Acta virol. 34 : 380—400, 1990

RELATIONSHIP BETWEEN THE PROSTAGLANDIN CASCADE AND VIRUS INFECTION

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Received October 31, 1988; revised August 4, 1989

Summary. — Several prostaglandins are continuously produced in every cell. They activate protein kinases by regulating cyclic nucleotide synthesis. Modifications of the phosphorylation of virus polypeptides and alterations in the microtubular system of host cells can result in the reactivation of latent viruses. Prostaglandins have a very important role in directing cell cycle. Abnormal tyrosine kinase activities during viral cell transformation are responsible for the malignant changes and consequently severe alterations are observed in the endogenous prostaglandin production. External modification of this cascade can revert malignant signs to normal. Furthermore, virus infection or cell transformation could be promoted by the immunosuppressive effects of overproduced prostaglandings. They damage interferon release and co-operation between the different cell types of the immune system. Enzyme inhibitors of the prostaglandin cascade or prostaglandin analogues may exert influence on all of these phenomenon, providing future therapeutic agents.

Key words: *prostaglandins*; *protein kinases*; *latency*; *transformation*; *interferons*

Among several endogenous and natural substances, prostaglandins are regarded as general modulators of cell metabolism. They have a well documented direct and indirect effect on cell-virus interaction, virus replication, and on reactivation process from latent state of viruses. Moreover, they can play a role in viral transformation as well.

The cascade of prostaglandins — cyclic nucleotides — protein kinases

Prostaglandins (PG) belong to the family of eicosanoids. They are synthesized from arachidonic acid by cyclooxygenase and peroxidase, while lipoxygenase convert leukotrienes (LT) from the same precursor. Arachidonic acid itself is derived from the cell membrane by phospholipase A (Berkow, 1977;

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Nelson and Johnson, 1982; Honn and Sloane, 1985). Both PGs and LTs form many further derivates which are designed by letters and a numerical index representing the number of double bonds in their side chains (Martin *et al.*, 1983). PGs are produced in ng quantities in every cell continuously, but they are not stored. Minor modifications in their structure are responsible for the different biological activities. They take part in several physiological functions, they behave as intracellular messengers (Ferreira *et al.*, 1971; Fitzpatrick and Stringfellow, 1980; Švec *et al.*, 1982). The most important fact, however, is that PGE increases the production of cyclic adenosine 3′, 5′-monophosphate (cAMP), PGF — and in smaller degree PGA, PGG, PGH — elevate the intracellular level of cyclic guanosine 3′, 5′-monophosphate (cGMP) by the activation of adenylate cyclase or guanylate cyclase, respectively (Harbour *et al.*, 1983; Lord *et al.*, 1989). The two types of cyclic nucleotides (CN) are of antagonistic effects, and they activate certain protein kinases (PK), the so called cAMP-dependent or cGMP-dependent PKs (McClung and Kletzien, 1984; Robert-Galliot *et al.*, 1985; Beushausen *et al.*, 1987). In the cells, the greater part of normal protein phosphorylation is carried out by these CN-dependent protein kinases, but there are more types of other PKs (Foreman, 1981). The substrate specificity of CN-dependent PKs is relatively wide, therefore they are able to utilize several structural and non-structural polypeptides of viral origin (Willis, 1984). Phosphorylation of proteins is a relatively simple way of regulating their enzymatic and other activities, functions (Abell and Monahan, 1973; Leader and Katan, 1983; Clinton and Roskoski, 1984; Michell, 1989).

Possible molecular mechanisms between the prostaglandin cascade and viral infections of cells

The effects of PG-CN-PK cascade have to do with the different forms of virus infections through a few molecular mechanisms only.

1. In eukaryotes, cAMP activates a histone kinase which phosphorylates basic histones rich in lysine, while cGMP increases the phosphorylation of acidic nuclear proteins on their serine or threonine residues. These modifications revert the nonspecific inhibition of transcription of certain genome sections maintained by histones. The subsequent induction of cellular enzymes is essential in the virus replication and viral transformation (Pantazis *et al.*, 1984; Willis, 1984).
2. PGs may take part in the posttranslational modification of viral proteins (Benavente *et al.*, 1984; Stevely *et al.*, 1985). This process alters not only the phosphorylation but glycosylation, too. Namely, PGA_1 *in vitro* strongly suppressed the synthesis of vesicular stomatitis virus (VSV) glycoprotein G (Santoro *et al.*, 1983*b*). PGJ_2 partially inhibited and caused an alteration in the synthesis of Sendai virus glycoproteins by the same way (Santoro *et al.*, 1987). Interestingly, both PGs caused a similar decrease of the molecular weights of the special glycoproteins as compared with their controls in these not related viruses.
3. The phosphorylating effect of the CN-PK system plays an important role

Table 1. The effect of prostaglandins and cyclic nucleotides on viruses

Compound	Viruses
PGA_1	Suppression of glycosylation of VSV polypeptide G
PGA_2	Suppression of replication of vaccinia-, encephalomyelitis-, Sendai virus, and VSV *in vitro*
	Enhancement of MuMTV replication in cell cultures
PGB_1	Enhancement of MuMTV replication in cell cultures
PGD_2	Antiherpetic activity *in vitro* and *in vivo*
	Enhancement of HIV production by MOLT-4 cells
PGE_1	Reactivation of latent HSV-1 and 2 *in vivo* or from
PGE_2	explanted ganglia
cAMP	Increased spread of HSV-1 and 2 from cell to cell
	Increased adherence of HSV-1 infected cells to uninfected cells
	Increased size of plaques by HSV-1 and 2
	Inhibiton of DNA synthesis by oncogenic human adenovirus type 12
	Inhibition of proliferation of 3T3 cells transformed by polyoma virus
	Normalization of functions of macrophages transformed by SV-40
	Suppression of replication of parainfluenza virus type 3, JHM virus and measles virus
	Enhancement of HIV production by MOLT-4 cells *in vitro*
	Enhancement of MuMTV replication in cell cultures
	Suppression of cell transformation by Rous and Kirsten sarcoma viruses
	Immunological effects:
	Allowing HSV-1 production by damaging ADCC and NKC
	Inhibition of IL-4 production to prevent Epstein-Barr virus induced B cell proliferation and IgM production
	Suppression of IgM production to Dengue-2 virus
	Inhibition of anti-VSV cytotoxic lymphocytes
	Inhibition of IFN release from NDV infected mouse L cells
	Reduction of yield of polio-, encephalomyocarditis virus and VSV
PGF_2	Stimulation of HSV-1 and 2 replication in case of infection with low multiplicity
cGMP	Stimulation of human adenovirus type 5 ts18 mutant replication *in vitro*
	Stimulation of MuMTV replication in cell cultures
	Enhancement of SV-40 transforming effect
PGI_2	Synergistic effect with IFN against vaccinia virus
PGJ_2	Inhibition and alteration in the glycosylation of Sendai virus glycoprotein

