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Original Research

Microarray Analysis of Ageing-related Signatures and Their Expression in Tumors Based on a Computational Biology Approach

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Abstract

Ageing and cancer have been associated with genetic and genomic changes. The identification of common signatures between ageing and cancer can reveal shared molecular mechanisms underlying them. In this study, we collected ageing-related gene signatures from ten published studies involved in six different human tissues and an online resource. We found that most of these gene signatures were tissue-specific and a few were related to multiple tissues. We performed a genome-wide examination of the expression of these signatures in various human tumor types, and found that a large proportion of these signatures were universally differentially expressed among normal vs. tumor phenotypes. Functional analyses of the highly-overlapping genes between ageing and cancer using DAVID tools have identified important functional categories and pathways linking ageing with cancer. The convergent and divergent mechanisms between ageing and cancer are discussed. This study provides insights into the biology of ageing and cancer, suggesting the possibility of potential interventions aimed at postponing ageing and preventing cancer.

Keywords: Microarray; Gene expression profiling; Ageing-related signatures; Tumor; Bioinformatics

Introduction

Ageing is characterized by the gradual decline of the functions of molecules, cells, tissues, organs and organisms. The use of microarray technology to analyze gene expression changes in ageing tissues is a powerful tool for identifying biomarkers of ageing. Several groups have performed genome-wide analyses of transcriptional profiling of ageing in some human tissues including brain [1–3], eye [4–7], kidney [8,9], muscle [10–12], skin [13] and blood [14,15], and several sets of tissue-specific signatures of aging were marked. Magalhaes et al. performed a meta-analysis of ageing-related gene expression profiles using 27 datasets from mice, rats and humans and identified several common signatures of aging [16]. McCarroll et al. systematically compared gene expression patterns across organisms and identified shared transcriptional profiles of ageing [17]. These studies have revealed that ageing and ageing-related diseases have been associated with genetic and genomic changes.

Ageing is the greatest risk factor for cancer as cancer incidence rises exponentially with age [18]. Therefore, uncovering the molecular links between ageing and cancer will be of great significance in preventing and treating cancer. Accumulated evidence has shown that ageing and carcinogenesis share some key molecular mechanisms such as telomerase activity [19–21], p53-mediated transcriptional programming [22–24], mitochondrial DNA mutation [25–27], FOXO transcriptional regulation [28–30] and stem cell turnover [31–33], etc.

A genome-wide examination of the expression of ageing-related signatures in tumors will deepen our understanding of the association between ageing and cancer. However, to our knowledge, no such study has been carried out. In this study, we investigate the association between ageing and cancer by an extensive examination of the expression of ageing-related genes in various human tumor types. Our

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results provide insights into the common biology of ageing and cancer.

Results

Human ageing-related genes

We identified 3359 ageing-related genes in human based on 10 relevant publications (**Table 1** and Table S1). We termed these 3359 genes as ageing-related gene set (AGS). The complete gene list of AGS along with their occurrence frequencies in the 10 gene sets (from 10 publications, respectively) are presented in Table S2.

Table S2 shows that six genes, including ANP32B, CA4, WNK1, YWHAZ, ZCCHC24 and ZEB2, have four occurrences, and 63 genes have three occurrences among the 10 gene sets. Some genes like ZEB2 are related to multiple tissues, suggesting that they are common signatures of ageing. Here we termed these 69 genes (with $\geqslant 3$ occurrences) as the common ageing-related signature gene set (CASGS), which may be signatures of ageing shared by multiple tissues. However, 2887 (86%) genes occurred only in one out of the 10 gene sets, suggesting that a large majority of ageing-related genes are tissue-specific. This is in line with the notion proposed by Zahn et al. [12].

For the CASGS, we carried out functional analysis using DAVID tools [34,35]. The functional annotation chart for pathways showed two important CASGS-related KEGG pathways: pathways in cancer and the MAPK signaling pathway (**Table 2**). In addition, the functional annotation table for pathways identified 34 sets of KEGG pathways related to a large portion of genes in CASGS (Table S3). Among them, the MAPK signaling pathway, pathways in cancer and metabolism-related pathways, were the most frequently identified pathways, indicative of certain shared mechanisms underlying ageing and cancer. Gene ontology (GO) analysis identified 51 GO terms (Table S4) and the five most frequently identified GO terms include cell fraction, intracellular signaling cascade, cytosol, mitochondrion and response to wounding, suggesting that oxidative stress, mitochondrial function, apoptosis and senescence, and DNA damage repair are closely associated with ageing.

