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Effect of host age on tumor growth rate in rodents

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1. ABSTRACT

There is growing evidence that accumulation of senescent cells in tissues may promote cancer in aged organisms. It is also generally believed that the growth of malignant tumors is slower and metastasis occurs less frequently in elderly than in young individuals. Here, experimental data on the effect of aging on the growth of transplanted tumors are discussed. No uniform pattern of behavior of tumor cells in old organisms can be observed. While some tumors grow faster in young compared to old animals, others grow slowly. This difference appears to depend on tumor and host factors. There is evidence that the implantation of metastatic tumor cells depends on humoral host factors, whereas the growth rate of metastasis mainly depends on local (microenvironmental) host factors. Age-associated changes in both humoral and local host factors are critical to the behavior and progression of transplanted tumors in the old host.

2. INTRODUCTION

One of the widely accepted paradigms in cancer biology and clinics is the opinion that tumor growth and metastasis are slower at the old age in both human and experimental tumors (1-4). In a series of recent exciting papers, J. Campisi (5-9) proposed an idea that senescent fibroblasts have little impact on the growth of normal epithelial cells. However, they clearly stimulate preneoplastic and malignant cell growth, largely due to the secretion of both soluble and insoluble factors. According to this hypothesis, since senescent cells accumulate in tissues with age, the transplantation of tumor cells into an old host will more likely form tumors in older animals. Thus, we face two contradictory points of view.

Observations that the behavior of malignant tumors varies with age are abundant (10,11). Thus, elderly breast cancer patients have a better prognosis than young

patients. The prognosis for different tumors, however, may worsen with the age of the patient, as is the case with acute myelogenic leukemia and large cell lymphoma (10,11). According to the UICC data, old age (> 70) of the patient is a prognostic factor for the majority of cancers (12,13).

In this paper the author will focus on experimental tumor models. According to the integral model of carcinogenesis, (14-16), the age-related changes in tissue microenvironment may both favor and oppose tumor development. According to Peto *et al.* (17), substantial arguments for Burnet's (18) point of view should be provided if tumors of the same age transplanted to the old host grew with a faster rate than tumors in younger hosts. These experiments rule out the effect of age on the initiation stage of carcinogenesis itself and explore the role of age-related changes in the organism on the growth and progression of transformed cells. The following criteria for the evaluation of the results of such experiments might be used: (a) tumor transplantability, (b) rate of tumor growth, and (c) survival time of tumor-bearing animals. Notably, age-related differences in transplantability mainly illustrate the role of age in the decline of immune vigor. When host animals are inoculated with an excess of tumor cells, the difference might not be evident. Carefully planned experiments, with a strictly counted and limited number of tumor cells injected into young and old animals, in some cases, allow a researcher to evaluate a dependency of tumor growth rate on the host age.

3. EPITHELIAL TUMORS

3.1. Lung tumors

The influence of the age of the tumor host on cancer growth was shown by the pivotal experiments of Ershler (3,4). He injected an equal number of melanoma B16 cell or Lewis lung carcinoma cells into younger and older mice and found that the survival was shorter and the number of metastases higher in younger animals.

The data of Thompson (19) show that the incidence of lung tumor colonies in old (71 weeks) C3H mice was directly proportional to the number of intravenously administered cells of Ehrlich's ascites carcinoma. However, this correlation has not been found in young (15-week-old) animals. These data provide convincing evidence for the existence of a certain "threshold" in the immune system of anti-tumor resistance and suggest that its level decrease with age.

In a study by Yuhas and Ulrich, mice were administered intravenously with equal numbers of lung carcinoma cells (line 1) at the age of 3, 8, 12, and 18 months (20). The authors showed an increased number of tumor colonies developed in the lungs with the increase of mouse age at the time of the injection.

Transplantability and growth of syngeneic Lewis lung carcinoma were studied in 2-, 10-, and 24-month-old C57BL/6J mice (21). It was shown that the incidence of developed tumors and growth rate increased in direct proportion to the age of mice. In our experiment, the tumor doubling time and the survival time of tumor-bearing C57BL/6 mice grafted with Lewis lung carcinoma at the age of 3 or 18 months did not reveal any significant differences (22). Sadovnikova *et al.* (23) injected equal number of Lewis lung carcinoma cells intraperitoneally to hybrid (CBA x C57BL)F1 mice aged 2, 6, 26 and 33 months. No difference was found in the growth rate of tumors in all age groups. However, the tumor diameter increased with a somewhat lower rate in 33-month-old mice compared with 2-month-old animals. The contradictions in the results of the experiments with Lewis lung carcinoma are difficult to explain. The difference in the age at the time of tumor inoculation, the site of inoculation, and the sex of the mice might be the causes of these controversies.

3.2. Melanoma B16

The injection of a dosed number of melanoma B16 cells to young or old mice brought about more contradictory results. In a study of Hirayama *et al.* (24) a different numbers of B16-F10 melanoma cells with a high pulmonary metastasizing potential was injected subcutaneously into the outer ear of female C57BL/6 mice at the age of 3 or 22 months. However, no differences in the tumor size between young and old animals were found. On the other hand, palpable metastases in cervical lymph nodes appeared earlier in old mice as compared to young animals. It was found that the number of metastatic colonies in the lungs of old mice was significantly higher than in young animals at the 29th day after the injection of tumor cells. In young mice, the size of lung metastases was homogenously similar, and these were large, while in old mice metastases were heterogeneous with prevalence of small colonies. Colonies with a diameter equal to or less than 0.1 mm appeared with an incidence of 36% in young mice and 70% in older ones, respectively, at the 6th week after the inoculation of tumor cells. The authors suggested that although B16 metastatic colonies are easily established in old mice, the microenvironment is less favorable for their growth in the lungs of old animals, than in young.

In the experiments of Ehrlich *et al.* (25), one-year-old mice appeared to be more resistant to the subthreshold number of B16 cells injected subcutaneously into dorsal area, than 3-month-old animals. The incidence of developed tumors and the rate of their growth were higher in younger mice compared with older ones.

In another study, male C57BL/6 mice aged 3 or 24 months were injected subcutaneously or intraperitoneally with 10^5 melanoma B16-F10 cells, or intravenously with 10^5 melanoma B16-F1 cells (2). It was found that subcutaneously grafted tumors appeared later, developed slower, and reached a smaller size in older mice. The survival time of the old mice inoculated subcutaneously with melanoma cells was longer than that in young animals. However, the survival time of young and old mice injected with melanoma cells intraperitoneally was similar. In two weeks after intravenous administration, the number of developing lung colonies was 5.1 ± 2.6 (mean ± S.E.M.) in old mice and 29.3 ± 5.7 in young mice ($p < 0.01$). In addition, the survival of old mice injected

with tumor cells intravenously was longer than the survival of young mice injected with the same number of melanoma B16 cells.