in the protein condition of microtubular system of cells: the cytoskeleton is stabilized by cAMP (Harbour *et al.*, 1983; Puck, 1984; Schulman, 1984). Membrane proteins are also stabilized in this manner, and cAMP stimulates the granular cell secretion and the permeability of the cell membrane (Nelson

and Johnson, 1982; Martin *et al.*, 1983; Weber and Osborn, 1985). The cGMP has an opposite effect. Polypeptides with abnormal PK activities, as Rous sarcoma virus (RSV) pp60^{src} transforming protein, can be bound to microfilaments and take part in the morphological changes of cells (Henderson and Rohrschneider, 1987). These changes can also have great importance in virus replication: in their adsorption to membrane receptors and maintenance of cell compartments, which are necessary for virus production. The damaged cytoskeleton can cause unequal distribution of chromosomes to daughter cells, resulting in karyotype dearangement and genetic drift, which can contribute to the increasing malignancy and resistency to therapy during carcinogenesis (Puck, 1984). Furthermore, the latency of viruses, which is one of the least cleared up areas of virology, will be explained by changes in cellular compartments and surface receptors. Recent works have demonstrated that PGs alter both mobility and expression of surface receptors on lymphocytes, so they can take part in virus induced immune modulation (Lewis *et al.*, 1985; Veillette *et al.*, 1989).

4. Partly these mechanisms, partly the effects of other compounds of eicosanoid family elucidated several functions of lymphocytes having antiviral activity (Doro-Duffy *et al.*, 1981), as well as the induction and pathomechanism of lymphokines and interferons (IFN) (Herz and Sen, 1983; Stringfellow and Brideau, 1984). PGs influence the antibody production and their biological activity, and they modify the nonspecific defence mechanisms of the organism (Goodwin and Webb, 1980).

Nonetheless, in spite of these, the effect of PGs should not be taken overstatingly, but they must be considered as significant factors which have effect in many changes (Lancet Editorial, 1988). PG derivates are available in many forms synthesized *in vitro*, and these can be applicable tools for modifying polypeptides of cells and viruses (Abell and Monahan, 1973; Collett *et al.*, 1979).

Unfortunately, the alterations of the endogenous PG system due to virus infections are less known. Available data are referred to in appropriate chapters (Tables 1 and 2).

Influence on latency and replication of viruses by prostaglandins and cyclic nucleotides

Metabolites which affect PKs through modification of the intracellular level of CNs show profound effect on virus replication in various cell types. This influence may be on either the activation of infectious progeny formation from a virus formerly in a latent state or the suppression of replication. These processes are frequently bound to metabolic events leading toward cellular differentiation (Beushausen *et al.*, 1987).

Earlier, latency of herpes simplex viruses (HSV) in the Gasserian and sacral ganglia (type 1 and 2) has been thought to be controlled by immunoglobulins, and that stimuli affecting the ganglion resulted in HSV activation. The exclusiveness of this "ganglion trigger theory" can be doubted. It is much more likely that infectious particles which get from the ganglion to

the skin or mucosa along the nerves would constitute infectious microfoci; These, in turn, are constantly eliminated by the immune response (Hill and Blyth, 1976; Harbour *et al.*, 1983; Kurane *et al.*, 1984). On the other hand, if the skin or the mucous membrane are affected by other stimuli, such as trauma, UV-radiation, certain groups of chemicals, bacterial or other microbial infection, heat, fever, their cAMP content rises locally, and this can lead to increased virus replication and its insufficient elimination resulting in a clinically diagnosable herpetic lesion, This process is referred to as "skin trigger theory". As a result of some stimuli to the nervous system by stress, PGE_2 is released at the nerve endings, which seems to support this theory (Kurane *et al.*, 1984). Herpetic lesions could also be induced by PGE_2 injection into the ear of mice infected latently with HSV-1, similarly as these lesions had been induced by mechanical and chemical stimuli (Hill and Blyth, 1976). Herpes recurrence was reduced by inhibitors of PG synthesis like aspirin and chlorpromazin in persons treated for other reasons with these drugs. About 90 percent of the ganglia from infected animals release the virus during explantation and/or cocultivation in culture. This can be inhibited by 10^{-4} M indomethacin. The effect is reversible and after removal of indomethacin HSV replication starts in culture. HSV replication in mouse L-cells and in other conventional cell cultures is inhibited by phospholipase inhibitors like tetracain, mepacrine or by some cyclooxygenase inhibitors (mefamic acid). The synthesis of viral DNA was significantly reduced by 10^{-5}—10^{-3} M indomethacin given within one hour after infection, but the cell DNA synthesis and cell division remained unaffected. The effect seemed virus-specific acting on the level of viral DNA synthesis and/or gene transcription. This is important, because a block in virus gene transcription could be one of the main mechanisms of latency (Kurane *et al.*, 1984). Up to recent knowledge, it is likely that these PG antagonists might be used in the therapy of other diseases caused by viruses belonging to the germs *Herpesviridae*, like varicella-zoster virus (Hill and Blyth, 1976; Steinberg, 1984). In a plaque assay VERO cells were infected with HSV-1 and subsequently treated with PGE. The size of plaques became significantly larger compared to conventionally infected cells. Other cells treated with PGE_2 then infected with the *syn*$^-$ mutant of HSV-1 adhered to uninfected VERO cells in a larger proportion than the infected but PG-untreated cells. This adherence was reduced by PG inhibitors (Harbour *et al.*, 1983; Kurane *et al.*, 1984). Modifiers of CN catabolism such as PGA_1, PGB_1, dibutiryl-cAMP, isoproterenol, imidazole and carbamylcholine had no effect (Dianzani *et al.*, 1972; Abell and Monahan, 1973). The conclusion is that PGs of E type independently of CNs facilitate the cell to cell spread of HSV. It is also possible that the greater fluidity of cell membrane supports the increased spread of the virus (Harbour *et al.*, 1983). In contrast, the spread of HSV was decreased by theophylline (inhibitor of cAMP degradation), but not by inhibition of adsorption or penetration (Trofatter and Daniels, 1980; Harbour *et al.*, 1983). The spread of HSV-2 from cell to cell was promoted by PGE_2, while cortisol and progesterone acted synergically with this class of PGs. Ibuprofen, a non-steroidal anti-inflammatory drug and inhibitor of cyclooxygenase,

