MEAN HEMISPHERIC EVAPORATION AND AIR TEMPERATURE FOR PRESENT-DAY CLIMATE

January

	Northern Hemisphere (winter hemisphere)	Southern Hemisphere (summer hemisphere)
Evaporation (mm month^{-1})	91, 92[1]	77, 84
Temperature (°C)	8.5, 7.3	16.6, 16.5

July

	Northern Hemisphere (summer hemisphere)	Southern Hemisphere (winter hemisphere)
Evaporation (mm month^{-1})	74, 87	102, 111
Temperature (°C)	22.0, 21.5	11.6, 11.0

[1]Red numbers (left), simulated with the ECHAM4 GCM; blue numbers (right), results from ERA15.

in terrestrial evaporation.

On page 1410 of this issue, Roderick and Farquhar offer a new explanation for the decreasing pan evaporation (*11*). They relate the downward pan evaporation trend to the decreasing solar radiation globally observed between 1957–1958 and 1990. The work is based on the concept of energy balance and is a valuable and interesting contribution to the present controversy.

The subject of evaporation changes is, however, far from settled with the present report. For instance, Xu has reported increasing pan evaporation over a large area in Asia (*12*). Further, it is not firmly established that global evaporation must increase under an enhanced greenhouse climate. When CO_2 was doubled in a simulation with the ECHAM3 general circulation model (GCM), a slight decrease in global evaporation was observed (*13*). A similar simulation with the GCM of the Meteorological Research Institute, Tsukuba, also showed a small decrease in global evaporation after doubling CO_2 (*14*).

Ultimately, what is important is the trend in actual evaporation. Pan evaporation matters insofar as it can offer a useful clue to the direction of the change in actual evaporation. Several issues remain to be resolved before we can fully understand the trend in global evaporation in our changing climate.

First, the direction of the evaporation trend is not determined by temperature alone. That a warmer atmosphere does not necessarily produce more evaporation can be seen in the fact that hemispheric evaporation is much more substantial in winter than in summer under the present climate. This fact was already established in 1963 (*15*) but passed largely unnoticed. A recent simulation of the present climate with the ECHAM4 GCM also clearly shows that a hemisphere evaporates more in winter than in summer. This result is supported by the European Re-Analysis (ERA) (*16*) by the European Centre for Medium-Range Weather Forecasts (ECMWF) (see the table).

Second, the evaporation trends from land and from the ocean must be studied separately. Under certain conditions they differ tremendously, especially when land evaporation is from drying soil surfaces. Ocean evaporation, on the other hand, depends heavily on nonatmospheric processes such as the ocean heat flux.

Third, the diurnal temperature range must be separated into two components: one due to the 24-hour periodicity and the other due to the non–24-hour variation. The former represents the effect of the diurnal cycle in radiation; the latter indicates the strength in advection. This treatment makes it possible to determine to what extent the trend in evaporation is due to changes in radiation fields or in the strength of circulation.

Finally, analyses of the evaporation and solar radiation of the last 10 years are urgently needed, because the increasing trend of global cloudiness reversed around 1990 (*17*). This type of study will clearly indicate whether the reported decrease is a segment of a longer trend caused by the human-made greenhouse effect or a short-term variation due to solar radiation.

References and Notes

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9. Terrestrial evaporation is the actual evaporation from the natural surface, whereas potential evaporation is the evaporation expected from a ground surface that has always sufficient water supply. Potential evaporation is thus the maximum possible evaporation.
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13. M. Wild, A. Ohmura, U. Cubasch, *J. Clim.* **10**, 3093 (1997).
14. Reported by T. Tokioka at the Workshop of the Japanese Committee for the World Climate Research Program (WCRP), October 1987, Tokyo.
15. M. I. Budyko, Ed., *Atlas of the Heat Balance of the Earth* (USSR Academy of Science, Moscow, 1963).
16. The ERA combines computed values and observed meteorological data. It reconstructs the three-dimensional atmosphere by combining the GCM-based calculation for weather forecasts and the subsequent observation of the same values. Satellite data are added for substantiating the atmosphere. This type of data set is called the "Analysis." The Re-analysis is the most comprehensive data set for climate research at present. It is made available to member countries of ECMWF for research purposes.
17. Reported by W. Rossow of NASA at the GEWEX (Global Energy and Water Cycle Experiment) Radiation Panel Meeting in Zürich, 1 August 2002.