In our own experiments, melanoma B16 cells were transplanted subcutaneously into young (3-month-old) or old (18-19-month-old) C57BL/6 mice (26). The growth rate of the melanoma was higher in old mice compared with young ones. However, the survival of melanoma B16 bearers was not influenced by the age of the animals. When 5×10^4 melanoma B16 cells were injected intraperitoneally, the mean number of lung colonies was 32.8 ± 7.5 in 12-month-old animals vs. 6.4 ± 1.0 in 3-month-old animals ($p < 0.01$). Intravenous inoculation of 1×10^5 melanoma cells into 12-month-old mice was followed by the development of 57.3 ± 7.9 lung metastatic colonies, whereas in 3-month-old animals only 36.8 ± 8.4 colonies developed. However, the majority of lung colonies were generally smaller in diameter in 12-month-old mice when compared with young mice (26).

B16 F10 melanoma cells were injected into the tail vein of young (6-week-old) or old (22-month-old) mice and into parabiotic mice constructed between young and old mice; the number and shape of pulmonary metastases were compared between these groups (27). In unpaired mice, the number of lung metastatic colonies was 10-fold higher in young mice compared to old ones. In parabiotic young mice, the number of metastases was almost equal to the number in unpaired young animals, but the number of lung metastases in old mice was similar to that in young animals. Metastatic colonies at the lung surface were mostly nodular in young mice and flat in old mice. The shape of colonies reflecting the tumor growth rate was not changed in parabiotic old mice in spite of an increase in the total number of these colonies. In young parabiotic mice, the number of large and intermediate size colonies has decreased, whereas the number of small lung metastatic colonies has increased in comparison with unpaired young mice. These results suggest that the implantation of metastatic colonies in the lung mainly depends on systemic humoral factors, and that their growth mainly depends on the local host factors (microenvironment). Thus, significant age-dependent changes of both systemic and local factors greatly influence the metastatic behavior of melanoma B16 (27).

Pili *et al.* (28) have subcutaneously injected 10^5 melanoma B16-F10 cells into 2- and 18-month-old C57BL mice. Twenty-four and 28 days after injection, tumors growing in old animals were in a size about 50% compared with tumors growing in young animals. The authors have also observed significantly fewer metastatic lung colonies in the older animals compared with young ones after they were injected intravenously with melanoma cells.

Compared to young (6-8 week-old) C57BL/6J mice inoculated with melanoma B16 cells, a reduced tumor growth rate was observed in middle-aged (12-13 month-old) and old (16-24 months-old) mice (29,30). Itzhaki *et al.* (31,32) have shown that decreased cell proliferation or immune response modifications are possible mechanisms of this phenomena. Additionally, an increased tendency to apoptotic tumor cell death in the aged could also contribute to the latter.

The differences in the rate of tumor growth and survival of tumor-bearing animals are determined by the age-related hormone-metabolic shifts and by some biological characteristics of the inoculated tumor. The importance of these factors was stressed by Hirayama *et al.* (24). He observed the difference in capacity of F1 and F10 sublines of B16 melanoma to grow and form lung metastatic colonies. Donin *et al.* (29) have further reported on the differences in the effect of age on the growth rate of the melanoma B16 and its highly malignant variant, the B16/Col./R melanoma.

3.3. Mammary tumors

Inoculation of tumors derived from the mammary gland epithelium (Ehrlich's ascites, EMT6, A-755) to the mice of various ages is usually followed by enhanced growth rate in older animals (22,33,34). In our experiment, transplantable mammary carcinoma, A-755, was inoculated subcutaneously into female C57BL/6 mice aged 3, 12 or 18 months (22). The doubling time of the mean tumor size was 33 ± 2.1, 29 ± 1.9 and 27 ± 2.3 days, respectively. Mean survival time of C57BL/6 mice inoculated subcutaneously with mammary carcinoma A-755 at the age of 3 months was 35 days; it was 22 days when tumor cells were transplanted into 19-month-old mice (26). The rate of growth of spontaneous mammary adenocarcinoma transplanted into old male C3H mice was increased, as compared to old females (19). The authors believe this to be the result of age-related hormone disturbances in old female C3H mice.

Sadovnikova *et al.* (23) have shown that spontaneous mammary tumors, developed in old (21 to 22 months) female SHK mice grew slower than similar tumors in 10 to 15-month-old mice. Walker 256 carcinoma, which is also derived from mammary gland epithelium, has grown slower than that in 20-week-old animals when transplanted into old (120-week-old) male rats (19).

Gravekamp *et al.* (34) injected different numbers (10^3, 10^4, 10^5) of non-metastasizing 64pT mammary tumor cells into a fat pad of normal BALB/c mice of different ages (3, 9, and 24 months). A significantly lower progression of 64pT breast tumors was observed in the mice at 24 months compared to the mice at the age of 3 months, when injected with 10^4 tumor cells. However, there was no difference in the tumor weight between young and old mice inoculated with 10^3 or 10^5 tumor cells. Similarly, no statistically significant difference in tumor weight was detected when 4TO7cg mammary tumor cells were injected into 3-, 9- or 21-month-old female BALB/c mice (35). The authors observed a 3-fold increase in the number of mice with metastases at the surface of the lungs or in the peritoneal cavity in old mice, compared with young mice (1/6 and 6/19, respectively). This alteration, however, was not statistically significant. Notably, no significant difference between young and old mice was observed in the transplantability or latency of 64pT and

4TO7cg mammary tumor (36).

It is important to note, that the estrous function is switched-off at the age of 13-16 months in the majority of mouse strains, whereas at the age of 15-18 months in rat of different strains (14). Thus, animals of oldest groups were anovulatory in all above mentioned experiments with transplantable mammary tumors.