Table 2. The effect of viruses on the endogenous PG-CN-PK activities of cells

Virus	Effect
HSV-1 and 2	Induction of phospholipase A_2 in cell membranes Elevation of PGE_2 synthesis during virus replication
Human adenovirus type 12	No alteration in the endogenous cAMP level during transformation of 3Y1 cells. Stimulation of PGE_2 synthesis in synovial cell cultures during replication Alterations in the phosphorylation of cellular proteins during replication
SV 40 and polyoma virus	Elevation of cGMP level Reduction of synthesis of cAMP, adenylate cyclase, PGE_2 during transformation *in vitro*
Influenza virus and VSV	Changes in the phosphorylation pattern of proteins in infected cells
Measles, rubeola and NDV	Stimulation of PGE_2 production in synovial cell cultures during virus replication
Dengue-2 virus	Stimulation of PGE_2 production in infected T lymphocytes
Sendai virus	Rapid stimulation of cAMP production, then suppression of cAMP production in infected fibroblast
Parainfluenza virus 3	Suppression of cAMP synthesis during replication
Rous sarcoma	Reduced adenylate cyclase activity and PGE_2 production in transformed NRK or chicken embryo fibroblast cells Alteration in the cellular distrubition of adenylate cyclase and phosphodiesterase during cell transformation Elevated cAMP level during virus replication Suppression of the activity of cellular cAMP dependent PKs and cAMP independent PKs Increase in cellular phosphotyrosine content during transformation
Kirsten sarcoma virus	Reduction in PGE_2 synthesis of transformed NRK cells
Harvey sarcoma virus	Reduction in PGE_2 synthesis of transformed MDCK cells
Moloney sarcoma virus	Reduction of cAMP synthesis *in vivo* during tumourigenesis

significantly decreased the multiplication and spread of this virus, while PGs with one double bond (A_1, B_1, E_1) had no effect (Baker *et al.*, 1982). Interestingly, PGD_2 has an antiherpetic activity both *in vitro* in amnion cells and *in vivo* (Tanaka *et al.*, 1986). PGF_{2alpha} which is antagonist to PGE_2 in other aspects, also stimulated HSV-2 replication in case of infection with low multiplicity. Even serum added routinely to the culture medium of cells stimulated HSV replication by raising the cGMP level (Harbour *et al.*, 1983). It has been shown later that both types of HSV can induce phospholipase A_2 on the surface of infected cells, and its activity contributes to the elevated PGE_2 synthesis and spread of viruses (Lehtinen *et al.*, 1988).

On the interaction of other DNA viruses with the PG system it is known that replication of vaccinia virus in cell cultures was decreased by 95.3% in the presence of 4 μg/ml PGA_1 (Santoro *et al.*, 1982; Santoro *et al.*, 1983*a*; Benavente *et al.*, 1984). PGA_2 had the same effect (Ankel *et al.*, 1985). Both drugs acted in a dose-dependent manner, neither of them affected the DNA-, RNA-, and protein-synthesis in uninfected cells, nor inhibited virus adsorption and penetration. Applied in the early phase of replication, they decreased the viral DNA-, RNA-, and polypeptide-synthesis significantly. Phosphorylation of several virus proteins, however, was altered by PGAs, as it could be concluded from their electrophoretic mobility. Proteins of the untreated cells remained unchanged. Some virus polypeptides did not appear or they appeared later, while the synthesis of others was not modified, proving that these changes did not take place as a result of toxic effect, but due to blocking of maturation specific steps of some virus polypeptides or at the level of virus mRNA transcription or translation. The presence of PGA must be continuous during virus replication to achieve these effects (Turner *et al.*, 1981).

PGA_1 and PGA_2 in a dose dependent manner also inhibit *in vitro* replication of encephalomyelitis virus, Sendai virus, and VSV (Santoro *et al.*, 1981; Santoro *et al.*, 1983*a*; Mukherjee and Simpson, 1984). The results were supported by the same molecular phenomena mentioned above. PGA_1 was even suitable in preventing latent infections. In green monkey kidney cells neither PGE_2 nor PGF_{2alpha} influenced vaccinia or the above mentioned RNA viruses (Santoro *et al.*, 1982; Ankel *et al.*, 1985). It is interesting that production of measles and Coxsackie B1 viruses was not modulated by PGE_1, while growth of parainfluenza virus 3 in WISH cells decreased in the presence of PGE. The reason for this was found in diminished cellular cAMP synthesis (Luczak *et al.*, 1975). Replication of a coronavirus, the JHM virus, is found to be suppressed in primary rat oligodendrocytes as a consequence of pretreatment with metabolites that stimulate or mimic increased intracellular cAMP level. Inhibition of transcription and translation without affecting either attachment or sequestration of the inoculum was observed, indicating that a block occurs at some stage after uptake but before expression of genomic functions. This draws attention to the possibility that uncoating was the critical event. Similarly to influenza and some retroviruses, dephosphorylation of the nucleic acid binding protein (N) might be a prerequisite for complete uncoating. Because this process is repressed in differentiated oligodendrocytes (the virus can establish latent infection in such cells), the authors emphasize an apparent linkage between increased intracellular cAMP level, differentiation and suppression of coronavirus replication. However, in primary rat oligodendrocytes pretreated with dibutiryl-cAMP, VSV and measles virus were reported by the same authors to replicate normally, demonstrating that this type of control over virus expression is somewhat specific for each virus group and the particular host cell (Beushausen *et al.*, 1987). Another strain of coronaviruses, murine hepatitis virus type 3 (MHV-3) can cause a fulminant illness. Fully susceptible Balb/cJ mice infected with 100 LD_{50} developed histologic and biochemical evidence of the disease. In

contrast, animals treated either before or after infection (up to 48 hours) with 16, 16-dimethyl-PGE_2, a known cytoprotective agent, demonstrated a marked reduction in these signs of liver damage (Falk *et al.*, 1987). Moreover, others proved that the effect of PGE or cAMP on certain RNA viruses, namely on the measles virus replication is dependent on the time of PG application. During absorption these compounds enhance the infectious titre, while in the late phase they have an opposite effect. This information suggests that measles virus, similarly to other viruses, may require PG at specific times during the replicative cycle (Dore-Duffy, 1982). A similar conclusion has been drawn from another experiment, as lately guanylate cyclase activity has been assigned to Sendai virus. This can only be observed *in vitro*, if disruption of particles has already been carried out by detergents such as Triton X-100 or Nonidet P-40. Trypsin or chymotrypsin are not able to eliminate this activity, whilst antibodies against the nucleocapsid liquidate this function (Kimura *et al.*, 1981). It is of interest that the level of cAMP in KB, MRC-5, or adult fibroblast cells is higher during the first hour after infection with this virus, then it becomes depressed during the two subsequent days continuously (Vallier *et al.*, 1981).

