Host Age Is a Systemic Regulator of Gene Expression Impacting Cancer Progression

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Abstract

Aging is the major determinant of cancer incidence, which, in turn, is likely dictated in large part by processes that influence the progression of early subclinical (occult) cancers. However, there is little understanding of how aging informs changes in aggregate host signaling that favor cancer progression. In this study, we provide direct evidence that aging can serve as an organizing axis to define cancer progression-modulating processes. As a model system to explore this concept, we employed adolescent (68 days), young adult (143 days), middle-aged (551 days), and old (736 days) C57BL/6 mice as syngeneic hosts for engraftment of Lewis lung cancer to identify signaling and functional processes varying with host age. Older hosts exhibited dysregulated angiogenesis, metabolism, and apoptosis, all of which are associated with cancer progression. TGFβ1, a central player in these systemic processes, was downregulated consistently in older hosts. Our findings directly supported the conclusion of a strong host age dependence in determining the host tumor control dynamic. Furthermore, our results offer initial mechanism-based insights into how aging modulates tumor progression in ways that may be actionable for therapy or prevention. Cancer Res; 75(6); 1134–43. ©2015 AACR.

Introduction

It is widely appreciated that with aging comes an increasing risk of cancer incidence, yet epidemiologic data indicate that at ages greater than about 60 years, the rate at which incidence increases begins to diminish, and at sufficiently old ages, may even decrease (1–3). Several factors likely contribute to the diminished incidence in older adults, including that the data may not be as reliable for older individuals (3). This explanation is insufficient, however, as studies in animal models demonstrate the same pattern (4). A second contributing factor is variation among individuals in intrinsic cancer susceptibility, also referred to as frailty (5). Genetically susceptible individuals develop and succumb to cancer earlier, leaving, on average, a population less susceptible.

Third, age-dependent host influences can modify tumor promotion and progression (3, 6), and at sufficiently old ages, may be sufficiently inhibitory to lower clinical incidence. Recently, Lopez-Otin and colleagues (7) identified nine ubiquitous "hallmarks" of aging: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication. Genomic instability and epigenetic alterations have also been identified as key processes in carcinogenesis (8). Mitochondrial dysfunction can induce increased cell apoptosis with age within the tumor and host, resulting in tumor growth, no tumor growth, or even tumor regression (8, 9). Older hosts may have a higher percentage of cells that are either senescent or have reduced proliferation capability, again impacting tumor growth and therapeutic response (3, 10).

In addition, the altered expression of angiogenic factors as a function of age (11) may cause tumors from older hosts to induce less vascular support from the host, reducing tumor capillary density (12), and a reduced functionality of hematopoietic stem cells in older hosts may compromise tumor progression (13, 14). The limited murine studies conducted to date have demonstrated that tumor progression is slowed in older hosts (1, 15–17). Among the models used include B16-F10 melanoma (15, 18), Ehrlich–Holm–Swann (EHS) carcinoma (17), Lewis lung carcinoma (LLC; refs. 1, 19), prostate TRAMP-C2 (11), and fibrosarcoma (20, 21). Proposed mechanistic rationales include decreased angiogenesis (11, 16), reduced proliferation capacity, increased cellular senescence (3, 10), and altered immune response (19–21).

Beyond being isolated associations between age and tumor progression, however, we propose such findings are glimpsing a broad set of carcinogenesis controls orchestrated by the host through the aging process. To identify these controls, the same tumor cells (LLC) were used throughout, assuring the observed modulation of tumor growth dynamics and molecular profiles in the resulting tumors stemmed specifically from host aging. In this setting, any influence of host age on tumor development would be expected to be the result of both host-specific adaptive and selective environmental pressures on the injected tumor cells themselves, along with the overall influence of host cells (e.g., stromal, epithelial, immune, etc.) recruited into the developing tumors.

Global differential transcriptome analyses performed on the excised tumors across the various age cohorts revealed genes
critical in the regulation of cancer progression. TGFβ1, involved in a considerable number of carcinogenesis steps (22, 23), was found to be key. Employing a systems approach, the cohort-dependent tumor growth dynamics were further linked to the underlying biology using a modified version of the widely used tumor growth model of Hahnfeldt and colleagues (24). This model pioneered the inclusion of a variable rather than constant tumor ‘carrying capacity,’ that is, the potential tumor size a host can support. In this study, a substantial age dependence in carrying capacity was found, as quantified by the model equation parameters capturing the age-dependent balance between molecular processes acting to stimulate versus inhibit tumor progression.