PERSPECTIVES: CANCER

DNA Damage, Deamidation, and Death

Chi Li and Craig B. Thompson

A major challenge in cancer therapy is the identification of drugs that kill tumor cells while preserving normal cells. Some DNA-damaging agents are effective antineoplastic drugs because they damage malignant tissues more than normal tissues (*1*). In vitro, tumor cell death in response to DNA-damaging agents appears to result from the induction of apoptosis (programmed cell death). Paradoxically, many, if not all, human cancer cells display resistance to apoptosis (*2*). Among the major apoptotic regulators of the cell are proteins of the Bcl-2 family, some of which are antiapoptotic (such as Bcl-2 and Bcl-x_L) and others proapoptotic (such as Bax and Bak). Cells from many tumor types have an increased ratio of antiapoptotic to proapoptotic proteins, which enables them to resist stimuli that would normally induce apoptosis (*3*). These observations have made it difficult to reconcile the clinical effectiveness of anticancer agents that damage DNA and induce apoptosis with the apparent increase in apoptotic resistance of tumor cells.

A recent study in *Cell* by Deverman and

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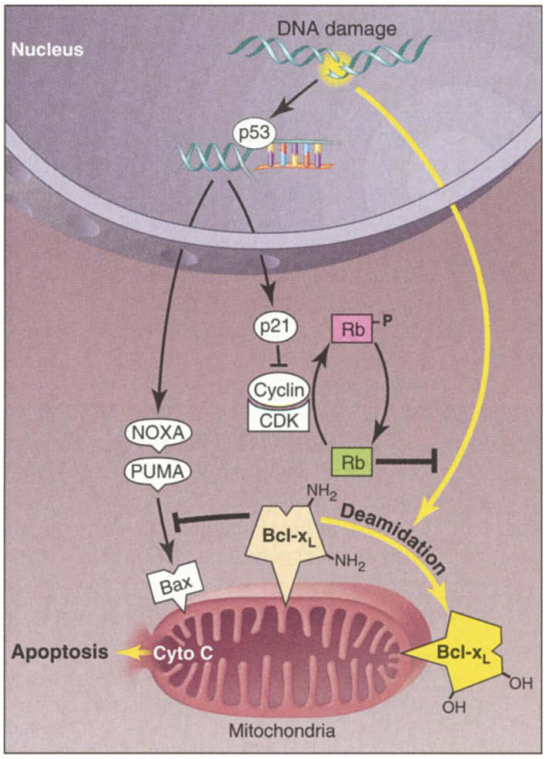
co-workers provides fresh insights into this paradox (*4*). Their data suggest that chemotherapy induces deamidation of the antiapoptotic protein Bcl-x_L in tumor cells but not in normal cells. Deamidation (removal of an amide group) was found to occur at two specific asparagine residues in a conserved region of the regulatory domain of Bcl-x_L. Deamidation of these asparagines converts the residues to aspartates and renders Bcl-x_L inactive. This results in the tumor cells becoming more sensitive to apoptosis than their normal counterparts.

The posttranslational modification of proteins is important for many cellular and developmental processes. Although modifications such as phosphorylation and acetylation have received the most attention, deamidation of asparaginyl and glutaminyl residues also has been observed (*5*). Deamidation results in the introduction of a negative charge at the site of modification and can lead to alterations in protein tertiary structure that affect the protein's biological activity. It has been proposed that deamidation could serve as a unique molecular clock regulating cellular aging (*6*). The most compelling evidence that deamidation is biologically significant comes from the correlation of in vivo protein turnover rate with deamidation rate (*7*).

