Cytokines in health and disease

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Cytokines are cellular regulators of non-immunoglobulin character. The studies of interferon, a representative cytokine, support the view that cytokines are information molecules forming a network in the animal organism. Their main task is to protect the homeostasis of the organism. This may be disturbed both by external and internal causes. The results of the studies of interferon appearing in patients with systemic lupus erythematosus do not support the assumption that interferons of this type may play a role in aetiology of autoimmune diseases.

The cytokines are polypeptides that regulate proliferation, differentiation and normal functioning of cells. The total numbers of cytokines in the organism are unknown. However, it is estimated that the cytokine network consists of about 100 to 200 regulatory polypeptides, but only about 20 were up to now sufficiently characterized. The basis of their activity is the discrimination of ‘self’ (non-altered) from ‘non-self’ (abnormal, altered). The cytokines mediate communication among cells which leads to their mobilization (T lymphocytes, NK cells, etc.) or to production of effector molecules, such as antibodies, cytokines and/or hormones, etc. (De Maeyer & De Maeyer-Guignard, 1988; Balkwill, 1989). The efficacy of effector molecules is estimated to range from $10^{-12}$ to $10^{-15}$ mol/mg of tissue. They exert their effect usually through receptors located at the cell surface, and 'second messengers' inside cells.

Common Properties of Cytokines

The results of studies of the known cytokines allow the following generalizations: (1) cytokines are produced by cells in miniscule amounts by autocrine and paracrine mechanisms; (2) cytokine receptors may react with different cytokines; (3) cytokines form in the animal organism a network with mutual regulatory effects; (4) inside the cell, the cytokines may modify the DNA, RNA and protein synthesis leading to a pleiotropic effect; (5) some cytokines may mimic hormones and/or neurotransmitters resulting in sympaticomimetic or opioid effects, etc., and (6) the production of cytokines is regulated by inducers, and interactions with other cytokines, hormones, etc. (Thymus hormones may have a central role in the cytokine cascade.)

The cytokines differ from classic hormones by: (a) absence of specialized producing organs (with exception of thymus hormones); (b) ubiquitous presence of cytokine receptors on cells; and (c) lacking evidence that cAMP (or cGMP) plays the role of a common 'second messenger' in their activity.

The production of cytokines in the cell can be characterized in the following way.

(1) Various types of cells are capable of producing the same type of cytokine and one type of cell may release different types of cytokines.

(2) Several types of cytokines may react with the same receptor at the cell surface.

(3) One type of cytokine may produce several effects in a cell. The effect depends on the differentiation stage, functional activity of the cell, etc.

(4) In the cell, cytokines may induce their own production (priming), production of other cytokines, and down- or up-regulation of various cell receptors.

(5) After appropriate stimulation, cytokines appear in the surrounding of the production cell very quickly (in minutes). They are not stored and may progress from a prohormone stage to a mature cytokine stage.

These characteristics of cytokine release shed light on the difficulties encountered in their research and attempts to classify cytokines.
Interferons as Prototype Cytokines

IFNs represent the most exactly characterized cytokines, when considered in a certain sense, as their prototype is used for comparison of their structure-function relationships, antigenic and biologic properties. IFN was discovered in 1957 and since then the primary structure of the main antigenic types and subtypes have been elucidated (Pestka et al. 1985). Also, more data are available on their tertiary structure (Eichmann et al. 1990) and antigenic behaviour (Kontsek et al. 1988).

In the period 1957 to 1960, IFN was considered an "autonomous antiviral mechanism", activated only after infection or proper stimulation with inducers. Now they are regarded as cellular regulators (normalizers) produced in the most threatened places strategically, such as the gastro-intestinal and respiratory tracts, skin and mucous membranes, the internal immune system, etc. The IFNs produced in these places do not usually reach the blood. However, if found in the blood, the presence of IFN signals an unphysiological overproduction or therapeutic application of high doses (Bocci 1987). IFNs, through their influence on cell proliferation and differentiation, regulate the normal development of cells as well as functioning of organs. The regulatory effects of IFNs on cells support the idea of a physiological role of IFNs in the organism. However, the mechanisms of the variable effects of IFNs are largely unknown (Borecký 1984).

The continuous production of IFNs by cells which are in the organism continuously exposed to the external world is supported by reports on finding IFN in human placenta and amniotic fluid between the 4th and 16th week of pregnancy (Lebon et al. 1982) as well as between the 13th and 21st days of pregnancy in sheep and calf (Roberts et al. 1989). Supposedly, such IFNs exert an immunosuppressive effect on lymphocytes invading the placenta and, in this way, they protect the embryo from rejection. (The steroids produced in the placenta concurrently may act in the immunosuppressive mechanism synergistically.)

'Spontaneous' IFNs were found also in healthy mice of some inbred lines between the 5th and 8th week of life. This finding corresponds with the enhanced sensitivity of mice to infections in early life and during aging (Blach-Olszewska & Cembrzynska-Nowak 1979). Others (De Maeyer-Guignard & De Maeyer 1986) found inbred lines of mice that produced antibodies against IFN spontaneously, suggesting endogenous stimulation.

Paulesu et al. (1985), Viti et al. (1985) and others reported enhanced IFN production in normal (healthy) individuals after digestion of food, physical exercise, during circadian rhythms, changes of ambient temperature, etc.

Physiological (spontaneous) IFN cannot be found in the blood of normal individuals in normal conditions probably because the minuscule amounts produced are quickly catabolized in the vicinity of the producing cell and the concentration gradient required for the transition of detectable amounts of IFN in the blood cannot be achieved. (The half-life of most cytokines is between a few minutes to hours (Bocci 1987).) It was also reported that in the resting organism the genes of IFN are only minimally transcribed (Tovey et al. 1989).

Can the Therapeutic Application of Interferon have Deleterious Consequences?

Despite the physiological role of IFN and other cytokines produced in the normal animal organism, attempts to exploit its regulatory capacity in viral and cancer diseases suggest that doses exceeding the physiological amounts may have deleterious consequences. This concerns, in addition to IFNs, other cytokines such as IL-2, TNF, etc. The 'toxic' effects most frequently observed were: fever, headache, fatigue, hypotension, depression and disorientation. Also, abnormal EEG and disturbances in the lipid metabolism were reported. Less frequent were the erythemas.

Such side (toxic) effects were surprising since they were not reported in adult animals. One of the possible explanations was the usually short duration of experiments in animals and the other, that toxic effects exerted by a homologous cell product were not expected.

Subsequent studies, however, showed that, in addition to the side effects observed during IFN therapy, endogenous IFN could be responsible also for several clinical symptoms of viral infection.

(1) The lymphopenia and the inclusion bodies in mononuclear cells (that often accompany viral diseases) could be found in persons treated with IFN in absence of viral infection (Schallteber et al. 1983).

(2) (a) The severity of Argentine hemorrhagic fever in man correlated with the IFN level in the blood of patients.

(b) Appearance of IFN in the blood of persons infected with HIV usually signals the clinical disease (AIDS).

(c) Administration of IFN to persons with autoimmune diseases (psoriasis) may lead to their exacerbation.

(d) In meningitis with meningococcal etiology the level of tumour necrosis factor (TNF, another cytokine) in the blood correlates with the severity of the disease (Friedland & Griffin 1990).

(3) In attempts to cure influenza with IFN, influenza-like symptoms were observed in non-infected (control) volunteers receiving IFN.

(4) In experiments with mice, Gresser (1982) showed that IFN may cause in newborn mice a wasting disease that was indistinguishable from the disease caused by LCM virus.