VSV proved to be one of the best models for similar investigations, because in HEp-2 cell cultures the virus production is completely abandonable by previous indomethacin treatment, the cells become practically non-permissive. One molecule of indomethacin per cell is enough to stop virus replication. Because phosphorylation of several viral polypeptides is required for complete replication, inhibition of any of these can explain the phenomenon. Phosphorylation of several cell proteins is altered in infected cultures by VSV and also by other viruses, like influenza or adenoviruses, which is partly a precondition, partly the consequence of virus replication, and their blockade can contribute to the inhibitory effect of indomethacin (Mukherjee and Simpson, 1982; Mukherjee and Simpson, 1984).

Recently, it has been found that PGE_2 and PGD_2 added to the culture medium of the human immunodeficiency virus (HIV) continuous-producer cell line (MOLT-4/HTLV-III) increases the release of virus in dose dependent fashion. Other PGs such as PGF_{2alpha} or 13, 14-dihydro-15-keto-PGE_2 did not affect virus production. While PGE_2 is one of the immunosuppressive compounds present in human semen it might directly facilitate the efficient transmission of infection during sexual intercourse (Kuno *et al.*, 1986).

Protein kinase (PK) activities are associated with several viral particles. PK activities can be of different type being present in the envelope of the same particle (Rous sarcoma, avian myeloblastosis, Semliki forest, Sendai, Sindbis, vaccinia, rabies virus, VSV) and can utilize distinct substrates. Herpes simplex virus and tupaia herpesvirus phosphorylate predominantly structural polypeptides but equine herpesvirus utilizes protamine and histones as well. In the virus envelope certain kinase activities can be of cellular origin. Such cAMP-dependent PKs convert certain major and minor structural polypeptides of HSV-1 (Stevely *et al.*, 1985). Among unenveloped viruses, adenoviruses possess more CN-independent PK activities, which phosphorylate serine or threonine residues of either minor structural polypeptides

(III/a, VI, X) (Blair and Russel, 1978), or core polypeptides (V, VII) and the 72kD single DNA binding polypeptide (Cajean-Feroldi *et al.*, 1981), but these enzymes are unable to utilize histones. On the other hand, all the structural polypeptides of adenoviruses contain residues which can be phosphorylated by cAMP dependent PKs obtained from rabbit reticulocytes or KB cells. The substrate specificity of these enzymes is wide, they utilize histones, casein, protamine (Blair and Russel, 1978). Certain polypeptides in temperature-sensitive mutants (ts18, ts19) of human adenovirus type 5 have altered confiuguration. These polypeptides can be phosphorylated by cAMP dependent PKs of the infected cells at semipermissive temperature (37 °C), but the viral PKs seem to be more specific than cellular ones (Taródi *et al.*, 1979). Using PGs for *in vitro* stimulation of the same mutants, moderate replication of ts18 mutant could be achieved at restrictive temperature (39 °C), showing further differences in the phosphorylation pattern between polypeptides VI and X (Ongrádi *et al.*, 1986). Phosphorylation of virus polypeptides at different sites and modes suggests their polyfunctional feature. The same phenomenon can be responsible for reactivation of latency in parallel mechanisms.

Cell transformation by viruses and the prostaglandin cascade

Both in normal and transformed cell-cycle, several changes of the PG-CN-PK cascade can be observed. The phosphorylation of acidic nuclear proteins takes place in the G_1 and S phases of normal cells. This process, however, takes hardly place in the G_2 phase and mitosis (McClung and Kletzien, 1984; Willis, 1984). The cAMP level rises in the G_1 phase, while it decreases in G_2 phase and it is lowest during mitosis (Abell and Monahan, 1973; McClung and Kletzien, 1984). The changes of cGMP are of opposite direction. PGF_{2alpha}, PGG_2, and PGH_2 increase the level of cGMP and through this the activity of a PKphosphorylating the serine residues (Menyhárt and Minárovits, 1977); In general, PGs facilitate the transition into S phase from G_1 phase, but when DNA synthesis starts, the quantity of cGMP decreases, as it was shown in tumour cells: during transformation with SV 40 and polyoma viruses, cAMP level was reduced to its half in 3T3 cells. A dog kidney cell line (MDCK) transformed with Harvey murine sarcoma virus showed markedly reduced PGE_2 producing ability compared to the parental line (Lin *et al.*, 1982), and PGE_2 production was also reduced in rat kidney fibroblast cells (NRK) after transformation by either RSV or Kirsten nurine virus (Lin *et al.*, 1986). A large quantity of cAMP, like PGE_1 and cortison synergic with the latter, exerts an inhibitory effect on cell growth, Theophylline has the same property (Abell and Monahan, 1973; Turner *et al.*, 1981). Cell transformation with viruses mentioned above could be diminished in a significant degree by applying PGE_1, and adding dibutiryl-cAMP to BHK-21 cells *in vitro*, stops the DNA synthesis of oncogenic adenovirus type 12 (Menyhárt and Minárovits, 1977). On the other hand in 3Y1 cells transformed with the wild type adenovirus 12 at permissive and restrictive temperatures and with its mutant ts401 defective at higher temperature, the endogenous