The tumor-selective deamidation of Bcl-x_L provides the first firm evidence that differential deamidation regulates a cellular response (*4*). Tumor-associated deamidation of Bcl-x_L appears to result from mutations in two key tumor suppressor genes, *p53* and *Rb*. Like many human cancer cells, the tumor cell line in which cisplatin-induced deamidation of Bcl-x_L was first observed lacked both the p53 and Rb tumor suppressor proteins. Surprisingly, when Rb was reintroduced into the cancer cells, Bcl-x_L was no longer deamidated after treatment with cisplatin and the tumor cells survived. Induction of Rb expression, however, failed to protect the tumor cells from apoptosis if the cells were rendered Bcl-x_L deficient. In normal cells, DNA damage results in p53-dependent transcription of the cyclin-dependent kinase inhibitor p21. This results in Rb activation because p21 suppresses the ability of cyclin-dependent kinases to inactivate Rb through phosphorylation (*8*) (see the figure).

There is now mounting evidence to suggest that differential regulation of Bcl-x_L activity may modulate sensitivity to apoptosis. One mechanism proposed for how Bcl-x_L prevents apoptosis is through its ability to bind to and suppress the proapoptotic activity of proteins containing BH3 domains (*9*). BH3-containing proteins are normally molecular triggers that activate proapoptotic Bax and Bak, leading to release of cytochrome c from mitochondria, caspase activation, and apoptotic cell death. Several BH3-containing proteins are transcriptionally induced in response to DNA-damaging agents, and functional Bcl-x_L is required to suppress their proapoptotic activity. Consistent with this mechanism, Bcl-x_L that has undergone deamidation at amino acids 52 and 66 is unable to bind to BH3-containing proteins, thus potentially accounting for the loss of antiapoptotic activity.



A deamidation death knell for tumor cells. Distinct signaling pathways are activated in normal cells and tumor cells in response to DNA-damaging agents. In normal cells, DNA-damaging agents activate the transcription factor p53, which then up-regulates the expression of the cyclin-dependent kinase (CDK) inhibitor p21 and BH3-containing proapoptotic proteins such as PUMA and NOXA. As a result of p21 suppression of cyclin/CDK activity, Rb is activated and suppresses deamidation of Bcl-x_L through an unknown mechanism. Unmodified Bcl-x_L inhibits the ability of BH3-containing proteins like PUMA and NOXA to induce Bak/Bax activation, mitochondrial release of cytochrome c, and caspase proteolysis. In contrast, in tumor cells that lack Rb, DNA-damaging agents induce deamidation of Bcl-x_L and inhibit the ability of Bcl-x_L to suppress the proapoptotic activities of BH3-containing proteins and Bax/Bak, leading to tumor cell apoptosis.

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These findings provide insight into how the loss of tumor suppressor protein activity—a hallmark of malignant transformation—is exploited by clinically effective chemotherapeutic drugs to induce tumor-selective apoptosis. These data have important implications for refining the use of alkylating agents in the treatment of human malignancies. The Deverman *et al.* work suggests that Rb-deficient tumors expressing Bcl-x_L will be specifically sensitive to such treatments. In addition, the data make the molecular prediction that Rb-deficient tumors expressing Bcl-x_L and p53 should be particularly susceptible to alkylating agents. In this genetic background, Bcl-x_L will be deamidated and induction of p53 will result in the expression of the proapoptotic BH3 proteins NOXA and PUMA. If clinical correlation studies can bear out this prediction, the new work may mark the start of a more refined and rational use of traditional alkylating agents in the treatment of human neoplasms.

As exciting as the Deverman *et al.* study is, their results raise as many questions as they answer. First, does deamidation play a bigger part in the regulation of biological properties than previously suspected? For example, it is possible that other apoptotic regulatory proteins are also susceptible to modification by deamidation, and this possibility will need to be explored. Second, it is unclear from the present studies whether deamidation of Bcl-x_L is mediated by specific enzyme regulators or by other nonenzymatic means. Enzymes involved in targeted deamidation of proteins have been identified in prokaryotic organisms. For example, the dermonecrotizing toxin from *Bordetella* deamidates glutaminyl residues of the small guanosine triphosphatases Rho, Rac1, and Cdc42, leading to their constitutive activation (*10*). To date, enzymes catalyzing deamidation reactions in eukaryotic cells have not been identified. However, given the rapid progress in proteomics and genomics, it should not be long before we are able to explore the importance of deamidation in the regulation of many other cellular and developmental processes.

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