

# AIDS

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# AIDS

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these subjects (Fig. 1). Decrease in MBP concentration ( $P < 0.05$ ) was associated with sustained cognitive and motor function improvement. Neuroradiological improvement of white-matter abnormalities was observed in one patient.

The data presented here show that measurement of MBP concentration in CSF is a simple and reproducible method, both for monitoring ADC severity and for studying the effect of zidovudine on HIV-induced neurological damage and impairment. A similar pattern was noted with CSF levels of  $\beta_2$ -microglobulin and HIV-p24 antigen, two of the laboratory parameters used routinely for monitoring antiretroviral activity [4,5]. Both markers declined earlier than MBP levels, confirming that the decrease of MBP levels in CSF is due to zidovudine treatment. However,  $\beta_2$ -microglobulin and HIV-p24 antigen do not enable a direct measurement of the degree of CNS damage, whereas CSF levels of MBP are directly related to the degree of white matter destruction during the course of ADC [3].

In conclusion, we suggest that CSF-MBP could be a more appropriate tool for the laboratory determination of the beneficial effect of zidovudine on myelin injury and CNS involvement in ADC.

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### Ajoene antagonizes integrin-dependent processes in HIV-infected T-lymphoblasts

Integrins, members of a superfamily of cell adhesion receptors, are necessary for HIV-induced syncytia formation [1-4]. Monoclonal antibodies against CD18 or CD11a block aggregation [1,2,5], cell fusion [4] and syncytia formation [1-4] in HIV-infected U937 cells, T-lymphoblasts, or monocytes. Moreover, the ability of HIV-infected cells to form giant cells has been correlated with the surface density of a leukocyte adhesion receptor (LFA-1) [2,3].

Ajoene [(E,Z)-4,5,9-trithiadodeca-1,6,11-triene-9-oxide] isolated from garlic extracts (*Allium sativum*) inhibits platelet aggregation by allosterically inactivating the platelet integrin, GPIIb/IIIa [6]. The structural and functional similarity of integrins (for example, their high degree of homology and immunological cross-reactivity) [7] prompted us to propose that ajoene may also inhibit both adhesive interactions and fusion of leukocytes [8].

Cell aggregation was assayed turbidimetrically [9,10] using a double-beam aggregometer (Thrombolyte-1006; JV BioChemMack, Moscow, Russia). Syncytium formation was assessed by cocultivation of H9 cells and H9 cells chronically infected with the RF strain of HIV-1 (H9: RF cells) (2:1) for 16 h. To assay HIV replication, CEM13 or H9 cells were inoculated with appropriate isolates of HIV-1 (LAV-BRU 1 and RF, respectively) to give a multiplicity of infection (m.o.i) of 0.1; after 72 h

the HIV antigens were determined by enzyme-linked immunosorbent assay (ELISA) [11].

(E)-, (Z)- and (E,Z)-ajoene inhibited platelet aggregation in platelet-rich plasma with a 50% inhibitory concentration ( $IC_{50}$ ) of approximately 50  $\mu$ mol/l, irrespective of the antagonist used to trigger the aggregatory response. (E,Z)-ajoene (which we used in subsequent studies) blocked N-formyl-L-methionyl-L-leucyl-L-phenylalanine-stimulated neutrophil aggregation ( $IC_{100} \approx 10 \mu$ mol/l) and caused rapid deaggregation when added to aggregated platelets and neutrophils. HIV-mediated syncytia formation was inhibited with an  $IC_{50}$  of 50 nmol/l (Fig. 1, curve 1). Interestingly, the clusters normally formed by non-infected H9 and Jurkat cells in culture were disrupted by ajoene in the same range of concentrations.

Although the need for integrins for contact interactions in these three systems is well established, the molecular mechanisms are clearly not the same: in platelets the relevant integrin is GPIIb/IIIa [7], neutrophils form contacts via interaction of LFA-1 and/or Mac-1 with their surface counter-structures [2,12,13], while T-cell cohesion is mediated by LFA-1 [14], VLA-4 and VLA-5 [15]. Hence, ajoene is apparently capable of inactivating at least several integrin receptors (GPIIb/IIIa, LFA-1, Mac-1, VLA-4, VLA-5). At the cellular level, this inactivation appears to be a severe deficiency



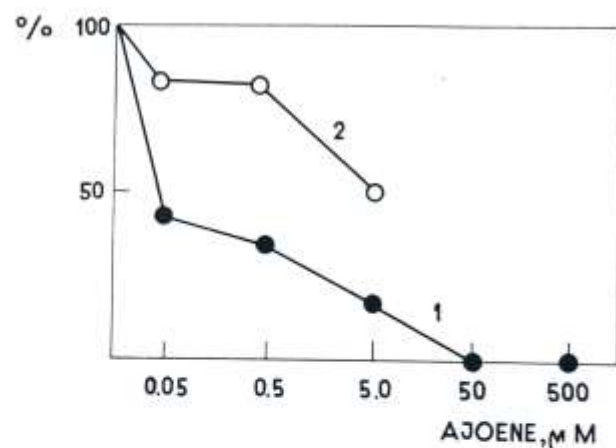


Fig. 1. Effect of ajoene on HIV-mediated syncytia formation and HIV replication. H9 and H9:RF cells were cocultivated (2:1) for 16 h with various concentrations of ajoene in 96-well flat-bottomed plates (Costar, Cambridge, Massachusetts, USA) ( $3 \times 10^4$  cells per well); relative amount of syncytia (percentage of those formed in the absence of the compound) was plotted against ajoene concentration (●). Ajoene (0.5  $\mu$ mol/l) was added to  $10^7$  CEM13 cells inoculated with LAV-BRU 1 isolate of HIV-1 (multiplicity of infection = 0.1), the cells were plated in 96-well flat-bottomed plates, and the bulk of HIV antigen was measured by solid-phase immunoassay after 72 h of incubation; relative amount of immunoassay-detectable viral antigen was plotted against ajoene concentration (○).

in the respective cell-specific integrins, i.e., de-aggregation (platelets and neutrophils), disintegration of cell clusters (intact H9 and Jurkat cells) or failure to fuse (HIV-infected cells).

