Method for Inducing Tumor Apoptosis

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Technology

Our method allows detecting compounds that induce apoptosis in tumor cells through reestablishing intercellular signaling mediated by reactive oxygen species (ROS). All tumor cells show the potential for ROS signaling, but protect themselves through expression of extracellular catalase. Modulation of tumor cell endogenous nitric oxide levels leads to a complex series of reactions in which singlet oxygen is generated. This reactive molecule destroys the active center of catalase and thus reestablishes intercellular ROS signaling, followed by selective cell death in tumor cells.
This principle allows detecting novel compounds with highly selective antitumor activity.

Innovation

- Use of specific tumor cell signaling pathways for apoptosis induction in tumor cells
- Use of membrane-assisted NADPH oxidase, specific for tumor cells, as driving force for signaling
- Use of the NO metabolism of tumor cells for singlet oxygen generation and destruction of catalase, a target that has been shown by us to protect tumor cells against their own ROS signaling
- The destroyed target structure and the subsequent ROS signaling are specific for tumor cells, normal tissue is not affected by this treatment
- The test system allows a rapid differentiation between compounds that selectively act on tumor cells from nonselective toxic compounds
- The test system is very sensitive
- Isolated compounds can be expected to be applicable to a great variety of human tumors

Application

We have been successful in direct targeting of catalase and inhibition of tumor growth and survival in-vitro and in-vivo. Our system can be used to search for novel mechanism-based selective anti-tumor compounds and for the establishment of synergistic interactions between different compounds. The latter approach has the potential to prevent side effects of certain drugs.

Market Potential

The market for antitumor drugs is in the range of several billions of EURO per year worldwide. Highly selective novel antitumor compounds can be expected to successful on this market.

Responsible Scientist

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Patent Status

European Patent Application
No. EP 1895012
Filed (PRD) August 30th 2006

Further European Patent
Applications pending
Filed (PRD) August 20th 2010
Filed (PRD) June 16th 2011

Reference Number

ZEE20051212a,
ZEE20100617a-c

Status: Jun-11

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signo Hochschulen
Schutz von Ideen für die gewerbliche Nutzung

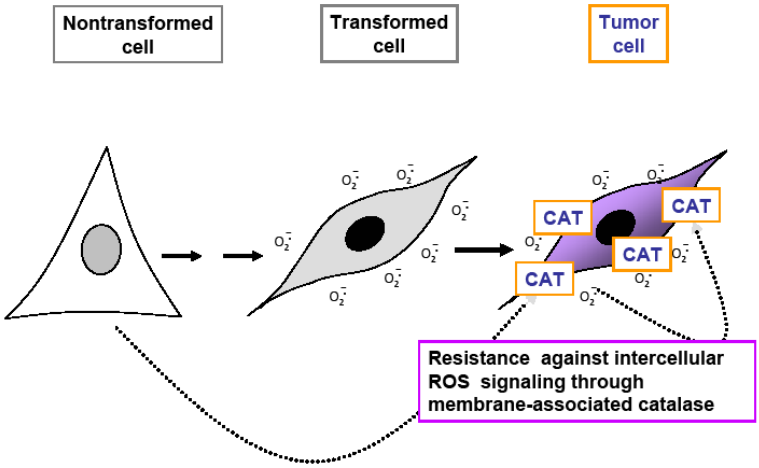

Figure 1
During multistep oncogenesis, activation of oncogenes, inactivation of tumor suppressor genes and abrogation of senescence control leads to the transformed state. Transformed cells have the potential to form tumors and are characterized by extracellular superoxide anion generation. Superoxide anions and their dismutation product hydrogen peroxide are involved in the stimulation of proliferation and maintenance of the transformed state. As a second side of the coin, extracellular superoxide anions of transformed cells control several intercellular reactive oxygen species-mediated signaling pathways that cause apoptosis induction selectively in transformed cells. During tumor progression, tumor cells regularly acquire resistance against ROS-mediated apoptotic signaling through expression of membrane-associated catalase.