To test the idea that senescent cells create a microenvironment that promotes the growth of preneoplastic cells *in vivo*, Krtolica *et al.* (8) injected epithelial cells cultivated *in vitro* alone or with fibroblasts, into 5-week-old immunocompromised (*nu/nu*) mice. Four epithelial cell lines have been used in the experiment. Three of those, namely human epidermal keratinocytes (HaCAT), S1 human mammary epithelial cells and SCp2 mouse mammary epithelial cells, were evaluated as preneoplastic, and the fourth (MDA231) is an aggressive human breast cancer line. In all the strains, when injected with senescent fibroblasts, both preneoplastic and neoplastic cells formed tumors in mice. Tumors did not develop if the inoculation of senescent fibroblasts was not performed simultaneously. Following that, it could be concluded that the senescent cells may create a microenvironment that facilitates the growth and progression of the mutant cells.

3.4. Hepatocellular cancer

The growth rate of subcutaneously transplanted murine hepatoma-22a tumors was similar in 3- and 14-month-old C3HA mice. However, in older animals (18-28-month-old) the tumor size was larger than those of young mice at any time interval after inoculation (22). On the other hand, the growth rate of Novikoff's hepatoma was higher in young rats (20-weeek-old), compared to old (120-week-old) rats (37).

In a series of experiments, McCullough *et al.* (38-40) have developed an experimental system for the analysis of the role of cellular phenotype and tissue microenvironment in the effect of age on tumor development. This experimental system employs the intrahepatic transplantation of aneuploid BAG2-GN6TF liver epithelial cells. These cells produce tumors in 100% of neonatal rat host (41) and a high percentage of adult hosts with short latency when transplanted to subcutaneous or intraperitoneal sites (39). The authors have shown that intrahepatic transplants of the hepatoma cells rapidly produce small tumors at the site of inoculation in young hosts. However, these tumors regressed within 1 month of their formation (39). In contrast, when the hepatoma BAG2-GN6TF cells were inoculated intrahepatically into old rats, they quickly produced expanding undifferentiated liver tumors causing the death of the host rat (39,40). Remarkably, when the tumor cells were transplanted into the spleen of young rats, the cells show individual distribution throughout the liver resulting in hepatocytic differentiation by tumor cells with concomitant suppression of their tumorigenicity. When transplanted into livers of old rats by splenic inoculation or when young hepatic-transplant recipients are allowed to age, hepatocytic progeny of BAG2-GN6TF cells proliferate to form foci, suggesting that the liver microenvironment of old rats incompletely regulates the proliferation and differentiation of tumor cell-derived hepatocytes (40).

3.5. Gastrointestinal tumors

A human stomach carcinoma (Shiraishi line) was transplanted from hairless mice to nude rats of different ages. Its transplantability was highest in 4- to 7-week-old rats and lowest in 10- to 17-week-old animals. The mean tumor weight was largest in 4-week-old animals and lowest in 13-week-old (42).

In our experiments with 1,2-dimethylhydrazine-treated rats of varying age (4, 8-10 and 18 month-old), multiplicity of induced colon tumors inversely correlated with the age of animals (43). However, large-size colon tumors were more frequent in 18-month-old rats than in younger groups. Additionally, the morphology of developed cancers showed enhanced tumor progression in older animals. Turusov *et al.* (44) observed greater incidence of intestinal tumors with invasive growth in 12-month-old 1,2-dimethylhydrazine-treated mice, as compared to 8-month-old animals. These data suggest the promoting effect of age on intestinal tumor development in rodents.

3.6. Other epithelial tumors

Eight x 10^6 OTT6050 teratocarcinoma cells were injected subcutaneously into 129/Sv mice and the rate of tumor growth has been registered (45). It was observed that the tumor growth rate was maximal in 2- to 3-week-old mice. Tumor growth rate was similar in male mice aged 10 or 70 weeks, but it was decreased in 70-week-old females in comparison to 10-week-old females. The survival time of old-tumor-bearing mice was longer in comparison to young ones (45).

The growth rates of transplantable squamous cell carcinoma of the cervix uteri (SCC strain) were similar in the 3- and 12-month-old Balb/c female mice; however, it was increased in mice inoculated with the tumor at the age of 18 months (22). The growth rate of a human epidermoid carcinoma H.Ep#3 grafted to Swiss mice was higher in old (20- to 23-month-old) mice, when compared with younger (4- to 8-month-old) hosts (46).

4. MESENCHYMAL TUMORS

4.1. Hematopoietic malignancies

In several studies the effect of age on the development of transplantable neoplasm's of the hematopoietic system has been evaluated. Perkins (47) has studied the immunocompetence and development of transplantable mastocytoma P815, inoculated into young (3-mont-old) and old (25-month-old) Balb/c mice. An increased rate of tumor cell division in the 25-month-old hosts in comparison to young ones has been observed. One week after the inoculation of 10^5 tumor cells into old mice, ascites developed, and all the animals died 1 to 2 weeks after the injection. In young mice, the development of ascites was delayed and their volumes were less than in old ones; the animals did not die before the 3rd week of the

experiment. Survival of DBA/2 mice inoculated with the leukemia P388 was not significantly different between young (3-month-old) and middle-aged (12-month-old) animals (26).

AKR lymphoma cells were inoculated subcutaneously into 6-8-week-old or 7-9-month-old AKR mice. The age-related reduction of the tumor growth rate was demonstrated by measuring the tumor incidence, tumor size and survival (30).

In another study, myeloma LCP-1 cells injected intraperitoneally have killed young (2- to 3-month-old) mice after 16.5 days and old (19- to 20 month-old) animals 20 days after administration (48). The survival time of DBA/2 hybrid mice inoculated with leukemia L1210 cells at the age of 2, 3 or 11 months was longer in comparison to those inoculated with the equivalent number of the tumor cells at the age of 1.5 months (49). The survival time of young (3- to 4-month-old) and old (18- to 20-month-old) C57BL/6 mice intraperitoneally injected with hemocytoblastosis La cells was similar (22). Statistically significant delay in tumor appearance and a decrease in the tumor growth rate were shown in 11- to 17-month-old NZB mice grafted with a reticulum-cell type A tumor, compared to younger animals aged from 12-14 days to 230-256 days (50).

4.2. Sarcomas

Numerous works reported the effect of age on the growth rate of various transplantable sarcomas. Loefer (51) has found that transplantability of rat fibrosarcoma in 4-month-old recipient rats was higher than in 1-year-old animals. However, the ascitic variant of rat fibrosarcoma has developed poorly in infant rats, somewhat better in 3- to 4- month-old rats, and much better in 12- to 16- to 18-month-old rats (52). Most young rats (under the age of 36 weeks) that were subcutaneously grafted with methylcholanthrene-induced fibrosarcoma have developed rapidly growing tumors (53). In older (15-month-old) rats, the transplantability of the tumors was decreased, and they regressed often. The transplantability and tumor growth rates were higher in rats inoculated at over 2 years of age, and these parameters were similar in young (3 to 35-week-old) rats (54).