Materials and Methods

Cell culture
Murine LLC cells, originally derived from a spontaneous tumor in a C57BL/6 mouse (25), were obtained from ATCC. Cells were cultured under standard conditions (25) in high-glucose DMEM (Gibco Invitrogen Cell Culture) with 10% FBS (Gibco In vitrogen Cell Culture), 100 μg/mL penicillin/streptomycin, and 5% CO2.

Tumor injections
Sixty C57BL/6 male mice, with an average lifespan of 878 days (26), were used in this study. At the time of injection, mice were 68 days (n = 20; Jackson Laboratory), 143 days (n = 10; Jackson Laboratory), 551 days (n = 10; National Institute on Aging, NIA), and 736 days (n = 20; NIA). Scaling of mouse to human age was accomplished using published criteria (27). Age comparisons are as follows: mouse ages in days were 68 (adolescent), 143 (young adult), 551 (middle-aged), and 736 (old), considered equivalent, respectively, to ages of 17, 23, 58, and 75 years for humans. Subcutaneous injections of 10⁶ LLC cells in 0.2-mL PBS were respectively, to ages of 17, 23, 58, and 75 years for humans.

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Real-time quantitative PCR
RNA was isolated from tumor tissue in TRIzol (Invitrogen) according to manufacturer’s instructions as was previously reported (1). Quality and quantity of RNA were measured by an Agilent 2100 Bioanalyzer (Agilent Technologies, Inc.). TGFβ1 TaqMan Gene Expression Assays (Applied Biosystems) were used to probe for TGFβ1 gene expression. Assays were performed with technical duplicates on the Applied Biosystems 7300 Real Time PCR System, and data were analyzed using the method of Schmittgen and Livak (28).

Transcriptome analysis
For genome-wide expression profiling of tumor tissue, mouse WG-6 bead array chips (Illumina) were used, and methods as previously reported (1). For tumor replicates, 20 tumor samples from adolescent, 10 from young adult, 10 from middle-aged, and 20 from old mice were used. Data were corrected through normalization of the housekeeping genes, quantile normalized, and then imported into MultiExperiment Viewer, MeV (29) for analysis. Statistically significant genes were determined by applying a one-way ANOVA with an adjusted Bonferroni correction and false discovery rate (FDR) < 0.05 that resulted in a list of 2,596 significant genes. Further details are available in the Supplementary Methods.

Immunofluorescence staining
Standard immunofluorescent staining protocols were used. More details appear in the Supplementary Methods.

Western blot analyses
Total protein was extracted from snap-frozen tissue by a standard extraction protocol and placed in RIPA lysis buffer. Tissue was homogenized using a Tissue Lyser II (Qiagen). Samples were centrifuged at 13,000 rpm for 15 minutes, and supernatant was collected for protein analysis. Quality and quantity of proteins were measured by a Beckman Coulter DU800 spectrophotometer. A 50-μg quantity of total protein from each tissue lysis was separated on a 10% Tricine protein gel (Life Technologies) at 125 V for 1 hour and transferred to nitrocellulose membranes (Amersham Biosciences) at 22 V for 1.5 hours. Membranes were blocked in PBS containing 0.05% Tween 20 and 5% nonfat dry milk for 1 hour and then probed with TGFβ1 antibody (catalog #: ab64715, Abcam), overnight at 4°C. After washing, membranes were incubated with horseradish peroxidase-conjugated secondary antibody (diluted 1:2000, catalog #: sc-2004, Santa Cruz Biotechnology) for 1 hour, room temperature. An ECL Plus Detection Kit (Amer sham Biosciences) was used to visualize bands by chemiluminescence. GAPDH (catalog #: sc25778, Santa Cruz Biotechnology) was used as a technical control.

Model for tumor dynamics
A well-established 2-dimensional ordinary differential equation model by Hahnfeldt and colleagues (24) was used that incorporates host influence on tumor growth, having as variables the tumor volume, V, and its carrying capacity, K, characterizing the tumor microenvironment. Details and calculations are available in the Supplementary Methods.

Statistical analysis
The Student t tests were used for statistical analysis as appropriate. All P values were calculated using 2-tailed tests. Differences were considered statistically significant if P < 0.05. Error bars in the graphs represent SEs.