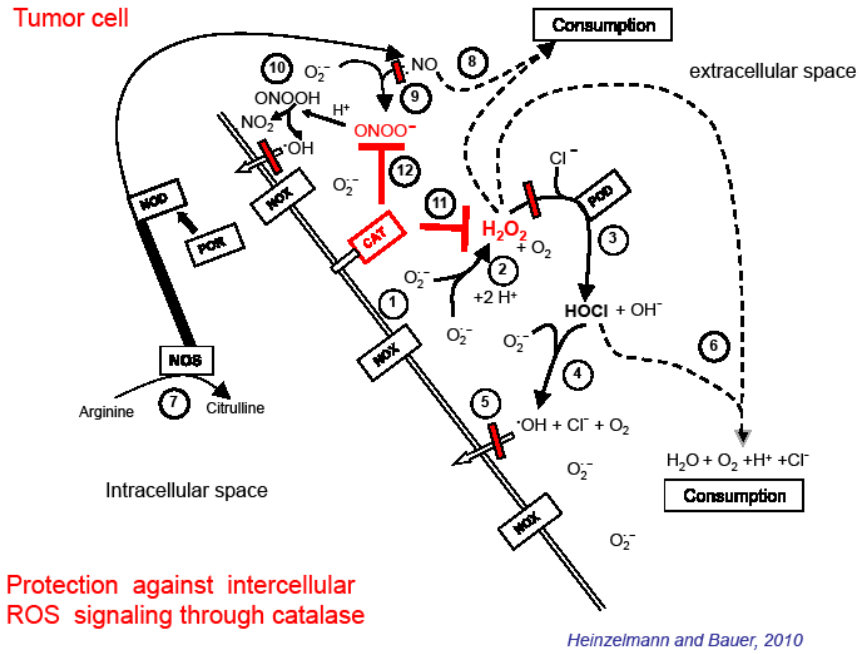

Figure 2
Malignant cells show activated NADPH oxidase (NOX-1) which generates extracellular superoxide anions (1) that spontaneously dismutate to form hydrogen peroxide (2). A cell-derived peroxidase converts hydrogen peroxide and chloride into HOCl (3). HOCl then interacts with superoxide anions, thereby generating apoptosis-inducing hydroxyl radicals (5). Excess hydrogen peroxide blunts HOCl signaling through a consumption reaction (6). NO is formed by NO synthase (7) and may either be consumed by hydrogen peroxide in a complex reaction (8) or react with superoxide anions to generate peroxynitrite (9). Peroxynitrite can be converted to peroxynitrous acid which decomposes into NO_2 and hydroxyl radicals (10). In contrast to transformed cells, tumor cells are protected against intercellular ROS signaling through expression of catalase (CAT). Catalase removes hydrogen peroxide and thus inhibits HOCl signaling (11). It also decomposes peroxynitrite and thus abrogates the NO/peroxynitrite signaling pathway (12).

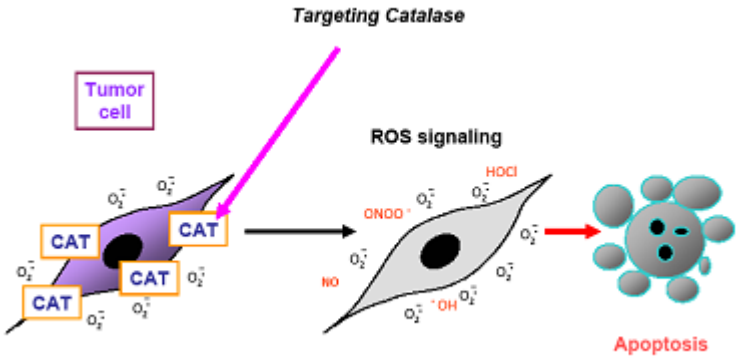

Figure 3
Targeting catalase (inhibition, inactivation, siRNA-mediated knockdown) sensitizes tumor cells for intercellular ROS signaling and causes selective apoptosis of tumor cells. We have characterized a complex inactivation mechanism that is based on modulation of the available NO concentration and subsequent generation of singlet oxygen, which inactivates catalase through reaction with its active center. **We have been successful in direct targeting of catalase and inhibition of tumor growth and survival in-vitro and in-vivo. Our system can be used to search for novel mechanism-based selective anti-tumor compounds and for the establishment of synergistic interactions between different compounds. The latter approach has the potential to prevent side effects of certain drugs.**