Stjensward (55) transplanted the first generation of methylcholanthrene sarcoma to mice aged 1 week and 1, 3, 4, 5, 6, 10, 15, or 22 months. The resistance to tumor growth was maximal in 6-month-old mice and minimal in 1-week-old and 22-month-old animals. At these ages the extent of cell immunity parameters was minimal, while it was maximal in 6-month-old mice.

Fibrosarcoma 1023 has been subcutaneously inoculated into 8- or 14- to 20-week-old mice (56). The growth rate of tumors was increased, and the survival time was decreased in the mice of the older age group. In the mice aged 2, 6, or 10 months, the transplantability of subcutaneously implanted UV light-induced fibrosarcoma 1591 was proportional to the age of the mice at the time of the transplantation (57).

The majority of methylcholanthrene-induced sarcoma grafts were successful in old (310- to 629-day-old) NZB mice, whereas only a proportion of young (70- to 87-day-old) mice had palpable tumors after 30 days; all young animals had rejected their tumors. In contrast, when the osteogenic sarcoma was transplanted into young and old NZB mice, a greater weight of tumors was found in the 37- to 44-day-old mice than in older (318- to 531-day-old) animals. This clear difference between young and old animals was not, however, reproduced when additional groups of young (75- to 98-day old) and old (362- to 541-day-old) NZB mice were assayed (50).

In our experiment, the growth rate of sarcoma 180 was higher in 18- than in 3-month-old C57BL/6 mice (22). A decrease of tumor mean diameter doubling time and significant shift to the left of the tumor growth curve in old mice was observed. The rate of growth of transplantable uterine sarcoma primary induced by 1,2-dimethylhydrazine and grafted to syngeneic young (2- to 3-month-old) and 1-year-old CBA mice was similar (58).

Engelbreth-Holm-Swarm (EHS) carcinoma (originally described as murine chondrosarcoma) cells were injected into C57BL mice of different ages (3, 6, 12, 18, 26, 28 months) (28). EHS tumors formed larger tumors in young mice than in old. The rate of DNA synthesis in tumor tissue from old animals in organ culture was lower than in tissue from young animals. Histologically, tumors grown in old animals exhibited a 3-fold higher ratio of extracellular matrix to tumor cells than those grown in young animals. Tumors from adult animals exhibited numerous small blood vessels, while those from old animals contained fewer, much larger vessels. The authors concluded that the rate of growth and morphology of the EHS tumor were altered with age, partly due to a reduced capacity of angiogenesis in the tumors, due to the lack of angiogenic factors or the presence of host inhibitors.

In our experiments, 2 $x10^3$; 5 x 10^3 or 10 x 10^3 cells of rat rhabdomyosarcoma RA-2 were intravenously inoculated into female and male rats of different ages (59). It was observed that the number of lung tumor colonies was highest in 1-month-old and 15-month-old females and lowest in 3- and 12-month-old animals. Proliferation activity of the tumor was higher in 1-and 15-month-old female rats compared with 3-month-old ones. A positive correlation was found between the number of lung tumor colonies and somatomedine activity in the lung tissue. In 24-month-old male rats which were injected intravenously with 5 x 10^3 RA-2 cells, the number of tumor clones in the lungs was significantly higher than in animals aged 2 or 6 months (59).

5. AGING, HOST MACRO- AND MICROENVIRONMENT AND TUMOR GROWTH

Available experimental data are contradictory and support the hypothesis that effects of host age on tumor development may vary (Table 1). Variation in the age of animals used in experiments might be one of the causes of

Table 1. Effect of age on the growth of transplantable tumors in rodents

Tumor strain	Species	Age groups, months	Effect of age[1]	Reference
Epidermoid carcinoma H.Ep.#3	Mouse	4-8 and 20-23	↑	46
Squamous cell cervical carcinoma (SCC)	Mouse	3 and 12	=	22
		3 and 18	↑	
Melanoma ?16	Mouse	3 and 12	↓	25
		3 and 18	↑	26
		2 and 18	↓	28
		3 and 22	=	24
		3 and 24	↓	2
		1.5-2 and 16-24	↓	30
Mammary carcinomas: Spontaneous	Mouse	3,5 and 16,5	↓	19
Ehrlich's ascites		10-11 and 21-22	↓	23
EMT6		3 and 16,5-18	↑	33
MAT-21		3-4 and 20-28	↑	34
A-755		2 and 4-5	↓	56
64pT		3 and 18	↑	22
4TO7cg		3 and 24	↓=	35
			=	36
Walker-256	Rat	2 and 24	↓	19
Lewis lung carcinoma	Mouse	3 and 18	=	22
		2 and 24	↑	21
		2-4 and 24	↓	2
		3 and 33	↓	23
Lung carcinoma-1	Mouse	3-8 and 18-23	↑	20
EHS carcinoma	Mouse	3 and 18-28	↓	28
Hepatoma-22?	Mouse	3 and 14-16	↑	22
Novikoff hepatoma	Rat	4,5 and 27,5	↓	37
Hepatoma BAG2-GB6TF	Rat	3-9 and 18-24	↑	39
Teratocarcinoma ??? 6050	Mouse	2 and 16	↓	45
Methylcholanthrene-induced sarcoma	Mouse	6 and 22	↑	55
		2-3 and 10-21	↑	50
	Rat	1-10 and 12-15	↓	53
		8-20 and 29-32	↑	54
Methylcholanthrene-induced SP1 fibrosarcoma	Mouse	2 and 19	=	61
Fibrosarcoma 1023	Mouse	2 and 4-5	↑	56
Fibrosarcoma 1591	Mouse	2-6 and 10	↑	57
Fibrosarcoma S180	Mouse	2-4 and 24	↑	4
Sarcoma 180	Mouse	3 and 18	↑	22
Osteogenic sarcoma	Mouse	2-3 and 10-17	=	50
Uterine sarcoma	Mouse	3 and 12	=	58
Fibrosarcoma	Rat	4 and 12	↓	51
Ascitic fibrosarcoma	Rat	3-4 and 16-18	↑	52
Mastocytoma ?815	Mouse	3 and 25	↑	47
		3-12 and 20-32	↑	62
Rethiculum-cell tumor type ?	Mouse	8 and 11-17	↓	50
Leukemia L1210	Mouse	3 and 11	=	49
Hemocytoblastoma La	Mouse	3 and 18	=	22
Leukemia P388	Mouse	3 and 12	=	26
AKR lymphoma	Mouse	1.5-2 and 7-9	↓	30
Myeloma LCP-1	Mouse	2-3 and 19-20	↓	48