cAMP level does not show any alteration neither in presence or in the absence of transformation (Ledinko *et al.*, 1979). The phenotypical signs of malignancy on cells can temporarily be concealed by extracellular application of PGE_1, theophylline and dibutiryl-cAMP (Abell and Monahan, 1973). Macrophages transformed with SV-40 regained their phagocytic activity (Tanigawa *et al.*, 1982). The above mentioned MDCK cells lost their ability to express functional glucagon receptors upon transformation. PGEs restored the differentiation of these cells and consequently induced the appearance of normal receptors on the cell surface (Lin *et al.*, 1982). Therefore, it seems conceivable that for certain tumours, transformation results in decreased PG production allowing a selective advantage fot those cells to escape from a normal PG induced state of differentiation (Lin *et al.*, 1986). These phenomena may be related to the fact that the stability of the tubular cell structures and its membranes is strengthened by cAMP (Puck, 1984). Feline leukaemia virus (FeLV) and other retroviruses could decrease the mobility of a concanavalin A (Con-A) receptor on the surface of lymphocytes as a part of leukaemogenesis and immunosuppression. Chicken embryo fibroblast cells transformed with temperature sensitive RSV mutant at permissive temperature, show decreased cAMP level within 10 minutes after infection. Infecting at restrictive temperature, the cAMP level remains the same and transformation does not take place. Virus replication, however, occurs in both cases. In mice infected with Moloney sarcoma virus, the development of sarcoma was delayed by indomethacin. In another experiment, creating immunosuppression with antilymphocyte serum in animals, the same virus was subsequently inoculated. The mice all died within 14 days. But in animals similarly immunosuppressed and virus-infected, a significant inhibition of tumour growth could be obtained by indomethacin treatment (Menyhárt and Minárovits, 1977). Thus, transformation was accompanied by decrease of the cAMP level (Izui *et al.*, 1980; Willis, 1984). Among some conflicting results it is remarkable that kidney cells could be transformed at restrictive temperature by cold-sensitive mouse sarcoma virus only if the endogenous cAMP level was raised by PGE_1. The effect was, however, only transitory, and the morphological signs ceased quickly (Somers, 1981). It was also reported that PGE_2 in 3T3 cells was elevated by polyomavirus (Roos *et al.*, 1980), while others published that increased cAMP level totally blocked proliferation of polyomavirus transformants derived from 3T3 cells without affecting proliferation of normal cells or SV-40 induced transformants of the same cell line. Proliferating polyoma transformants contained threefold less cAMP than did proliferating SV-40 transformants. Adenylate cyclase activity was threefold less active in the membranes of polyoma transformants. A mitogen, Con-A had different effect: it could totally block proliferation of both normal cells and SV-40 transformants of 3T3 but reduced proliferation of polyoma transformants only twofold (Kamech *et al.*, 1987). In the light of these observations one cannot conclude that changes in PG effects do not depend on viruses (Lin *et al.*, 1986). Neoplastic progression is a multistep process: whether the alteration of the PG production is an early occurrence, or some enzymes in the biosynthetic pathway for PG synthesis become modified upon transformation,

remains unknown. If so, the change of PG production may potentially be used for monitoring the progression of viral transformation of cultured cells (Lin *et al.*, 1986).

Interesting observations were obtained using murine mammary tumour virus (MuMTV) regarding to the possible synergism of PGs and certain steroid hormones in the initiation and maintenance of breast cancer. Its replication in cell cultures was enhanced by both PGA_1 and PGE_1. Similar, but less effective influence was found, when PGB_1 and PGF_{2alpha} were applied (Švec *et al.*, 1982). However, other authors found that PGF_{2alpha} markedly increased the MuMTV production in cell culture (Karmali *et al.*, 1982). The synthetic glucocorticoid dexamethasone increased MuMTV production and both the above mentioned PGs and dibutiryl-cAMP were able to potentiate its effect and increase virus replication. Norepinephrin and isoproterenol also enhanced the dexamethasone mediated MuMTV stimulation (Švec *et al.*, 1982). The similar effect of prolactin also has been observed (Karmali *et al.*, 1982). So, it may be conceivable that synergism between PGs and hormones is fundamental in the activation of tumour viruses (Tisdale, 1984). Another aspect was revealed among cell transformation, PG-CN-PK cascade and hormones using RSV. The cellular distribution of adenylate cyclase and phosphodiesterase activity changed after transformation by RSV that results from the alteration in cell morphology. These changes depend on the expression of the *src* gene, because the non-transforming virus relative of RSV that is called Rous-associated virus (RAV) and lacks *src* gene, was not able to modify these processes. It was found that the beta-adrenergic agonist isoproterenol elevated the cAMP level for a short period of time, then a progressive loss of cAMP has been observed in the cell despite the continued presence of hormone. The RSV transformed cells had an increased number of beta-adrenergic receptors on the cell surface, they synthesized much more cAMP and also were able to maintain the elevated cAMP level for longer period than did the uninfected or RSV infected cells. The adenylate cyclase activity of membranes prepared from transformed cells is less than or equal to that of the untransformed cells. An activation of this enzyme in transformed cells can be reached by adding PGE_1 or isoproterenol (Howard *et al.*, 1982).

The cGMP given continuously and in a great concentration causes cell proliferation due to the phosphorylation of acidic nuclear proteins (Abell and Monahan, 1973). During cell transformation with SV-40 or polyoma virus, cGMP level raises to twofold in 3T3 cells. PGF_{2alpha}, and insulin potentiating its effect and added after PGF_{2alpha}, increased transformation. Further consequences of the elevated cGMP level are the greater membrane fluidity and lack of contact inhibition. Proteolysis also was found increased due to higher cGMP concentration in the cell membrane (Menyhárt and Mináróvits, 1977). From these experimental results it has been postulated that cGMP and compounds increasing its level like PGF_{2alpha}, can be regarded as positive signals of cell division while the rise of cAMP level, on the other hand, can be taken for the negative signal. The regulating role of cGMP seems to be more important in starting mitosis (Abell and Monahan, 1973;

Michell, 1989). While PGE can serve as a differentiation inducer of transformed cells and as a growth factor for most normal cells, there is no evidence that PGEs are responsible for promoting the abnormal growth rate seen in the case of transformed cells (Lin *et al.*, 1986), but some exceptions have been reported (Roos *et al.*, 1980; Lewis *et al.*, 1981; Gottesman *et al.*, 1984). The signal character seems to be affirmed by the fact that half-life period of the PGs is very short, and also by those observations that in macrophages and in fibroblasts transformed by SV-40, CNs cannot be influenced by external factors, including PGs (Tanigawa *et al.*, 1982). Interestingly, it was found that the effects of PGs on cell division were similar to their influence on the replication of oncogenic adenoviruses (Ongrádi *et al.*, 1986).