Nonlinear regression was used to fit the tumor growth phase data with curves of the form V = bV², where V is tumor volume and t is time, as described in Supplementary Methods.

Results
Tumor dynamics as a function of age
A syngeneic in vivo model was constructed to assess modulation of posttransformation tumor advancement as a function of host age by implanting LLC cells, a tumor line originating from a spontaneous cancer in a C57BL/6 mouse (30), into adolescent, young adult, middle-aged, and old wild-type C57BL/6 mice. Our intent was to identify host age–dependent differentials in genetic regulation and tumor growth dynamics.
in a population of already-transformed cells, as opposed to age-dependent processes that may act in a more generalized manner at other stages in carcinogenesis; for example, at cancer cell initiation or transformation.

Measurements of tumor growth rates showed tumor advancement/progression to be substantially inhibited in the old mice compared with all other age groups (Fig. 1A). Interestingly, tumor growth was slower in the adolescent than in the young adult and middle-aged mice but was still significantly faster than in the old mice.

**Signaling differentials in tumors as a function of age**

Despite all mice being injected with the same LLC cells, a host age–dependent regulation of the tumor transcriptome was evident. An examination of the 2,596 significant genes expressed in tumor samples (FDR < 0.05) revealed overall expression profiles for tumors grown in old mice to deviate significantly from those in mice of other ages (Fig. 1B and C). A 1.2-fold regulation change limit revealed 571 common genes (304 upregulated and 267 downregulated; Fig. 1D).

Upstream regulator analysis using Ingenuity Pathway Analysis (IPA) additionally suggests a progressive shift of upstream regulation toward inhibition of signalings enabling tumor advancement with increasing age, with the exception of the “Adolescent” group, ordered as follows: “Young Adult” (Y), “Middle-Aged” (M), “Adolescent” (A), “Old” (O), referred to henceforth by the acronym “YMAO” (Table 1, Supplementary Table S1, and Fig. 2). To demonstrate the pervasiveness of this finding, information from the literature was compiled on the impact on tumor progression (i.e., inhibition, promotion, or both) for each activated upstream regulator for all age groups (Supplementary Table S1). When comparing any age category with another on its left in the sequence YMAO, the vast majority of the inhibited upstream regulators were found to be associated with enhancement of tumor progression, whereas the sizeable majority of the activated upstream regulators was found to inhibit tumor progression (Fig. 2 and Supplementary Table S1). Interestingly, the Y>M>A>O ordering of tumor growth rates, exhibited among the 4 age groups (Fig. 1A), recapitulates these findings.

To identify mechanisms of age-dependent tumor control, upstream regulators were determined and compared (Table 1, columns 4–6). Four highly differentially expressed regulators were identified: FGF2, ANGPT2, IL5, and TGFβ1 (Table 1). These 4, all tumor promoters (22, 31–33), were predicted to be significantly inhibited in old mice. Both FGF2 (31) and ANGPT2 (32) are angiogenesis-associated factors, whereas IL5 is involved in angiogenesis and immune response (34, 35) and TGFβ1 in many functions including vascular development and angiogenesis (36). FGF2 has also been shown to induce proliferation of fibroblasts through TGFβ1 signaling, which affects extracellular matrix...
ECM production (37). Increased production of ECM has been associated with an increased degree of angiogenesis (38). In aggregate, the predicted inhibition of all these regulators suggests a lowered angiogenic state for tumors growing in aged hosts.

Apart from angiogenesis modulation, two additional functions were determined by IPA to be downregulated in old hosts: metabolism (Supplementary Table S2) and apoptosis (Supplementary Table S3). Curiously, our findings support the paradoxical implication that downregulation of apoptosis tends to slow tumor growth, a dynamic we previously rationalized in another context (39). Overall, these regulations may be revealing a global gene and biofunction alignment of action closely tied to the aging process.

