Relationship between Cancer and Aging: Experimental Evidence and Mathematical Modeling Considerations

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In this paper we investigate how various factors associated with external stresses and internal biological parameters influence processes of aging and tumor development. We present and discuss experimental findings confirming diversity of impact of different factors on cancer and longevity in rodents (LIO rats, CBA, SHR, SAMR-1, SAMP-1, HER-2/neu mice). Among factors influencing cancer and longevity are treatment with medicaments (melatonin, epithalon, DSIP), number of pregnancies and ovariectomy, body weight and body weight gain. These findings provide valuable insights on the relationship between the processes of carcinogenesis and aging in humans. We present the results of analysis of experimental data and suggest several mathematical models relating longevity, carcinogenesis, external stress parameters and internal biological mechanisms. The models exploit the concepts of hidden heterogeneity, two-stage process of carcinogenesis, repair of damages at cellular level, and components of individual aging process. Implications and possibilities for future research are discussed.

Experimental Studies.

The effect of various regimens of treatment with melatonin on the development of mammary tumors in HER2/neu transgenic mice was investigated. Treatment with melatonin slowed down age-related disturbances in estrous function most in the group exposed to interrupted treatment with the hormone. Constant treatment with melatonin decreased incidence and size of mammary adenocarcinomas, and incidence of lung metastases, compared to controls. The data demonstrate the regimen-dependent inhibitory effect of melatonin on the development of spontaneous mammary tumors in HER-2/neu mice but not on overall survival.

The results of study of female SHR mice show that the treatment of melatonin did not significantly influence food consumption, but its administration at lower doses did decrease the body weight of mice; it slowed down the age-related switching-off of estrous function; it did not influence the frequency of chromosome aberrations in bone marrow cells; it did not influence mean life span; and it increased life span of the last 10% of the survivors in comparison to controls. That treatment with low dose melatonin significantly decreased spontaneous tumor incidence, mainly mammary carcinomas, in mice whereas higher doses failed to influence tumor incidence as compared to controls.

The results of female SHR mice show that the treatment with Deltaran did not influence food consumption, but decreased the body weight of mice; it slowed down the age-related switching-off of estrous function; it decreased the frequency of chromosome aberrations in bone marrow cells; it did not influence mean life span; and it increased life span of the last 10% of the survivors and maximum life span in comparison with the control group. Treatment with Deltaran significantly decreased total spontaneous tumor incidence, mainly mammary carcinomas and leukemias in mice as compared with the control group.

Female transgenic FVB/N mice carrying the breast cancer gene HER-2/neu treated with Epithalon showed prolonged average and maximum lifetimes. The peptide prolonged the average lifetime of animals without neoplasms. Epithalon

decelerated the development of age-related disturbances in reproductive activity and suppressed the formation of neoplasms. The peptide decreased the incidence of breast adenocarcinomas, lungs metastases, and multiple tumors. Epithalon increased the number of mice without breast tumors, while the number of animals with 6 or more breast tumors decreased by 3 times. Epithalon prolonged the lifetime of mice with breast tumors by 1.4 times. These results indicate that Epithalon possesses geroprotective activity and inhibits breast carcinogenesis in transgenic mice.

We studied effect of pregnancy and ovariectomy on the development of mammary tumors in homozygous female HER-2/neu transgenic mice. The mean life span of uniparous mice was decreased by 16% in comparison to the control and of mice which have two pregnancies decreased by 11%. Ovariectomy at the age of 2 months was followed by 32.7% increase in mean life span of mice. The incidence or multiplicity of mammary adenocarcinomas did not change in uniparous mice, whereas the size of the tumors and metastatic potential were decreased as compared to the virgins. When mice have two full-time pregnancies, there was an increase in multiplicity of mammary carcinomas and significant decrease in the survival time of tumor-bearing mice. Ovariectomy significantly decreased the total incidence of mammary carcinomas, the number of tumors per tumor-bearing animal, and inhibited metastasizing into lungs. Our results indicate that pregnancy accelerated the development of mammary adenocarcinomas in transgenic HER-2/neu mice whereas ovariectomy inhibits their development.

To further investigate the interactions among body weight, longevity and spontaneous tumor development, we measured correlation between the body weight in early life and in a middle life and parameters of life span and tumorigenesis in male and female in outbred rats and mice of various strains (CBA, SHR, SAMR-1, SAMP-1, HER-2/neu). The data show that the body weight (BW) at the age of 3 and 12 months is a significant predictor for longevity in rats, with heavier female rats tending to be longer lived. In males, animals being lighter at the age of 3 months live longer, and being lighter at the age of 1 year live shorter than more heavy males. Fast BW gain reduced LS in females bot not in males. The BW at the age of 3 months has no predictor value for tumor risk, however, being heavier at the age of 1 year both males and females have an increased risk of tumor development. The results for mice are strain-dependent.

Mathematical models.

Experimental studies reveal complicated interconnections between cancer, process of aging and biological parameters such as estrous function, frequency of chromosome aberrations in bone marrow cells, body weight, and number of pregnancies in rodents. While the results are obtained for rodents and some of the effects can be due to specific transgenic strains used in the experiments, these findings can be used to shed additional light on mechanisms responsible for processes of aging and carcinogenesis in humans. The mechanisms relating these processes with changes in biological parameters during life course can be common for rodents and humans. For example, heavy body weight is thought to be associated with reduced longevity and age-associated diseases, including cancer both in laboratory rodents and humans.

A unique advantage of these experimental studies is the availability of various parameters (life span, tumors, mean food consumption, mean length of estrus cycle, mean body temperature, and body weight) in the same group of animals. This allows for extensive analysis of impact of various factors on longevity and carcinogenesis.

Availability of parameters at different ages gives a possibility to investigate dynamic aspects of influence of the parameters on the processes of aging and carcinogenesis.

Mathematical modeling provides a useful tool to investigate such sophisticated relationships. In this paper we propose several such models. Availability of rich data sets permits fitting the models and interpretation of the results.

First, we use the concept of heterogeneous population and a proportional hazard model with gamma-distributed frailty and non-parametric baseline hazard. This model allows us to avoid widely used but biologically unjustified technical assumption about parametric form of the underlying hazard, because in such a representation of the model we use observed survival function in the non-stressed (control) group.

We also investigate the classical two-stage model of carcinogenesis in relation to process of aging. We assume that the processes responsible for cancer and aging at cellular level (cell proliferation and differentiation) are related to various factors measured in the experiments but the factors may influence these processes in a different way. We incorporate this dependency into the model.

The model of spontaneous tumor recurrence includes a parameter associated with unrepaired DNA formation. These damages in DNA can propagate both cancer and aging and be related to the measured parameters. This relationship is analyzed in the model.

Different components of individual aging process (basal, ontogenetic and exposure-related) can be associated with the observed trajectories of mortality and cancer incidence. We explore the respective in relation to ontogenetic events (such as length and regularity of estrus cycles and number of pregnancies). We model the association between these events and processes of individual aging and carcinogenesis.

All the models are tested on simulated data and then applied to the experimental data on different rodent strains. Parameters are estimated and compared. The results suggest complicated relationship between the processes of carcinogenesis and aging.