In addition, we obtained 261 human ageing-related genes from the Human Ageing Genomic Resources (http://www.genomics.senescence.info/genes/allgenes.php). We referred these 261 genes as human ageing-related genes (HARG). There were 84 overlaps between HARG and AGS, including five overlaps between HARG and CASGS (Table S5). These five overlapping genes were YWHAZ, HSPA8, FOS, FOXO1 and TP63, most of which are important signatures of ageing and cancer. For example, YWHAZ encodes the protein involved in regulating insulin sensitivity, and therefore plays a role in regulation of ageing by affecting insulin/IGF-1 signaling [36,37]. HSPA8 appears to be associated with both ageing and cancer [38,39]. FOS plays a role in regulating cell proliferation, differentiation, apoptotic cell death and transformation, and has been associated with ageing and cancer [40]. FOXO1 belongs to the forkhead family of transcription factors which are strongly associated with human longevity [41] as well as cancer [42]. TP63 encodes a member of the p53 family of transcription factors, and has been associated with ageing and cancer-related pathology [43,44].

Expression of human ageing-related signatures in tumors

We identified 28 sets of differentially expressed genes by the 28 normal vs. tumor phenotypes class comparisons in 25 human tumor gene expression datasets. We analyzed the overlap between each of the 28 gene sets and each of the three aforementioned human ageing-related gene sets: HARG, AGS and CASGS. The occurrence frequency and ratio of each human ageing-related gene in the 28 tumor-related gene sets are presented in Table S6, which shows the occurrence frequency is considerably high. The percentage of genes with $\geqslant 5$ occurrences in the tumor-related gene sets is 90%, 81% and 100% for HARG, AGS

Table 1 Human ageing-related gene sets from 10 publications

Tissue	Gene set (Reference)	No. of genes	Statistics[a]			Age group (years old)	
			Fold[b] change	FDR[c]	*P* value[d]	Young	Aged
Brain	[1]	419	$\geqslant$1.5	<0.01	N/A	$\leqslant$42	$\geqslant$73
	[2]	517	>1.5	<0.05	N/A	$\leqslant$30	$\geqslant$60
Eye	[7]	279	$\geqslant$2[e]	N/A	N/A	N/A	N/A
Kidney	[8]	345	$\geqslant$2	N/A	<0.05	Mean 3.1	Mean 78.5
	[9]	638	N/A	N/A	<0.001[f]	N/A	N/A
Muscle	[10]	386	N/A	<0.1	<0.01	21-27	67-75
	[11]	1021	$\geqslant$1.2	<0.1	<0.01	20-29	65-71
	[12]	170	N/A	N/A	<0.001[g]	N/A	N/A
Skin	[13]	104	>1.7	N/A	<0.01	3-4	68-72
Blood	[15]	27	N/A	N/A	<0.05	<30	$\geqslant$70

Note: [a]Statistical methods used to determine genes that correlated with ageing. [b]The fold changes of gene expression between young and aged groups. [c]FDR, false discovery rate. [d]The *P* values were based on *t*-tests or rank sum tests. [e]The fold changes of gene expression between age-related cataract and clear lenses. [f]The *P* values were based on *t*-tests from standard linear regression theory. [g]The *P* values were based on multiple regression analysis.

Table 2 KEGG pathways related to CASGS

Pathway	Genes	*P* value[a]	Fold enrichment[a]	FDR (%)[a]
Pathways in cancer	FOS, FOXO1, FGF1, PRKCB, CSF1R, FN1, TPM3	0.0173	3.19	17
MAPK signaling pathway	FOS, CACNB2, ECSIT, FGF1, HSPA8, PRKCB	0.0273	3.36	25

Note: [a]The definition of related statistical parameters can be found in Ref. [34,35].

and CASGS, respectively (**Table 3**). Some representative highly-overlapping genes between ageing and tumors were also listed in Table 3. Among them, in addition to the aforementioned YWHAZ, FOS, FOXO1 and TP63, some other genes like APOD [45], IGF1 [46] and FOXM1 [30] also tightly link ageing with cancer. Gene function enrichment analyses (GO) suggested that the highly-overlapping genes are mainly involved in metabolic processes, cell cycle regulation, DNA damage response, apoptosis, cell proliferation and transcriptional regulation (**Table 4**). KEGG pathway analysis for highly-overlapping genes with the DAVID tool identified several important convergent pathways between ageing and cancer like MAPK signaling pathway, cell cycle, p53 signaling pathway etc. (**Table 5**).

Discussion

Microarray analysis of gene expression profiling of ageing tissues and cancer tissues is a powerful approach to discovering molecular mechanisms underlying ageing and cancer. Revealing the common molecular signatures between ageing and cancer may aid humans to extend their life-span by protecting against ageing and cancer. In the present study, we used computational biology methods to identify the shared signatures of ageing and cancer, which provides a strong addition to the conventional experimental methods. Our results revealed that there were some shared signatures of ageing concerned with multiple different tissues, although most of the ageing-related signatures were tissue-specific. This study also indicated some convergent signatures between ageing and cancer, which need to be experimentally verified. It should be noted that in this study we investigated the molecular mechanisms linking ageing and cancer mainly based on genetic and genomic components, whereas epigenetic components like DNA methylation, chromatin remodeling etc., may be equally important in contributing to ageing and cancer [47].