Modeling age-dependent tumor progression dynamics

Changes in the growth dynamics attributable to the age-dependent tumor-carrying capacity (the capacity of the host to support tumor development) were examined from a quantitative perspective to link and integrate these findings with the mechanistic insight gained from the transcriptome studies. A connection between tumor dynamics and host age was made using a standard mathematical model, originally constructed by...
Hahnfeldt and colleagues (24), which accounts for a varying carrying capacity:

\[
\frac{dV}{dt} = aV \ln \left( \frac{K}{V} \right), \quad V(0) = V_0
\]

\[
\frac{dK}{dt} = bV - dV^2K, \quad K(0) = K_0
\]

with \( V \) = tumor volume, \( K \) = host-carrying capacity, \( V_0 \) = initial volume at time \( t = 0 \), \( K_0 \) = initial carrying capacity at time \( t = 0 \), \( a \) = proliferation of the tumor cells, \( b \) = net carrying capacity stimulation, and \( d \) = net carrying capacity inhibition. The value \( V_0 \) was fixed to the first nonzero data value for each mouse. The four remaining parameters, \( a, b, d, \) and \( K_0 \), were estimated by fitting to individual mouse mouse tumor growth data points for all age groups. The average per age group was taken from the individual fits to each mouse (Fig. 3A). This model assumes that age-related changes in the host-carrying capacity will directly influence tumor growth characteristics; and that tumor growth, conversely, has the potential to influence host-carrying capacity.

Not unexpectedly, changes in the parameter \( a \), reflecting intrinsic tumor cell proliferation ability, did not increase to significance among the different age groups (Fig. 1A), whereas the remaining parameters were all heavily dependent on changes occurring in the host tissues. Interestingly, the host-carrying capacity inhibition coefficient, \( d \), was significantly larger for the old mice than for the adolescent group. At the same time, a corresponding downward trend in carrying capacity stimulation \( b \) was observed with age. Protein and transcriptome differentials observed in tumors from old mice compared with other age groups underscore these findings from quantitative analysis (Fig. 3A), pointing again to host mechanisms that inhibit tumor advancement to a greater degree in the old animals.

**Tumor proliferation and angiogenic expression**

Proangiogenic factors within the tumors were predicted by upstream regulator analysis to depend on host age, with the greatest downregulation being in tumors of old mice (Table 1). Quantitative examination of tumor tissue stained with CD31, a glycoprotein marker of endothelial cells (12) determined that the microvascular density was reduced in tumors of old mice (Fig. 5F).

Immunofluorescent staining of tumors with the cell proliferation marker Ki67 did not show a significant dependence of tumor proliferation on host age. This result is in agreement with the finding of less-than-significant differences in the model parameter "\( a \)" (tumor cell proliferation capacity; Fig. 3A), although the tumor growth curve fits previously discussed do suggest some limited dependence on "\( a \)" in the case of the adolescent versus the young adult and middle-aged cohort comparisons (see Discussion).

**Modulation of TGFβ1 in tumors as function of host age**

TGFβ1, well known to be actively involved in cell growth, differentiation, and migration in cancer cells (23, 40), was found to be significantly downregulated in tumors of old mice compared with the other cohorts (Table 1). This finding is reconciled with the reported biphasic behavior of TGFβ1—as an early-stage tumor suppressor and a late-stage tumor promoter (40–43)—when it is considered that tumors collected in this study all represent late-stage disease from the carcinogenesis perspective.
Tumor samples from old mice were further compared with those from the other age groups to assess biofunction regulations associated with common genes predicted to be involved in upstream regulation of tumor advancement and progression. A network of 18 key genes was found to be important (Fig. 4 and Supplementary Table S4), including TGFβ1 as a central node upstream of most (Fig. 4). This finding strongly indicates that TGFβ1 plays a central role in regulating key age-dependent molecular processes impacting tumor advancement.

Interestingly, these 18 genes share the same YMAO ordering in cohort comparisons as did tumor growth rates and the general set of upstream regulators of progression discussed earlier. Specifically, they tended to have a net inhibitory or stimulatory influence on tumor progression, depending on whether the comparisons were between a cohort and one to its left in the YMAO ordering, specifically, O vs. M, O vs. Y, O vs. A, and M vs. Y (Fig. 4, Fig. 5A, Supplementary Table S4), or between a cohort and one to its right in that ordering, specifically, M vs. A, and Y vs. A (Fig. 4 and Supplementary Table S4). Accordingly, the impact of these genes on tumor progression as reported from the literature, combined with fold change analysis, show that the majority will contribute to slower tumor progression in older hosts (Fig. 5A).