The role of integrins in HIV-induced cell fusion remains obscure. It is generally thought that these molecules are involved in an early adhesion step preceding membrane fusion [2]. Nevertheless, the possibility that LFA-1 at least may be the putative 'fusion receptor' mediating giant cell formation both by macrophages [1] and HIV-infected CD4+ T-lymphoblasts [3] cannot be excluded.

To determine whether ajoene could also influence HIV replication, we measured the level of immunoreactive viral antigens in supernatants of infected cells cultured in the presence or the absence of the compound. Replication of HIV-1 (RF) in H9 cells was inhibited with an  $IC_{50}$  of 25  $\mu$ mol/l. Assessment of HIV-1 (LAV-BRU 1) replication in CEM13 cells revealed more pronounced antiviral activity ( $IC_{50} \approx 5$   $\mu$ mol/l; Fig. 1, curve 2). A considerable increase in this activity became evident when the concentration of the compound was increased stepwise (50 nmol/l per 12 h incubation; CEM13-LAV-BRU 1 system; 30% inhibition; total concentration, 0.25  $\mu$ mol/l; m.o.i. = 0.1; 72 h incubation).

The observed antiviral activity of ajoene suggests that integrins are essential for both syncytia formation and expression of the viral genome. This interpretation is consistent with the current concept of integrins as surface receptors regulating intracellular processes [14].

Alternatively, integrins may mediate both recognition and endocytosis of the viral particles by cells. Indeed, platelets and megakaryocytes internalize HIV-1 particles via endocytosis, but not fusion [16]. Moreover, internalization of VLA-5 [17], Mac-1 [18] and GPIIb/IIIa [19] and integrin involvement in adhesion of various cell lines to immobilized Tat protein [20] have also been reported. If this putative integrin-mediated pathway exists, ajoene would be expected to preclude HIV incorporation into CD4-negative cells and thereby reduce the number of potential reservoirs of infection.

In conclusion, we suggest that administration of ajoene (possibly in combination with conventional anti-HIV drugs) could be a promising approach for the treatment of AIDS.

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#### Disseminated infection as a result of *Mycobacterium gordonae* in an AIDS patient

A 31-year-old female long-term heroin user was diagnosed with HIV-1 in 1984 and with AIDS in May 1989 (pulmonary pneumocystosis with two relapses). She was hospitalized in April 1991 in order to assess a 1-month intermittent fever associated with hepatosplenomegaly. Her CD4 count was  $10 \times 10^6/l$  and tests for acute opportunistic infections were negative. Following a transitory period of improvement, the patient was re-hospitalized in June 1991 for the same type of fever, associated with polyarthritides of the elbows, knees, and metacarpal phalanx of the right thumb, inflammatory dermo-epidermal cutaneous lesions measuring 4-5 cm in diameter (predominantly on the extension surfaces of the legs and arms), hypodermic nodules measuring 5 cm in diameter, and vesicles containing cloudy liquid on the four limbs.

Direct examination of the articular puncture liquid revealed numerous Ziehl-Nielsen acid-fast stain-positive bacilli. Histological examination revealed the following: necrotic material containing free polynuclear and macrophagic elements in the synovia; one unilocular and subcorneal pustule containing cellular debris and numerous polymorphous inflammatory elements on skin biopsy; and inflammatory septal and lobular granulomatous lesions corresponding to confluent tuberculoid granulomas with caseation necrosis in the subcutaneous tissue (Fig. 1). In these three different samples, numerous intra- and extramacrophagic large pseudofilamentous bacteria tested positive on Ziehl-Nielsen and periodic acid Schiff staining. *Mycobacterium gordonae* (resistant to isoniazid, rifampicin and pyrazinamide) was isolated in the blood cultures, the medulloculture, in the articular puncture and on the skin lesions. In March 1990, the patient became afebrile after a 1-month course of combination therapy with kanamycin and capreomycin, which was followed by ciprofloxacin, clofazimine and ethambutol because of renal intolerance.

The subcutaneous nodules regressed and blood cultures became negative. Six months have now elapsed.



Fig. 1. Subcorneal pustule containing numerous neutrophils and macrophages (periodic acid Schiff  $\times 80$ ). Intracellular acid-fast pseudofilamentous bacilli (Ziehl-Nielsen  $\times 800$ ).

*M. gordonae*, the atypically ubiquitous mycobacterium classified in Runyon group II, is usually a non-pathogenic agent. Given its role as an opportunistic pathogen responsible for pulmonary or disseminated infection [1,2], as seen in our patient, the isolation of *M. gordonae* in an HIV-positive patient at an advanced stage of disease should be taken into consideration. A satisfactory outcome can be obtained with appropriate treatment [3].

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