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ARTICLE

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The bottleneck in AZT activation

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Nucleoside-based inhibitors of reverse transcriptase were the first drugs to be used in the chemotherapy of AIDS. After entering the cell, these substances are activated to their triphosphate form by cellular kinases, and they are potent chain terminators for the viral DNA (ref. 1). The two main factors limiting their efficacy are probably interrelated. The insufficient degree of reduction of viral DNA at the commencement of treatment and the emergence of resistant variants of the virus are the reason for the relatively poor suppression of viral replication. It appears to be inefficient metabolic activation. Thus, for the most extensively used drug, 3'-azido-3'-deoxythymidine (AZT), whereas phosphorylation to the monophosphate is facile, the product is a very poor substrate for the next kinase in the cascade, thymidylate kinase^{2,3}. Because of this, although high concentrations of the monophosphate can be reached in the cell, the achievable concentration of the active triphosphate is several orders of magnitude lower. Determination of the structure of thymidylate kinase as a complex with the monophosphate (AZTMP) together with studies on the kinetics of its phosphorylation have led to a detailed understanding of the reaction and consequences of the poor substrate properties.

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