Figure 4. Gene network analysis for 18 key genes involved in age-dependent tumor progression. Pathway analysis was done with IPA software. The network depicted contains a central node for TGFβ1 connected to the other 17 genes with direct (solid lines) and indirect (dashed lines) relationships to these molecules. Log₂-fold changes to the gene expression were used to obtain shades of green for regulation levels for the downregulated (>1.2-fold) genes, whereas shades of red depict regulation levels for the upregulated (>12-fold) genes. Gray, genes that exist in the network without a significant 12-fold change under the perturbation investigated. The darker the shade of green or red, the greater the fold change.

Gene Set Enrichment Analysis (GSEA) was additionally performed (Supplementary Table S5). Three genes in common with the GSEA gene sets and the 18 genes found through IPA were found: TGFβ1, EIF3A, and PDIA3 (Fig. 5A and Supplementary Table S4). EIF3A and PDIA3 are known to increase apoptosis in tumors and have been associated with increased tumor malignancy (44, 45). Three statistically significant functional analyses of the array data show TGFβ1, EIF3A, and PDIA3 to be common genes affecting many biologic functions impacting growth dynamics in an age-dependent manner, with TGFβ1 likely a critical driver.

To validate the regulation of TGFβ1, real-time PCR (RT-PCR) and Western blot analysis, along with immunofluorescent protein staining, were performed. As expected, RT-PCR confirmed the age dependence of TGFβ1 mRNA expression closely paralleled as shown by the array analysis (Fig. 5B). Tumors from old mice
exhibited significantly reduced TGFβ1 expression compared with young and adolescent mice and a very substantial decrease compared with middle-aged mice. TGFβ1 protein levels were lowest for tumors from old mice. This was confirmed by immunofluorescent staining and Western blot analysis (Fig. 5C and D). Immunofluorescent staining for TGFβ1 was done along with staining for vimentin (typically found in mesenchymal or stromal cells) to distinguish host cells from injected LLC (epithelial) cells. TGFβ1 staining tended to colocalize with regions of vimentin staining (Fig. 5D), indicating host tissue involvement.

To examine TGFβ1 activity, tumors were dual-stained for TGFβ1 and α-smooth muscle actin (αSMA), a recognized marker for fibroblast activation and myofibroblast differentiation in tumors (46, 47). Of note, active TGFβ1 has been shown to increase the number of αSMA-positive fibroblasts, and at high enough levels, leads to alterations in the stroma, facilitating tumor promotion through the conversion of activated fibroblasts to the myofibroblast phenotype, along with an increased production of angiogenic factors (46, 47). Tumors in young adult and middle-aged hosts exhibited higher levels of both αSMA and TGFβ1 staining, with evident co-localization in areas, suggesting that TGFβ1 may be actively involved with the tumor dynamics observed (Fig. 5E).

**Discussion**

We demonstrated that aging has considerable impact on the ability of the host to support and advance tumor development. While epidemiologic data show cancer incidence to increase with age, whether age-dependent changes in the host can limit tumor growth enough to actually offset the drivers of cancer incidence remains open due to the scant effort to date to decouple the age-dependent processes of tumor cell initiation and progression. However, the potentially critical importance of the age-dependent tumor–host interaction is underscored by 2 considerations: (i) there is increasing evidence suggesting that microscopic cancers are present in a much greater fraction of people than become symptomatic with disease and (ii) aging is a strong determinant of both cancer incidence and the state of host tissues that interact with cancer to modulate progression. It follows that aging may be
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Figure 6.
Overlap of genes associated with the nine hallmarks of aging, with those 2,596 significant genes identified with tumor progression and aging with FDR < 0.05. Average signal log2-fold change comparing adolescent (A), young adult (Y), middle-aged (M), and old (O) are shown as both dot and box plots for each hallmark. Whiskers show the range of the outliers, with maximum and minimum values as ○ and the 1st and 99th percentile outliers as ×. The percentage of genes from each hallmark that are represented among the 2,596 significant genes is given in the bottom left for each plot. The location of TGFβ1 is highlighted with a red open circle to indicate in which hallmarks it is involved.

an organizing axis for understanding (progression-driven) clinical cancer incidence. The focus of this study was therefore not on the early stages of tumor formation with accumulation of mutations and carcinogenic factors over time but on the direct effect of the host on tumor progression as a function of age.

In the recent review by Lopez-Otin and colleagues (7), nine hallmarks were enumerated as indicative of the aging process. We demonstrated that expression of genes associated with these hallmarks within tumors from old hosts was mostly downregulated compared with the other cohorts (Fig. 1) and largely paralleled regulation of the aging hallmarks (Fig. 6 and Supplementary Table S6). A notable exception was genomic instability (Fig. 6). This finding may be of considerable importance in that it points to host-driven induction of instability.

