

METHODS OF INHIBITING UNDESIRABLE CELL GROWTH USING AN AMINOGUANIDINE COMPOUND

RELATED APPLICATIONS

This application claims priority to U.S. Provisional Patent Application Ser. No. 60/086,585 filed on May 22, 1998, the entire contents of which are hereby expressly incorporated by reference. The entire contents of each of U.S. Ser. No. 07/610,418, filed Nov. 7, 1990, U.S. Ser. No. 07/467,147 filed Jan. 18, 1990, U.S. Ser. No. 07/344,963 filed Apr. 28, 1989, U.S. Ser. No. 07/310,773 filed Feb. 14, 1989, and U.S. Ser. No. 07/812,561 are hereby also expressly incorporated by reference. The entire contents of each of U.S. Provisional Patent Application Ser. No. 60/086,504 filed on May 22, 1998 and U.S. Patent Application Ser. No. (yet to be assigned) entitled "Use of Aminoguanidine or Aminoguanidine Analogs for the Treatment of Diseases of the Nervous System," filed on even date herewith, also are hereby expressly incorporated herein by reference.

BACKGROUND OF THE INVENTION

Worldwide, cancer is a leading cause of death. Presently, few cures exist for treating the various types of cancer. Among the possible cures that do exist include the application of tumor-inhibiting compounds (chemotherapy), radiation therapy, and bone-marrow transplants.

Transformation of cells results in changes in their growth characteristics and can cause them to form tumors in animals into whom they are introduced. For example, transformation of adherent cells can be associated with certain alterations such as changes in growth control, cell morphology, membrane characteristics, protein secretion and gene expression. Although transformation can occur spontaneously, it can be caused by a chemical or irradiation or may result from infection by a tumor virus. Little is known about the underlying molecular events. One type of RNA viruses (the retroviruses) and many different types of DNA viruses can act to transform cells and collectively are referred to as tumor viruses. In the case of tumor viruses, it is clear that the virus does not itself carry all of the genes necessary to produce the phenotypic changes characteristic of infected cells. Tumor viruses may act through a gene or genes in their genome (oncogenes) which, in some way, influence or induce target cell genes. The induced target cell genes, in turn, act to carry out the changes observed in transformed cells. There are at least three major classes of transforming DNA viruses: adenoviruses, which have two groups of oncogenes, E1A and E1B, which act together to produce transformation; papovaviruses, which synthesize proteins, called T antigens, which may work together to transform cells; and herpes viruses, for which no oncogene has been identified as yet.

Although considerable effort has been expended in identifying transforming genes or oncogenes and, in some cases, has also resulted in identification of their protein products, very little is known about the cellular mechanisms affected in the transformation process. There is a consensus that these oncogenes perturb cell growth by modifying the expression or activity of key growth related genes. It would be very helpful to have a better understanding of how transformation occurs, particularly if the biochemical pathways affected can be identified. Such knowledge would make it possible to design compounds which can interfere with or counter the effects of the transforming signals and, thus, are useful in preventing transformation or minimizing the extent to which

it occurs, once begun, and, thus, to reduce effects on individuals in whom it occurs.

Prior art chemotherapy treatments typically include the application of chemotherapeutic agents to a patient in selected dosages to achieve and maintain a therapeutically effective level of the agents in the patient. However, most known chemotherapeutic agents used for the treatment of cancer display significant side effects. Thus, a drawback of typical chemotherapy treatments is that the compounds employed are non-specific in their activity and accumulate to toxic levels, and hence kill rapidly proliferating normal cells, as well as tumor cells.

Creatine Kinase (CK) is a purine metabolic enzyme that is intimately involved in the maintenance of ATP at various sites of cellular work. Typically, increased levels of CK are associated with cell transformation, and are thus used as markers to identify the same.

The creatine kinase (CK; EC 2.7.3.2) isozymes and their substrates, creatine and creatine phosphate (Cr-P), are believed to play a pivotal role in energy transduction in tissues with large fluctuating energy demands such as skeletal muscle heart and brain. The enzymes catalyze reversibly the transfer of the γ -phosphoryl group of ATP to creatine (Cr) to yield creatine phosphate (Cr-P) and ADP. The CK isozymes include three cytosolic forms, brain (CK-BB), muscle (CK-MM) and heart (CK-MB), as well as two mitochondrial forms, ubiquitous and sarcomeric.

A variety of important functions have been associated with the creatine kinase/creatine phosphate system (CK/CrP). Walliman et al., *Biochem. J.*, 281: 21-40 (1992). The Cr-P molecule seems to serve as an energy carrier connecting sites of energy production with sites of energy utilization via the subcellularly compartmentalized CK isoenzymes. A main function of the system is to provide appropriate local ATP/ADP ratios at subcellular sites where CK is functionally coupled to ATP consuming enzymes or processes. Another important function is to prevent increases in intracellular ADP levels during periods of cellular work, thus avoiding inactivation of cellular ATPases and net loss of adenine nucleotides.

It is now known that this enzyme system plays an important part in the metabolic events that take place during cell transformation. First, several studies of tumor cells have reported elevated levels of the brain isozyme of CK in several human tumors and in the serum of cancer patients. (see Ishiguro et al., *Cancer*, 65: 2014-2019 (1990); Gazdar et al., *Cancer Research*, 41: 2773-2777 (1981); Feld et al., *Clin. Chem.*, 23: 1930-1932 (1977); Homburger et al., *Clin. Chem.*, 26: 1821-1824 (1980); and Lillie et al., *Cancer Res.*, 53: 1-7 (1993). Second, the CK-BB gene is induced by the transforming domains of the adenovirus E1a oncogene (Kaddurah-Daouk et al., *Mol. Cell. Biol.*, 10: 1476-1483 (1990). Third, it has been noted that creatine is important for the growth of Ehrlich ascites tumors (Ohira et al., *Biochem. Biophys. Acta*, 1097: 117-122 (1991) and Becker S. and Schneider F., *Bio. Chem. Hoppe-Seyler*, 370: 357-365 (1989)).

SUMMARY OF THE INVENTION

The present invention is based, at least in part, on the discovery that aminoguanidine compounds inhibit undesirable cell growth, e.g. inappropriate cell growth resulting in undesirable benign conditions or tumor growth. The present invention provides for the use of aminoguanidine compounds for prophylactic and/or therapeutic treatments of undesirable cell growth. The present invention provides