[1] ↑ - Increase in transplantability, tumor growth rate or a decrease of survival of tumor-bearing animal; ↓ - opposite effects; = no effect of age.

those contradictions. It seems that the transplanted tumors developed slower in 5- to 13-month-old mice and rats than in younger (1- to 3-month-old) or older (18- to 22-month-old) rodents. Age-related peculiarities of the activity of the anti-tumor immune system probably play leading roles in this phenomenon (4,60). It is well known that the age-related decline in immunity and changes in the neuroendocrine system develop at various rates, and the significant immune deficiency could occur at different ages in animals of various strains. However, using mice of one particular strain (C57BL/6) as a host for transplantation of tumors of different histogenesis, we have found that the behavior of tumors frequently depends on the tissue origin of the grafted tumor (22).

The growth rate of the tumor could be determined either by the origin (histogenesis) of the tumor cells *per se*, or the complex factors of the host environment where tumor cells proliferate, or both of these. The host environmental factors could be classified into two types: 1) local factors that cannot be transported by the blood stream, and 2) humoral factors that can be supplied by the blood or lymphatic streams (27). Local sites where tumor cells implant and grow are composed of local organ cells with capillary networks and extracellular matrix (63,64). Possible candidate humoral factors are hormones, growth factors, cytokines and other factors of the immune system (4,14,24,45,60,65,66). For example, female mice older than 14-15 months and female rats older than 15-17 months usually have no ovulations and revealed persistent estrus syndrome followed by anestrous (14). The persistent estrus syndrome characterizes by acyclic normal or elevated level of estrogens in the serum, whereas estrogen deficit is common for anestrus (14).

The histological type of the tumor plays an apparently important role in tumor progression in the animals of different ages. Old age promotes the growth of squamous cell epidermal cancers and various adenocarcinomas. Hematopietic neoplasms grow either at the same rate in animals of varying ages or faster in young animals. However, the susceptibility to sarcomas and their growth rate are increased in old mice and rats (Table 1).

The microenvironment of cancer cells, composed of extracellular matrix macromolecules, plays a pivotal function in tumor progression (63,64,66,67). Aging considerably modifies extracellular matrix architecture and host cell proteolytic phenotype (67-69). Senescent fibroblasts might therefore influence crosstalk with tumor cells and the regulation of proteolytic cascades. Some details of this process have been discussed in a number of works (6,9,67,70).

The immunogeneity of the tumor is one of the principal factors determining age-related differences in tumor growth. The role of immunesenescence in the effect of age on the growth of transplantable tumors has been discussed in several comprehensive reviews (1,4,30,60,71). Briefly, strongly antigenic tumors induce sound immunosuppressive responses only in immuno-competent hosts, and tumor growth is therefore inhibited. Immunodeficient hosts produce a weak immunosuppressive response to a strongly antigenic tumor, and tumor growth is correspondingly greater. Weakly antigenic tumors induce little immunosuppressive response in either immunocompetent or immunosuppressive hosts. The immunocompetent host will produce a greater immune-facilitating response, and tumor growth will be greater than in the immunosuppressive host (71). This hypothesis predicts that in immuno-deficient (aged) host with a weakly antigenic tumor, the tumor growth would be slow compared with the growth of the same tumor in immunocompetent young host. This hypothesis can explain some contradictions in the results described in Sections 3 and 4.

Many research studies are now devoted to determining the impact of angiogenesis on tumor development and progression, and the reciprocal influences of tumor production upon the microvasculature (72). Age-associated change in angiogenesis could be the factor responsible for slow growth of some tumors in old animals (3,61). In late generation telomerase-deficient mice *Terc*$^{-/-}$ inoculated subcutaneously with melanoma B16F10 cells, short telomeres result in a sharp decrease in microvessel counts followed by diminished tumor cell proliferation and increased tumor cell apoptosis, and finally, a lower tumor growth rate (73). It was shown that the extent and intensity of expression of mapsin (a member of serine protease inhibitor family and an epithelial cell tumor suppressor with anti-invasive and anti-angiogenic activities) in the human skin is significantly correlated with chronological age (74). Authors suggest that senescent keratinocytes exert a paracrine anti-angiogenic activity, and mapsin is the principal contributor to this potentially suppressive effect of cellular senescence.

Significant changes in the level of cytokines, hormones, growth factors and metabolites during the normal aging in mice and rats, as well as in humans, are commonly known. It is *a priori* clear that the internal milieu of young and old hosts can reveal some differences, which can promote or prevent tumor growth. Numerous pieces of evidence suggest that following age-associated disturbances in the organism that develop during normal aging at molecular, tissue, systemic and organism levels, microenvironmental conditions promoting the tumor growth are formed in the elderly age (for review see: 5,6,14-16,65,75-77).

A concept was substantiated that the most common feature of all malignant tumors would be their interference with host metabolism inducing various biochemical, endocrine, and immune disturbances of the host homeostasis, underlying certain paraneoplastic syndromes (78). The capacity of malignant tumors to exert hypoglycemic pressure on the host functioning as a chronic stress factor leads to the activation of the hypothalamus-pituitary system along with the energy-consuming process of stimulation of endogenous glucose formation from amino acids and glycerol. The compensatory role of the stimulated lipolysis supplying (in addition to glycerol) free fatty acids and ketone bodies for host tissues as energy

Table 2. Factors modifying the tumor growth in the elderly

Tumor's factors	**Host factors**		
	Humoral factors		**Local factors**
Tumor origin (histogenesis)	Hormones	Estrogens, androgens	Senescent cells
Differentiation		Glucocorticoids	Extracellular matrix
Estrogen receptors[1]		Growth hormone	Growth factors
Immunogenicity		IGF-1	Vascularization
Paracrine hormones and growth factors		Insulin	Beta-1 integrin
	Immunocompetent cells		TGF- beta-1
	Cytokines		
	Angiogenic factors		
	Cholesterol, VLDL		
	Free fatty acids		
	Glucose		

[1] Mainly for mammary tumors

sources is emphasized. It is suggested that the adaptive nature of reduced insulin secretion and glucose tolerance in the tumor-bearing host facilitates the synergistic effect of glucagon, catecholamines, and glucocorticoids counteracting hypoglycemic pressure of the tumor (78).