The following findings support our argument that there exist shared mechanisms underlying ageing and cancer. First, using ageing-related datasets, we identified two highly significant ageing-related pathways: pathways in cancer and the MAPK signaling pathway. The first pathway apparently links ageing with cancer, and the second one is involved in various cellular functions including cell proliferation, differentiation and migration that are strongly implicated in tumorigenesis as well. Next, we found that most of the ageing-related gene signatures were differentially expressed among normal vs. tumor samples, indicative of their association with tumor.

The present study also reveals some critical molecular mechanisms that underlie both ageing and cancer such as cell cycle regulation, metabolic processes, DNA damage response, apoptosis, P53 signaling pathway and immune/inflammatory response. Among them, the immune/inflammatory response is a particularly interesting clue in that the convergent pathways between ageing and cancer in Table 5 include multiple pathways correlated with immune/inflammatory response: T cell receptor signaling pathway, mTOR signaling pathway, B cell receptor signaling pathway and chemokine signaling pathway. In fact, ample studies have indicated that dysregulation in the immune/inflammatory response was a key factor in causing ageing and cancer [48–50].

Previous studies have suggested that there were some crucial clues that linked ageing with cancer among which DNA damage, tumor-suppressor mechanisms, telomerase activity and stem cell turnover were four key components. DNA damage is a convergent factor driving both ageing and tumorigenesis as the accumulation of a large amount of DNA damage can force the cell into one of three possible states: senescence, apoptosis and uncontrolled cell

Table 3 Overlaps between the human ageing-related gene sets and the tumor-related gene sets

Gene sets	No. of genes with $\geqslant 5$ overlaps	Highly-overlapping representative genes
HARG	234 (90%)	CLU, JUND, APP, MAPT, NR3C1, PML, YWHAZ, TCF3, TOP2A, VEGFA, APOE, PRKCA, CDKN2A, HOXB7, IGFBP3, PTK2, SHC1, TERF1, ATP5O, CCNA2, FGFR1, FOXM1, IGF1, TP53
AGS	2723 (81%)	PGK1, FGFR2, CD59, FN1, COL1A1, PDE4DIP, CDH11, PICALM, PLOD2, TCF4, CLU, CXCL12, SOX4, STAT1, YWHAZ, ID4, TGFBI, MAPK1, CCND2, IGFBP3, ATP1B1
CASGS	69 (100%)	PGK1, FN1, YWHAZ, AHNAK, NEBL, VCAN, ABI2, PRKCB, WNK1, FGF1, GATM, SFPQ, HPGD, PTGER3, COX7C, LAMP1, H2AFV, APOD, FOXO1, TP63, FOS

Note: The percentage of the overlapping gene number relative to the total gene number for each of the three human ageing-related gene sets is given in parenthesis.

Table 4 Functional categories of the highly-overlapping genes

Functional category	Representative genes	*P* value	Fold enrichment	FDR (%)
Cell proliferation	MAPK1, SOX4, BCL2, CLU, FGF1, FGFR1, SHC1,VCAN, ID4	1.49E-24	1.83	2.84E-21
Regulation of apoptosis	APP, ANXA4, CLU, MAPK1, TOP2A, PRDX2, PRKCA, TP53, TP63	2.51E-20	1.73	4.78E-17
Cell cycle regulation	HAPA8, CCND2, CDKN2A, CCNA2, TERF1, ID4, PML, TP53	1.03E-14	2.01	1.97E-11
Metabolic process	VEGFA, TCF3, TCF4, CREB1, APOE, PBX1, APOD, SOX4	1.05E-13	1.56	2.00E-10
DNA damage response	TOP2A, TP63, H2AFX, PML, DYRK2, CCNA2, MAPK14, TP53	5.80E-07	2.41	0.001
Transcriptional regulation	FOXO1, FOXM1, IGF1, STAT1, TP53, TP63, FOS, VEGF, CCNA2	4.00E-4	1.56	0.76

differentiation, which can lead to ageing or tumorigenesis [51]. However, the other three clues may be implicated in certain divergent mechanisms between ageing and cancer. For example, for tumor-suppressor mechanisms, one possibility is that some tumor-suppressor genes like TP53 and RB1 contribute to ageing by promoting apoptosis and cellular senescence, which suppress the development of cancer [52]. For telomerase activity, although telomerase reactivation may protect against age-related diseases and premature ageing by maintenance of telomere length, it can raise the risk of the development of cancer [21]. For stem cell turnover, although a decline in the replicative function of certain stem-cell types can suppress the development of cancer, the decreased regenerative capacity appears to contribute to some aspects of human ageing [53]. The interrelationship between stem cell, cancer and ageing is intricate and worthy of an in-depth investigation [54].