Gene products of different viruses have an intrinsic CN-dependent tyrosyl kinase activity (Bell *et al.*, 1987). Phosphorylation of tyrosine of acidic nuclear proteins, the RNA polymerases, by the effect of Abelson leukaemia virus was elevated by 300 per cent (Frausen *et al.*, 1983; McClung and Kletzien, 1984; Willis, 1984). Normal kinases phosphorylate on serine or threonine (Michell, 1989). The consequence of this difference can be that regulatory key polypeptides with their increased negative charge react with positive histones, resulting in the removal of the latter, and consecutively transcription starts. This process can also take place in case of insertion of the cistron of an oncogenic virus, which cistron possesses kinase activity. *Src* gene product of RSV ($p60^{v\text{-}src}$) has a tyrosyl kinase activity, which significantly decreases the serine phosphorylating activity of both cAMP-dependent cellular PK and cAMP-independent PK. The reduction of AMP-dependent PK activity is a direct consequence of the expression of viral *src* gene, but the exact mechanism is not yet known (Clinton and Roskoski, 1984). Since more types of oncogenic viruses code tyrosine specific kinase, it is conceivable that this enzyme is an antagonistic type to other cAMP dependent cellular PKs phosphorylating serine or threonine (McClung and Kletzien, 1984). The *v-src* product itself consists of 526 amino acid residues (Czernilofsky *et al.*, 1980), and the molecule is phosphorylated at both serine and tyrosine residues, the former phosphorylation is catalysed by a cAMP-dependent PK (Collett *et al.*, 1979). The major phosphate acceptor for this autophosphorylation is located at the 416 tyrosine (Brugge and Darrow, 1984). Total cellular content of phosphotyrosine was to increase 5- to 10-fold in RSV-transformed cells, and many types of cellular proteins were found to be phosphorylated on tyrosine residues. Using various spontaneous and *in vitro* constructed mutants of the virus, the kinase activity appears to be essential for transformation. However, the kinase activity is not sufficient for the transforming ability and tumourigenicity (Cross *et al.*, 1985; Resh and Erikson, 1985; Wang and Hanafusa, 1988). It has been well established that for each viral oncogene (*v-onc*) has a cellular homologous counterpart, known as cellular oncogene (*c-onc*) or protooncogene. The *v-onc* in a transforming virus has been acquired from the corresponding protooncogene by retroviruses. Many details of them were studied on *v-src* of RSV, and sequences related to it have been detected in all vertebrates (Wang and Hanafusa, 1988). The *c-onc* gene codes for a product very similar in structure and enzymatic property to that of

$p60^{v\text{-}src}$, but the over-expression of *c-src* is not sufficient to cause cell transformation. The $p60^{c\text{-}src}$ is also phosphorylated *in vivo* at both serine and tyrosine residues (Iba *et al.*, 1985). The major *in vivo* tyrosine phosphorylation site of $p60^{c\text{-}src}$ was mapped at tyrosine 527 instead of 416 as in $p60^{v\text{-}src}$ (Cooper *et al.*, 1986). Recombinant viruses containing *c-src* do not transform cell (Levy *et al.*, 1986), but mutations resulting in phosphorylation at tyrosine 416 of $p60^{c\text{-}src}$ convert these variants to transforming ones (Iba *et al.*, 1986; Cartwright *et al.*, 1987). These changes in phosphorylation can be important targets for PG-directed kinases. It would be worthwhile to investigate the effect of PG analogues with altered specificity in this respect (Honn and Sloane, 1985; Falk *et al.*, 1987).

A further correlation was found between the polyomavirus middle T antigen (mTAg) and the above mentioned cellular protooncogen, $p60^{c\text{-}src}$ (Kornbluth *et al.*, 1987). Originally, a protein kinase activity was bound directly to the mTAg (Eckhart *et al.*, 1979), and good correlation between the level of this kinase activity and the degree of oncogenic transformation of cultured rodent cells has been established. Also, the expression of mTAg seemed to be required for the decreased level of PGE_2 synthesis found in polyomavirus transformed cell lines (Segawa and Ito, 1982; Lin *et al.*, 1986). It is known now that the polyoma mTAg itself is a 56 kD phosphoprotein which is found in cellular membrane fractions of transformed cells and is capable of associating with a variety of cellular proteins to form high molecular weight complexes. The mTAg can activate $p60^{c\text{-}src}$, which becomes underphosphorylated at tyrosine 527 and phosphorylated at tyrosine 416 (Cartwright *et al.*, 1987). Both RSV $p60^{v\text{-}src}$ and activated $p60^{c\text{-}src}$ alter the subsequent phosphorylation of the same 36 kD cellular protein (Amini *et al.*, 1986; Bolen *et al.*, 1987; Yonemoto *et al.*, 1987). This means that the inhibition of a viral PK and that of an activated cellular PK could be mediated by the same external agents, namely by PG antagonists. Other sarcoma viruses possess similar oncogenes, and their very high amino acid sequence homology, especially in the kinase domain, explains their similar PK activities (Bryant and Parsons, 1984). Studies on modification of phosphorylation pattern by PG analogues or other members of the cascade system may lead to the understanding sterical requirements for oncogenic polypeptides.

Further comparisons between products of viral and cellular oncogenes, certain growth factors and receptors of growth factors, as well as polypeptide hormones synergic with PG effects showed physical and physiological homologies (Kamata *et al.*, 1987). All of these products are associated with the plasma membrane and exhibit tyrosine kinase activity (Hirai *et al.*, 1987), and they also share conserved kinase domains. Their genes are likely derived from a common ancestor sequence. Retroviral tyrosine kinases can phosphorylate various growth factors or receptors. The bulk quantity in their phosphorylation sites offers a unique opportunity to study divergent — activator or suppressive — effects of eicosanoids (Wang and Hanafusa, 1988; Michell, 1989).

According to the most recent observations, PK-C, a key regulatory enzyme involved in lipid phosphorylation and calcium metabolism, may have a

significant role in the transforming process (Nishizuka, 1984; Michell, 1989). This enzyme is activated by another secondary messenger, namely, by diacylglycerol (DAG). DAG is generated after a previous breakdown of receptor-induced hydrolysis of membrane polyphosphoinositides (PPI) (Imboden, 1988). DAG also acts as a substrate for arachidonic acid release during PG synthesis (Bell *et al.*, 1979), and this is a common site of the two separate systems. PK-C phosphorylates at serine or threonine in normal cells, and has a great homology with the cAMP- or cGMP-dependent PKs, but it does not correspond to any other Pks encoded by any oncogene (Carpenter *et al.*, 1987; House and Kemp, 1987). It phosphorylates a histone, and may take part in gene expression (Imboden, 1988). It was shown that PK-C stimulates the transforming ability of polyomavirus mTAg by increasing its association with $p60^{c\text{-}src}$ (Raptis *et al.*, 1986). This is in accordance with other findings that in a ras-resistant, morphologically transformed cell line by Kirsten sarcoma virus, the activity of PK-C was shown to be threefold reduced when compared to ras-sensitive NIH/3T3 cells (Kamata *et al.*, 1987). Probably, *ras* oncogene activates a phospholipase which catalyses the breakdown of PPI to DAG. This activation involves DAG in PK-C turnover, while as a consequence of it, PGE synthesis decreases. Another interesting overlapping with the PG-CN system is that *v-ras* oncogene proteins show similarities to G-proteins, which are important factors at the cell surface to generate CNs (Hurley *et al.*, 1984; McGrath *et al.*, 1984; Roos and Gilman, 1984).

