species ($cPLA_2$) [26]. $cPLA_2$ is normally in the cytosol, but in the presence of Ca^{++} it becomes associated with membranes. It is phosphorylated and activated by MAP kinase [26]. $cPLA_2$ is activated after treatment of cells with phorbol esters plus Ca^{++} ionophores, thrombin, ATP, platelet derived growth factor [26], and undoubtedly other agonists. Although the 14.7K protein and the 10.4K/14.5K complex block release of AA in response to TNF, they do not block release of AA in response to IL-1 plus CHI or phorbol ester plus Ca^{++} ionophore [25; unpublished results]. This indicates that the viral proteins must act at a signal transduction step that is unique to TNF. Since 14.7K and 10.4K/14.5K are such different types of proteins, 14.7K in the cytosol and nucleus and 10.4K/14.5K in the plasma membrane, it is likely that they act at different steps in the TNF signal transduction pathway(s). It will be interesting to determine whether E1B-19K, the other adenovirus protein that prevents TNF cytolysis, also blocks TNF activation of $cPLA_2$.

These adenovirus/TNF/$cPLA_2$ findings are summarized in Figure 4. In most cells types, TNF does not activate $cPLA_2$, perhaps because a hypothetical labile protein or mechanism (e.g., the phosphorylation state of a certain protein) blocks the signal transduction pathway. In the presence of E1A or CHI, this blocking protein or mechanism turns over and $cPLA_2$ is activated. The products of $cPLA_2$, AA and lysophospholipid, are further metabolized to leukotriennes, prostaglandins, and platelet activating factor. These $cPLA_2$ products are important in TNF cytolysis [25]. Oxygen radicals produced during eicosinoid metabolism could be part of the cytolytic response, as could lysophospholipids acting as agents that disrupt membranes. The E3 proteins, by blocking TNF activation of $cPLA_2$, block TNF cytolysis. The eicosinoids produced from AA and lysophospholipid are also potent second messengers that mediate the inflammatory response. Of great interest, by blocking TNF activation of $cPLA_2$, 14.7K and 10.4K/14.5K could inhibit the inflammatory response. The putative ability of 14.7K and 10.4K/14.5K to inhibit inflammation could explain why there is increased infiltration of neutrophils into the lungs of cotton rats infected by mutants that lack 14.7K and 10.4K/14.5K but retain gp19K (see below). Indeed, inhibition of the inflammatory response by 14.7K and 10.4K/14.5K may be a much more important function in adenovirus pathogenesis than their ability to prevent TNF cytolysis.

The E3 transcription unit appears to be a cassette of genes that counteracts immunosurveillance, gp19K preventing killing of infected cells by CTL and 14.7K and 10.4K/14.5K preventing killing by TNF. The regulation of the E3 promoter is also in accord with this idea. E3 is the only adenovirus promoter that contains binding sites for NFκB, a transcription factor that is commonly activated during immune and inflammatory responses. The NFκB sites allow for E1A-independent expression from the E3 promoter in lymphoid cells [27], and probably also for E1A-independent TNF-induced expression from the E3 promoter in stably transfected cells [28]. It is appealing to consider that during acute and persistent infections, TNF activates the E3 promoter and thereby superinduces the E3 proteins that block the antiviral effects of TNF [28]. Since E3 is expressed independently of E1A in lymphoid cells, we can even imagine that E3 is the only transcription unit that is expressed, thereby allowing the virus to persist in lymphoid cells [27].

FUNCTIONS OF THE ADENOVIRUS E3 PROTEINS IN VIVO

The studies discussed previously have all been carried out in cultured cells. It is important to consider whether the adenovirus proteins have

similar functions in vivo. Ginsberg et al. [1] have used cotton rats, which are permissive for subgroup C human adenovirus replication, to study the pathogenesis of adenovirus. Ad2 or Ad5 induces a pneumonia in cotton rats that resembles that in humans. Infection occurs in two phases, an early phase affecting the alveoli, bronchiolar epithelia, and peribronchiolar regions and characterized by infiltration of monocytes and neutrophils, and a later phase affecting peribronchiolar and perivascular regions with infiltration of lymphocytes. The pathology appears to be a response to host immune defenses to virus infection. In accord with this idea, mutants that lack gp19K are considerably more pathogenic than wild-type virus, presumably because these mutants do not block a CTL response or synthesis of cytokines associated with this response [1]. With a mutant that expresses gp19K but lacks the 10.4K/14.5K and 14.7K proteins, there is also an increase in pathology which is characterized by increased numbers of polymorphonuclear leukocytes rather than monocytes [1]. Thus, the adenovirus E3 proteins do appear to function in adenovirus pathogenesis in the cotton rat, although at this point it cannot be discerned whether the proteins have the same function in vivo as they do in cultured cells.

ACKNOWLEDGMENTS

This work was supported by grant CA24710 from the National Institutes of Health.

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