Inhibition of angiogenic activity, as predicted through upstream regulator analysis, was consistent with the decreased microvascular density (12) observed in tumors from aged hosts (Fig. 5F) and in agreement with previous reports (16). Two additional hallmark functions, metabolism and apoptosis (48, 49), were found to be dysregulated in tumors of old hosts. The proapoptotic genes PDIA3 (ERp57) and EIF3A (44, 45) were strongly suppressed in tumors from the aged mice, a response consistent with the observed inhibition of tumor progression (Fig. 5A and Supplementary Table S4). This, along with the observed dysregulation of the apoptosis pathway generally (Supplementary Table S3), suggests a generalized downregulation of apoptosis in these tumors. Some recent studies have shown a decreased tumor cell apoptosis associated with a decreased tumor growth (50).

Analysis of age-dependent tumor dynamics was also made via a quantitative carrying capacity model, originally constructed to analyze how tumor-host interactions define host support for tumor growth (24) but extended here to measure the host age dependence of this support. The model fittings are consistent with a corresponding net increase in expression of inhibitory factors, for example, tumor-suppressive proteins, in old hosts (parameter \( d \) in Fig. 3A) that contribute to inhibit tumor advancement (Fig. 1A). It is interesting to note that although old hosts show the slowest tumor progression, adolescent hosts also exhibit slower tumor progression when compared with that seen for the young adults or middle-aged hosts (Fig. 3B). Lower values for tumor growth rate (Fig. 1A) and TGFβ1 expression (Fig. 5) for the adolescent group versus young adult and middle-aged hosts were also observed. This occurred despite the substantially lower carrying capacity inhibition \( d^* \) and slightly higher carrying capacity stimulation \( b^* \), seen in the adolescent hosts (Fig. 3A). In terms of the quantitative modeling, it would appear a lower value for the remaining growth-modulating parameter \( a^* \) may be contributory despite the insignificance of the difference of these values when measured directly. Further work is currently being performed to explore this phenomenon.

Additional analysis was able to pinpoint three key genes involved in facilitating the slow-down in tumor advancement observed in the older hosts, with TGFβ1 being the critical player (Supplementary Table S3 and Fig. 5A). From the upstream regulator analysis, the predicted inhibition of TGFβ1 in tumors from older hosts (Table 1) was consistent with the observed inhibition of progression. Of the three key genes downregulated (Supplementary Table S4), TGFβ1 appears to be a dominant factor involved in slowing tumor progression in older hosts (Fig. 4). Differences in TGFβ1 expression within the tumors of the various age cohorts (Fig. 5D and E), confirm the host regulation of this tumor factor. The active form of TGFβ1 appears to be regulating αSMA in tumors from the young adult and middle-aged hosts, whereas the reduced activity of TGFβ1 significantly reduced the αSMA levels for the oldest hosts (Fig. 5E), suggesting that the...
reduction of tumor growth observed for old hosts may be potentially driven by modulation of activated fibroblasts in the stroma as a function of age (46, 47). TGFβ1 is involved in seven of the nine hallmarks of aging (Fig. 6). The finding of lower levels of TGFβ within tumors from aged hosts has some support in clinical literature (51, 52).

In conclusion, we have shown that tumor progression is generally inhibited with age in this model, with the exception of a possible suppression in youngest hosts (human equivalent of 17-year olds) that rivals the inhibition seen with the oldest hosts. Whether that exception is somehow connected to the clinically unique aspects of pediatric cancers is not known. What is clear is that the decreases in progression exhibited at the older ages consistently involve a number of processes considered to be both cancer (8) and aging hallmarks (7). These age-dependent tumor-inhibitory effects were attributed to classes of genes, including those regulating metabolism, and transcriptional regulators affecting angiogenesis and apoptosis. More generally, aging itself appears to be a powerful orchestrator of global gene regulations and tissue functions that collectively tend to resist changes characteristic of advancing cancer disease (53). The ability of host age to exert control over such a panoply of tumor progression regulators should allow the use of age as an “organizing axis” to gain a more sweeping understanding of a cancer progression process that has heretofore challenged such understanding at the level of individual genes.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

References


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