New observations indicate that HIV after binding to the CD4 molecule, induces its phosphorylation by PK-C. This process results from the specific interaction of CD4 receptor and viral gp120, but purified gp120 alone is unable to induce phosphorylation of the receptor (Fields *et al.*, 1988). CD4 can transduce an other independent signal during T cell activation resulting in a rapid increase of tyrosine phosphorylation of one subunit of the T cell receptor complex (Veillette *et al.*, 1989). These phenomena mean that HIV induced phosphorylation could be involved in the mechanism of viral entry. Blockade of HIV induced phosphorylation could represent a potential target for antiviral therapy (Fields *et al.*, 1988).

Connection between the PG cascade and the immune system infected by viruses

Prostaglandins have an important role in the physiology of inflammation (Martin *et al.*, 1983). Several non-steroidal anti-inflammatory drugs, just through inhibiting a great part of the PG cascade, achieve their curative effects (Kantor and Hampton, 1978). Within this complicated mechanism, the elimination of viruses as foreign antigens can occur under control of PGs (Goodwin and Webb, 1980). It must be emphasized that within the effects of non-specific defence mechanism, the phagocyting cells are very sensitive to PG inducers (Fitzpatrick and Stringfellow, 1980). For example, as a result of the transformation of mouse macrophages by SV-40, their phagocyting activity declines, however, by stimulating PG synthesis, the phagocytosis improves again (Tanigawa *et al.*, 1982). Aminophylline and isoproterenol inhibiting the catabolism of PGs suppress the phagocytosis of

both polymorphonuclear (PMNL) and mononuclear phagocytes (MNPh (Russel *et al.*, 1979). PGE_1, PGE_2, dibutiryl-cAMP and theophylline inhibit the motility of MNPh (Lomnitzer *et al.*, 1976) and that of PMNL (Berkow, 1977; Nelson and Johnson, 1982; Hildebrandt *et al.*, 1983). Next, the number of cells taking part in the antibody-dependent cellular cytotoxicity (ADCC) can be decreased by PGA and PGE with one or two unsaturated bonds. Based on this, it is supposed that HSV-1 production can be stimulated by PGE by damaging ADCC of the organism. The lysis of target cells was proved to be inhibited by 10^{-7}—10^{-8} M PGE_1 or PGE_2 through the contribution of cAMP, while PGF_{2alpha} had an inhibitory effect only in a great, 10^{-5} M concentration. PGI_2 and LTD_4 were not effective in the range of 10^{-8}—10^{-5} M concentration (Russel *et al.*, 1979). PGE_1 and PGE_2 damage both ADCC and the activity of natural killer cells (NKC), and therefore these reactions can be increased with drugs inhibiting PG synthesis: 2×10^{-6} M indomethacin given together with 5×10^6 MNPh protected newborn mice from otherwise fatal HSV-1 infection (Kohl *et al.*, 1982). It seems to be that PGE has an immunosuppressive effect (Berkow, 1977; Goodwin and Webb, 1980; Lahmy and Virelizer, 1981). In the case of other microbes, whose elimination depends primarily on the function of T lymphocytes, this process takes place earlier in the presence of indomethacin (Caldwell and Sprouse, 1982). It is also established that PGE_1 and PGE_2 inhibit the induction of anti-VSV cytotoxic T lymphocytes, however, they have no apparent effect on the lytic activity of the same cells (Hale *et al.*, 1982). Rubella-, measles-, Newcastle disease-, and adenoviruses all stimulated both PGE and hyaluronic acid in synovial fibroblast cultures. Stimulation of PGE synthesis by measles virus was dose dependent. Indomethacin (4 μg/ml) and hydrocortisone (2 μg/ml) inhibited overproduction of both PGE and hyaluronic acid induced by measles. It is known that PGE is a mediator of inflammation therefore this process may enlighten the role of viruses in rheumatic diseases (Yaron *et al.*, 1981).

The production of antibodies is also inhibited by PGE_1 and PGE_2 (Berkow, 1977; Goodwin and Webb, 1980; Zavagno *et al.*, 1987). Dengue-2 virus affects in the suppressor T lymphocytes the production of a "suppressor factor", which is actually PGE, and this is made responsible for the decreased production of virus specific IgM antibodies. Using indomethacin, the antibody formation can be enhanced (Shukla and Chaturvedi, 1982). Interestingly, the production of antibodies against a retroviral gp70 is selectively suppressed by PGE_1 but this compound hardly affects the production of antibodies to DNA (Izui *et al.*, 1980). A further indirect evidence of the role of PGs is that indomethacin normalizes the immunocompromised state of mice caused by hepatitis virus type 3 (Lahmy and Virelizer, 1981). Furthermore, histamine release from basophil cells sensitized by Ig-antibodies was inhibited by PGE_1 and PGE_2 (Berkow, 1977).

Leukotrienes (LT) can play a similar role in the pathogenesis of immunocomplex diseases, allergic or non-allergic inflammations. Among them the "slow reacting substance of anaphylaxis (SRS-A)" is well known. It is a mixture of LTC_4, LTD_4, and LTE_4 (Martin *et al.*, 1983; Lancet Editorial, 1988). LTC_4 and LTD_4 rather have humoral effects, LTB_4 takes part in

regulation of PMNLs, in releasing lysosomal enzymes and in activating guanylate and adenylate cyclases (Foreman, 1981; Lewis and Austen, 1981). These were observed in guinea pigs infected with VSV (Moshonov *et al.*, 1986) or an arenavirus (Liu *et al.*, 1986). The metabolites and endproducts of the PG and LT system can modify each other's function because of derivating from the same precursor (Lee, 1982).

There is some evidence to show that the reaction of lymphocytes to different mitogen stimuli is influenced by the PG-CN system. Their activation and proliferation for the effect of mitogens are usually inhibited by PGE_1, PGE_2, and dibutiryl-cAMP, theophylline (Abell and Monahan, 1973; Lomnitzer *et al.*, 1976; Johnson, 1977; Giron, 1982). Lymphocyte transformation induced by phytohaemagglutinin (PHA) was inhibited by PGA_1, PGE_1, and dibutiryl-cAMP, as it was shown by measuring protein-, DNA-, RNA- synthesis. Lymphocyte proliferation is stimulated by indomethacin. Otherwise, there is a significant difference in respect of which lymphocytes are affected by the stimuli. Normal cells are brought to mitosis by PHA or Con-A through cGMP elevation, but in the early phase cAMP rises to activate histone kinase. It is possible that the cAMP induces mitosis of such thymocytes, which have already been programmed (Abell and Monahan, 1973; Berkow, 1977). PHA also activates PK-C (Imboden, 1988).