The experiments of Shapot and Shelepov (78) and some of our own studies show that transplantation of tumors of different histogenesis is followed by the development of different hormonal and metabolic shifts in these animals. Thus, the serum insulin level is decreased in rats with subcutaneously transplanted Pliss' lymphosarcoma, whereas in the rats bearing Walker-256 carcinoma or sarcoma-45 a trend to the increase in serum insulin level has been observed (14). The level of serum glucose and triglycerides was significantly different in rats bearing transplanted thyroid tumor or Walker-256 carcinoma (14). We suggest that such differences in the paraneoplastic syndrome parameters observed in animals bearing transplanted tumors of various histogenesis might be a cause of differences in the behavior of tumors transplanted into young and old hosts. In some cases, transplanted tumor can stimulate age-related hormone metabolic disturbances in the host that, in turn, could promote a tumor growth. In other cases, the shifts induced by the tumor in the internal milieu of the organism can alleviate the development of age-related changes promoting tumor growth, thus decreasing the rate of tumor growth in old organisms. Regional differences and variations in the vascular supply, pattern of nervous system development, expression of temperature differentials, and the establishment of metabolic gradients during development could also influence the rate of tumor growth (79).

6. CONCLUSION

Finalizing a discussion on clinical evidence for changes in tumor aggressiveness with age, Holmes (11) has stressed that those who believe that slowly growing tumors are associated with old age are correct, as are those who believe that rapidly growing tumors are associated with old age. He has also noted that site and tumor stage are two important determinants, and tumors in the elderly are just as diverse as groups of old people. Our analysis of available data on transplanted tumors in rodents performed two decades ago (14,22,76) as well as presented above in this paper, shows that there is no uniform pattern of the behavior of tumor cells in old organisms. Some tumors grow faster in young than in old, whereas others grow more slowly in young than in old. These differences depend on a number of factors, including those that are tumor-dependent and host-dependent (Table 2). There is evidence that implantation of metastatic tumor cells depends on humoral host factors, whereas the growth rate of metastases mainly depends on local (microenvironmental) host factors. Age-associated changes in both humoral and local host factors are critical for the behavior and progression of transplanted tumors in the old host, limiting the transplantability, growth rate and survival time of the tumor-bearer.

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8. REFERENCES

1. Ershler W.B., R.L. Gamelli, A.L. Moore, M.P. Hacker and A.J. Blow: Experimental tumors and aging: local factors that may account for the observed age advantage in the B16 murine melanoma model. *Exp Gerontol* 19, 367-376 (1984)
2. Ershler W.B., J.A. Steward, M.P. Hacjer, A.L. Moore and B.H. Tindle: B16 murine melanoma and aging: slower growth and longer survival in old mice. *J Natl Cancer Inst* 72, 161-164 (1984)
3. Ershler W.B.: Explanations for reduced tumor proliferative capacity with age. *Exp Gerontol* 27, 551-558 (1992)
4. Ershler W.B.: Tumor-host interactions, aging, and tumor growth. In: Comprehensive Geriatric Oncology. Eds: Balducci L., Lyman G.H., Ershler W.B. and Extermann M. Taylor and Francis Group, London 147-157 (2004)