Although the common molecular mechanisms underlying ageing and cancer seem to be complex, the discovery of shared relationships between ageing and cancer might hold the potential promise of interventions that aim at extending human life-span by postponing ageing and preventing cancer.

It should be noted that the present results may be subject to bias related to the individual bioinformatics approach used in each original ageing and tumor gene expression dataset. These gene expression datasets involve different microarray platforms that used different analysis tools, normalization strategies and statistical approaches. An improved approach would be to analyze all the raw ageing and tumor microarray data under one united computational framework with the same statistical standards including *P* values, fold change cut-offs and FDR etc. This would greatly enhance the accuracy of results arising from comparison of different studies.

Materials and methods

Datasets

Three classes of datasets were analyzed in this study. The first one was obtained from 10 publications which identified ageing-related genes by microarray from six different human tissues including brain, eye, kidney, muscle, skin and blood (Table 1). The second one was obtained from a web resource that collected a list of human ageing-related genes (http://www.genomics.senescence.info/genes/allgenes.php). The third one encompassed 25 human tumor gene expression datasets related to 15 different tumor types (Table S7).

Identification of human ageing-related genes

Based on the first class of datasets, we identified ageing-related human genes by the set union operation of the 10 gene sets derived from the 10 publications (only named genes were included).

Gene set function analysis

We performed functional analysis of gene sets using DAVID tools to identify the important GO terms and KEGG pathways relevant to gene sets.

Identification of tumor-related genes

We identified tumor-related genes for the 25 human tumor gene expression datasets by carrying out a class comparison algorithm. A total of 28 normal vs. tumor phenotype classes comparisons were carried out (some datasets were involved in multiple tumor subtypes). We identified differentially expressed genes among normal vs. tumor phenotype classes using univariate *F*-test for unpaired samples or *t*-test for paired samples at 0.05 significance threshold level ($P < 0.05$). This procedure was implemented with the class comparison between groups of array tools in BRB-ArrayTools, an integrated package for the visualization and statistical analysis of DNA microarray gene expression data [55]. The software can be freely downloaded from the website: http://www.linus.nci.nih.gov/BRB-ArrayTools.html. We identified the differentially expressed genes as tumor-related genes.

Competing interests

The author declares that he has no competing interests.

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Table 5 Convergent pathways between ageing and cancer

Pathway	Related genes[a]	*P* value	Fold enrichment	FDR (%)
Pathways in cancer	MYC, VEGFA, STAT1, STAT3, IGF1, EGFR, FGF1, MAPK1, TP53	6.45E-10	1.65	8.06E-07
ErbB signaling pathway	PRKCA, EGFR, ERBB3, ERBB2, PRKCB, MAPK1, PTK2, MAPK3, SHC1, MYC	3.49E-08	2.22	4.36E-05
MAPK signaling pathway	MAPK1, MAPK3, MAPK14, MAPT, FAS, MAX, JUND, HSPA8	6.61E-07	1.58	8.26E-04
Cell cycle	CDK1, CCND2, CDKN2A, CCNA2, TP53, MYC, YWHAZ, E2F1	1.48E-06	1.86	0.002
T cell receptor signaling pathway	CDC42, MAPK1, FOS, FYN, RELA, MAPK14, NCK1, MAPK3, NFKBIA	4.32E-05	1.79	0.05
mTOR signaling pathway	IGF1, IGF2, MAPK1, HIF1A, EIF4E, VEGFA, RPS6KA1, MAPK3, MTOR	4.82E-05	2.20	0.06
B cell receptor signaling pathway	HRAS, NFKB1, AKT1, FOS, KRAS, RAC2, PTPN6, LYN, PIK3CB, GRB2	8.67E-05	1.93	0.11
P53 signaling pathway	IGF1, TP53, FAS, MDM2, ATR, CDK1, CCND2, CYCS, CDKN2A	1.86E-04	1.94	0.23
Insulin signaling pathway	FOXO1, AKT1, SHC1, INSR, PIK3CG, MAPK1, PKLR, MAPK3, IGF2	8.11E-04	1.56	1.01
VEGF signaling pathway	PRKCA, VEGFA, PTK2, MAPK14, PRKCB, CDC42, MAPK1, MAPK3	0.001	1.76	1.6
Chemokine signaling pathway	FOXO3, SHC1, PAK1, RELA, CCNL2, PRKCB, MAPK1, MAPK3, PTK2, KRAS, STAT1, STAT3, CXCL14	0.002	1.43	2.17

Note: [a] Not all but some key genes are presented.

Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.gpb.2012.01.001.

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