The other important response of lymphocytes to mitogens, among them to viruses, is the immune interferon (IFN) production, which is under control of PGs and CNs (Johnson, 1977; Fitzpatrick and Stringfellow, 1980; Santoro *et al.*, 1982). High concentration of cAMP (10^{-3} M) inhibits its release from PHA stimulated human peripheral lymphocytes (Epstein and Bourne, 1976), and that from mouse L-cells infected by Newcastle disease virus (NDV) or Chikungunya virus (Dianzani *et al.*, 1972; Johnson, 1977). PGE_1, PGE_2, cAMP, and theophylline inhibit the production of other lymphokines, like interleukin-2 (IL-2), MIF or LIF (Lomnitzer *et al.*, 1976; Goodwin and Webb, 1980; Römer *et al.*, 1986). These mediators induce other changes which can interfere with IFN release (Dianzani *et al.*, 1972). Vice versa, IFN inducers can also promote PG synthesis, nay, VSV, and NDV elevate PG production in certain cell types without IFN generation (Yaron *et al.*, 1977). On the other side, HSV-1 and 2, vaccinia and adenoviruses can neither induce IFN nor more PG in most chicken, mouse, hamster, monkey, and human cells (Fitzpatrick and Stringfellow, 1980). PGI_2 can block the fatal outcome of the disease caused by vaccinia virus in mice, but the use of PGE_1 or the inhibition of PG synthesis in vivo worsens the disease. These findings might be relevant to IFN effects *in vivo*, since IFN and PGI_2 act synergistically against virus infections by preventing virus induced endothelial damages to limit virus spread (Zavagno *et al.*, 1987). It was also found that several types of PGs restored IFN response in hyporeactive animals (Stringfellow, 1978). It is supposed that PGE_1 and others enhance IFN generation. This could explain the fact that PGE_1 reduced the yield of poliovirus and encephalomyocarditis virus in cell cultures (Giron, 1982). The IFN binds to the receptors of the cell membrane, consecutively diminishing its fluidity and the lateral mobility of specific receptors resulting in

establishment of the antiviral state. Both IFNs and PGs possess several identical effects on the antibody formation, lymphocyte cytotoxicity, phagocytosis, preventing metastases. More non-antiviral effects of IFN are enhanced by cAMP (Fitzpatrick and Stringfellow, 1980), suggesting a positive feed-back mechanism of PGs on the production of IFN (Stringfellow and Brideau, 1984). The antiviral state in cells induced by IFN and measured by VSV was increased by dibutiryl-cAMP. Similarly, the intracellular cAMP level is elevated already within 30 minutes after treatment with alpha-IFN, and the maximum can be reached after one hour, then the effect lasts at least 24 hours. The antiviral effect of alpha-IFN was more or less parallel with cAMP concentration (Degré and Glasgow, 1981). After treatment with alpha-IFN, the synthesis of PGA_2, PGE_2, and PGF_{2alpha} increase significantly (Santoro *et al.*, 1982). On the other hand, PGs can repress certain cellular functions, which are enhanced by IFN. These include macrophage activation, NKC activity and lymphocyte blastogenesis. This would imply a negative feed-back role for PGs on some IFN stimulated cells. They might act in a counterbalancing fashion. Understanding the relationship and pharmacogical modulation may lead to control the side effects and enhance the potential of IFNs clinically (Stringfellow and Brideau, 1984).

In mice infected with encephalomyocarditis virus or in mouse L-cells infected with leukaemia virus, the antiviral effect of alpha-IFN was not suspended by indomethacin or aspirin, while the effect of a different IFN induced partly in mouse C-243 cells, partly in human lymphoblastoid cells, was greatly inhibited by oxyphenylbutazone, was moderately inhibited by aspirin, indomethacin, and naproxen, phenylbutazone. Sodium salicylate and phenacetin, having no cyclooxigenase inhibitory effect, did not alter the antiviral property of IFN (Tovey *et al.*, 1982; Herz and Sen, 1983). PGE_1, PGE_2, and PGF_1 given extracellularly could not prevent the effect of these compounds, nay, in certain cases they decreased further the defensive effect of IFN. Since a labile metabolite, PGH_2 prevented the effect of cyclooxygenase inhibitors, the data suggest that PGH_2 or another labile metabolite (PGG_2) may have a role in the pathomechanism of IFN. Neither a stabile PGI_2 analogue carbaprostacyclin nor metabolites of the lipoxygenase pathway influenced the antiviral effect of IFN. It seems that one of the cyclooxigenase products has a basic role in accomplishing antiviral effect (Pottathil *et al.*, 1980).

Other actions of the IFNs can be affected by eicosanoids as well. PGs antagonize gamma-IFN induced monocyte cytotoxic activity, and indomethacin prolongs the gamma-IFN induced MHC-II antigen expression *in vitro*. PGE_2 mediates the bone resorption activity of all IFNs, etc. The highly pleotropic influence depends on the specific cell type and the role of PGs and LTs in that system (Browing, 1987). The above results are sometimes conflicting. This may be explained by the observation that the phosphorylated state of IFN molecule is a prerequisite for any antiviral activity. Serine phosphorylating kinases are able to utilize recombinant gamma-IFN, while the same enzymes cannot convert alpha- or beta-IFNs being their configuration is very different. At present it is not known which phospho-

rylation at different sites results in divergent activities against other ones (Robert-Galliot *et al.*, 1985), but influencing these functions separately promines an extreme therapeutical utilization (Browning, 1987).

The effect of PGE_2 is synergic to IL-1 and the macrophage activating property of gamma-IFN can lead to enhanced IL-1 production. PGE also enhances the early phase of B cell activation by supporting IL-4 action on B cells, and later it can inhibit consequent steps (Goodman, 1986; Browning, 1987). It was also proposed that the effective inhibition by gamma-IFN of Epstein-Barr virus induced B cell proliferation and subsequent IgM production may be a result of interaction between eicosanoids and gamma-IFN, which later blocks the effect of IL-4 on B cells and antibodies. This speculation explains the therapeutic effect of IFN in rheumatic diseases (Lotz *et al.*, 1986).

Acknowledgements. The authors thank Dr. G. B. Clements (Institute of Virology, University of Glasgow) for critical reading of the manuscript and suggestions.

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