5. Campisi J.: Cellular senescence as a tumor-suppressor mechanism. *Trends Cell Biol* 11, 27-31 (2001)
6. Campisi J.: Cellular senescence and apoptosis: how cellular responses might influence aging phenotypes. *Exp Gerontol* 38, 5-11 (2003)
7. Campisi J.: Aging, tumor suppression and cancer: high wire-act! *Mech Ageing Dev* 126, 51-58 (2005)
8. Krtolica A., S. Parinello, S. Lockett, P.Y. Desprez and J. Campisi: Senescent fibroblasts promote epithelial cell growth and tumorigenesis: a link between cancer and aging. *Proc Natl Acad Sci* USA 98,12072-12077 (2001)
9. Krtolica A. and J. Campisi: Integrating epithelial cancer, aging stroma and cellular senescence. *Adv Gerontol* 11, 109-116 (2003)
10. Balducci L.: Geriatric oncology. *Crit Rev Oncol Hematol* 46, 211-220 (2003)
11. Holmes F.F. Clinical evidence for change in tumor aggressiveness with age: A historical perspective. In: Comprehensive Geriatric Oncology. Eds: Balducci L., Lyman G.H., Ershler W.B. and.Extermann M. Taylor and Francis Group London, 180-186 (2004)
12. Gospodarowicz M.K., D.E. Henson, R.V.P. Hutter, B. O'Sullivan, L.H. Sobin and Ch. Wittekind: Eds: Prognostic Factors in Cancer, 2nd Edition., Geneva: UICC (2001)
13. Blinov N.N.: Age as a factor of prognisis in cancer. In: Cancer in the Elderly. Eds: Anisimov V.N., Moisseyenko V.M., Hanson K.P. St.Petersburg 138-151 (2004)
14. Anisimov V.N.: Carcinogenesis and Aging. Vol. 2. CRC Press, Boca Raton (1987)
15. Anisimov V.N.: The relationship between aging and carcinogenesis: a critical appraisal. *Crit Rev Oncol Hematol* 45, 277-304 (2003)
16. Anisimov V.N.: Age as a risk factor in multistage carcinogenesis. In: Comprehensive Geriatric Oncology. Eds: Balducci L, Lyman GH, Ershler WB and Extermann M. Taylor and Francis Group, London 75-101 (2004)
17. Peto R., F.J.C. Roe, P.N. Lee, L. Levy and J. Clack: Cancer and ageing in mice and men. *Br J Cancer* 32, 411-426 (1975)
18. Burnet F.M. Innmunology, Aging and Cancer. Medical Aspects of Mutation and Selection. Freeman and Co, San Francisco (1976)
19. Thompson S.C.: Effect of age and sex on lung colony forming efficiency of injected mouse tumour cells. *Br J Cancer* 34, 566-770 (1976)
20. Yuhas J.M. and R.L. Ullrich: Responsiveness of senescent mice to the antitumor properties of *Corynebacterium parvum. Cancer Res* 36, 161-166 (1976)
21. Gozes Y. and N. Trainin: Enhancement of Lewis lung carcinoma in a syngeneic host by spleen cells of C57BL/6 old mice. *Eur J Immunol* 7, 159-164 (1977)
22. Anisimov V.N. and N.V. Zhukovskaya: Effecr of age on the growth of transplantable tumors in mice. *Vopr Onkol* 27(8), 52-59 (1981)
23. Sadovnikova I.P., L.K. Obukhova, T.V. Bunto and L.D. Smirnov: Effect of age on kinetics of development of spontaneous and transplanted tumors and on the effectivity of chemotherapy. *Izv Acad Nauk SSSR, Ser Biol* 2, 543-550 (1984)
24. Hirayama R., K. Hirokawa and T. Makinodan: Change of metastatic mode of B16 malignant melanoma in C57BL/6 mice by aging and sex. In: Age-Related Factors in Carcinogenesis, IARC Sci. Publ. No. 58. Eds: Likhachev A., Anisimov V., Montesano R. IARC, Lyon 85-96 (1985)
25. Ehrlich R., N. Smorodinsky, M. Efrati, M. Yakubowicz and I.P. Witz: B16 melanoma development, NK activity and natural antibodies in 3 and 12 months old mice. *Br J Cancer* 49, 769-777 (1984)
26. Baumgart J., N.V. Zhukovskaya and V.N. Anisimov: Carcinogenesis and aging. VIII. Effect of host age on tumour growth, metastatic potential, and chemotherapeutic sensitivity to 1,4-benzoquinone-guanylhydrazone thiosemicarbazone (ambazone) and 5-fluorouracil in mice and rats. *Exp Pathol* 33, 239-248 (1988)
27. Hirayama R., K. Takemura, Z. Nihei, W. Ichikawa, Y. Takagi, Y. Mishima, M. Utsuyama and K. Hirokawa: Differential effect of host microenvironment and systemic humoral factors on the implantation and the growth rate of metastatic tumor in parabiotic mice constructed between young and old mice. *Mech Ageing Dev* 71, 213-221 (1993)
28. Pili R., Y. Guo, J. Chang, H. Nakanishi, G.R. Martin and A. Passaniti: Altered angiogenesis underlying age-dependent changes in tumor growth. *J Natl Cancer Inst* 86, 1303-1314 (1994)
29. Donin N., J. Sinai, A. Staroselsky, T. Mahlin, J. Nordenberg and J. Leibovici: Comparison of growth rate of two B16 melanomas differing in metastatic potential in young versus middle-aged mice. *Cancer Invest* 15, 416-421 (1997)
30. Kaptzan T., E. Skutelsky, O. Itzhaki, J. Sinai, M. Mechowitz, Y. Yossipov, G. Schiby and J. Leibovici: Age-dependent differences in the efficacy of cancer immunotherapy in C57BL and AKR mouse strains. *Exp Gerontol* 39, 1035-1048 (2004)
31. Itzhaki O., E. Skutelsky, T. Kaptzan, J. Sinai, M. Michowitz, M. Huszar and J. Leibovici: Ageing-apoptosis relation in murine spleen. *Mech Ageing Dev* 124, 999-1012 (2003)
32. Itzhaki O., T. Kaptzan, E. Skutelsky, J. Sinai, M. Michowitz, A. Siegal, G. Schibi, M. Huszar, L. Ben-Dor and J. Leibovici: Age-adjusted antitumoral therapy based on the demonstration of increased apoptosis as a mechanism underlying the reduced malignancy of tumors in the aged. *Biochim Biophys Acta* 1688, 145-159 (2004)
33. Aoki T., M.N. Teller and M-L. Robitaille: Aging and carcinogenesis. II. Effect of age on phagocytic activity of the reticuloendothelial system and on tumor growth. *J Natl Cancer Inst* 34, 255-264 (1965)
34. Rockwell, S.: Effect of host age on the transplantation, growth, and radiation response of EMT6 tumors. *Cancer Res* 41, 527-531 (1981)
35. Gravekamp C., R. Sypniewska and L. Hoflack: The usefulness of mouse breast tumor models for testing and optimization of breast cancer vaccines at old age. *Mech Ageing Dev* 125, 125-127 (2004)
36. Gravekamp C., R. Sypniewska, S. Gaunte, M. Tarango, P. Price and R. Reddick: Behavior of metastatic and nonmetastatic breast tumors in old mice. *Exp Biol Med* 229, 665-675 (2004)
37. Bellami D. and S.M. Hinsull: Effect of host age on the growth and mitotic index of experimental tumors in laboratory rat. *J Clin Exp Gerontol* 1, 57-77 (1979)
38. McCullough K.D., W.B. Coleman, G.J. Smith and J.W. Grisham: Age-dependent regulation of the tumorigenic

potential of neoplastically transformed rat liver epithelial cells by the liver microenvironment. *Cancer Res* 54, 3668-3671 (1994)
39. McCullough K.D., W.B. Coleman, G.J. Smith and J.W. Grisham: Age-dependent induction of hepatic tumor regression by the tissue microenvironment after transplantation of neoplastically transformed rat liver epithelial cells into the liver. *Cancer Res* 57, 1807-1813 (1997)
40. McCullough K.D., W.B. Coleman, S.L. Ricketts, J.W. Wilson, G.J. Smith and L.W. Grisham: Plasticity of the neoplastic phenotype n vivo is regulated by epigenetic factors. *Proc Natl Acad Sci USA* 95, 15333-15338 (1998)
41. Coleman W.B., A.E. Wennerberg, G.J. Smith and J.W. Grisham: Regulation of the differentiation of diploid and some aneuploid rat liver epithelial (stem-like) cells by the hepatic microenvironment. *Am J Pathol* 142, 1373-1382 (1993)
42. Maruo K., Y. Ueyama, Y. Kuwahara, K. Hioki, M. Saito, T. Nomura and N. Tamaoki: Human tumour xenografts in athymiv rats and their age dependence. *Br J Cancer* 45, 786-789 (1982)
43. Pozharisski K.M., L.G. Prvanova, V.N. Anisimov and V.F. Klimashevski. Effect of ageing on colon carcinogenesis. *Exp Oncol* 2 (2), 20-22 (1980)
44. Turusov V.S., N.S. Lanko and Yu.D. Parfenov. Influence of age on induction of colon tumors in mice by 1,2-dimethylhysrazine. *Bull Exp Biol Med* 92, 705-707 (1981)
45. Kubota K., R. Kubota, S. Takeda and T. Matsuzawa: Effect of age and sex of host mice on growth and differentiation of teratocarcinoma OTT6050. *Exp Gerontol* 16, 371-384 (1981)
46. Teller M.N., G. Stohr, W. Curlett, M.L. Kubisek and D. Curtis: Aging and carcinogenesis. I. Immunity to tumor and skin grafts. *J Natl Cancer Inst* 33, 649- 656 (1964)
47. Perkins E.H.: A multiple parameter comparison of immunocompetence and tumor resistance in aged BALB/c mice. *Mech Ageing Dev* 6, 15-24 (1977)
48. Teller M.N., M. Bowie and I.M. Mountain: Influence of age of host on the chemotherapy of murine myeloma LCP-1. *J Gerontol* 29, 360-365 (1974)
49. Goldin A., J.M. Vendetti and S.R. Humphreys: Factors influencing the specificity of action of an antileukemic agent (aminopterin): host age and weight. *J Natl Cancer Inst* 16, 709-721 (1955)
50. Rodriguez P.E., Y.P. De Bonaparte, L. D'Elia and D. Klein: Studies on NZB mice. III. Failure of growth of isogeneic tumors transplanted to old NZB mice. *Sangre* 21, 805-813 (1976)
51. Loefer J.B.: Effect of age of the donor on development of rat tumor grafts. *Cancer* 5, 163-165 (1952)
52. Keller R.: Reduced spontaneous antitumor resistance of the elderly rat is restored by *Corynebacterium parvum*. Br. *J Cancer* 38, 557-560 (1978)
53. Hollingsworth M.A., J. Barrowclough and D.L. Evans: Age-related increases in mitogenic responses and natural immunity to a syngeneic fibrosarcoma in rats. *Mech Ageing Dev* 14, 95-106 (1981)
54. Hollingsworth M.A. and D.L. Evans: Changes in spleen cell proliferative responses and resistance to syngeneic tumor challenge in aging NBR rats. *Mech Ageing Dev* 22, 321-333 (1983)
55. Stjernward J.: Age-dependent tumor-host barrier and effect of carcinogen-induced immunodepression on rejection of isografted methylcholanthrene-induced sarcoma cells. *J Natl Cancer Inst* 37, 505-512 (1966)
56. Tagliabue A., W. Luini, G. De Vito and D. Boraschi: Effect of the age-related immune depression induced by MTV on *in vivo* growth of a mammary carcinoma. *Br J Cancer* 44, 460-463 (1981)
57. Flood P.M., J.L. Urban, M.L. Kripke and H. Schreiber: Loss of tumor-specific and idiotype-specific immunity with age. *J Exp Med* 154, 275-290 (1981)
58. Bazlova L.S.: Transplantation of uterine sarcoma induced in CBA mice by 1,2-dimethylhydrazine. *Vopr Onkol* 9, 80-82 (1978)
59. Anisimov V.N., N.V. Zhukovskaya, A.S. Loktionov and Yu.B. Vakhtin: Influence of host age on lung colony forming capacity of injected rat rhabdomyosarcoma cells. *Cancer Lett* 40, 77-82 (1988)
60. Burns E.A. and J.S. Goodwing: Immunological changes of aging. In: Comprehensive Geriatric Oncology. Eds: Balducci L., Lyman G.H., Ershler W.B. and.Extermann M, Taylor and Francis Group, London, 158-170 (2004)
62. Kreisle R.A., B.A. Stebler and W.B. Ershler: Effect of host age on tumor- associated angiogenesis in mice. *J Natl Cancer Inst* 82, 44-47 (1990)
63. Goodman S.A. and T. Makinodan. Effect of age on cell-mediated immunity in long-lived mice. *Clin Exp Immunol* 19, 533-542 (1975)
64. Park C.C., M.J. Bissell and M. Barcellos-Hoff: The influence of the microenvironment on the malignant phenotype. *Mol Med Today* 6, 324-329 (2000)
65. Liotta L.A. and E.C. Kohn. The microenvironment of the tumor-host interface. *Nature* 411, 375-379 (2001)
66. Dilman V.M.: Development, Aging and Disease. A New Rationale for an Intervention Strategy. Chur: Harwood Academic Publ (1994)
67. Fernandez-Pol J.A.: Growth factors, oncogenes, and aging. In: Comprehensive Geriatric Oncology. Eds: Balducci L, Lyman GH,.Ershler WB and Extermann M.: Taylor and Francis Group., London 102-126 (2004)
68. Hornebeck W., H. Emonard, J.C. Monboisse and G. Bellon: Matrix-directed regulation ofpericellular proteolysis andtumor progression. *Sem Cancer Biol* 12, 231-241 (2002)
69. Robert L.: Cell-matrix interactions in cancer spreading – effect of aging. *Sem Cancer Biol* 12, 157-163 (2002)
70. Robert L. and J. Labat-Robert: Aging of connective tissues: from genetic to epigenetic mechanisms. *Biogerontology* 1, 123-131 (2001)
71. Itahana K., J. Campisi and G.P. Dimri: Mechanisms of cellular senescence in human and mouse cells. *Biogerontology* 5, 1-10 (2004)
72. Ershler W.B. and D.L. Longo: The biology of aging. The current research agenda. *Cancer* 80, 1284-1293 (1997)
73. Bergers G. and L.E. Benjamin: Tumorigenesis and the angiogenic switch. *Nature Rev Cancer* 3, 401-410 (2003)
74. Franco S., I. Segura, H.H. Riese and M.A. Blasco: Decreased B16F10 melanoma growth and impaired vascularization in telomerase-deficient mice with critically short telomeres. *Cancer Res* 62, 552-559 (2002)
75. Nickoloff B.J., M.W. Lingen, B.D. Chang, M. Shen, M. Swift, J. Curry, P. Bacon, B. Bodner and I.B. Roninson:

Tumor suppressor mapsin is up-regulated during keratinocyte senescence, exerting a paracrine antiangiogenic activity. *Cancer Res* 64, 5. 2956-2961 (2004)
76. Anisimov V.N. Carcinogenesis and aging. *Adv Cancer Res* 40, 365-424 (1983)
77. DePinho R.A.: The age of cancer. *Nature* 408, 248-254 (2000)
78. Shapot V.S. and V.P. Shelepov: Interrelations and trigger mechanisms of homeostatic disorders in a tumor-bearing host. *Arkh Pathol* 45(8), 3-12 (1983)
79. Auerbach R. and W. Auerbach: Regional differences in the growth of normal and neoplastic cells. *Sciences* 215, 127-134. (1982)

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