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TREATING CANCER WITH EMBRYONIC STEM CELLS: RATIONALE COMES FROM AGING STUDIES

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1. ABSTRACT

In an earlier poster paper (1) we proposed that cancer can be viewed not only as a fatal disease but also as a local aberrant "rejuvenation" in an organism, and this fact can be useful for developing new anti-aging and anti-cancer treatments. In this paper we provide additional evidence from human and experimental animal studies in support of this view. First, we discuss cancer genes as candidate targets for anti-aging interventions. We review examples in which the life of experimental animals has been prolonged in situations of increased activity of proto-oncogenes - or decreased activity of tumor suppressors - in normal (non-cancerous) cells *in vivo.* Studies of genetic polymorphisms revealed similar effects on longevity in humans. Second, we discuss the possibility of treating cancer with embryonic stem cells. The fact that cancer cells do not "age" means that these cells overcome aging host cells. However, cancer cells can be suppressed by young and quickly proliferating non-cancer cells, such as embryonic stem cells. The grafting of these cells in the tumor environment could be a prospective non-toxic anti-cancer treatment. We discuss recent evidence in support of this view.

2. INTRODUCTION: CONTRAST BETWEEN CANCER AND AGING

In our earlier (poster) paper (1), we suggested that cancer can be viewed not only as a fatal disease but also as a local aberrant "rejuvenation" in an organism. Indeed, a comparison between malignant and aging cells shows that cancer cells do not "age"; their metabolic, proliferative and growth characteristics are the opposite of those observed in cellular aging (both replicative and functional) (2, 3, 4). Cancer cells are potentially immortal (they may avoid apoptosis) and can proliferate to an unlimited extent. Aging cells, both proliferating and post-mitotic, normally die via apoptosis (5, 6, 7). Aging proliferating cells exhibit a decline in proliferative ability with each cell division and finally suffer irreversible growth arrest (also called replicative senescence). It is recognized that cells in a state of irreversible growth arrest (such as mature neurons *in vivo* or replicatively senescent cells *in vitro*) are not prone to malignant transformation (e.g., 8, 9, 3). Whereas cancer cells are de-differentiating, the final stage of normal cellular development is terminal differentiation. Cancer cells often have an increased metabolism, while functionally aging cells (e.g., neurons) decline in metabolic activity. Cancer cells may secrete factors that increase blood supply and produce embryonic proteins such as α-fetoprotein, while aging cells do not (2, 3) (Table 1).

Many of these cancer features are inherent to most "young" cells in an organism, that is, embryonic cells. Embryonic cells are capable of extensive proliferation, migration, they secrete factors that increase the local supply of blood, and produce enzymes degrading basal membranes (3) (Table 2).

Thus, cancer and aging are in many instances opposite phenotypic conditions. Recent evidence suggests that these arise from the opposite expression of genes participating in apoptosis/growth arrest and growth signal transduction pathways in cell (such as proto-oncogenes and tumor suppressors). The proto-oncogenes are often suppressed in aging cells, while in cancer cells they are upregulated. Tumor suppressors are permanently expressed in aging cells, while in cancer cells they are downregulated (Table 3). We proposed that controlled "cancer-like" expression of some of these genes may have an anti-aging effect on cells and organisms.

Table 1. Distinctive features of cancer and aging cells

Cancer cells	Aging cells
• potential immortality	• programmed death (apoptosis)
• unlimited proliferation	• decline in proliferative potential/growth arrest
• de-differentiation	• terminal differentiation
• able to migrate	• not able to migrate
• increased metabolism	• decline in metabolism
• may secret embryonic proteins	• no embryonic proteins
• may promote angiogenesis	• do not promote angiogenesis

Sources: 2, 3, 4, 6, 61

Table 2. Common features of cancer and embryonic cells

Cancer cells	Embryonic cells
• unlimited proliferative potential	• high/unlimited proliferative potential
• able to migrate	• able to migrate
• increased metabolism	• increased metabolism
• de-differentiated	• undifferentiated
• able to promote angiogenesis	• able to promote angiogenesis
• produce embryonic proteins and enzymes degrading basement membranes	• produce embryonic proteins and enzymes degrading basement membranes

Sources: 2, 3, 4, 62

Table 3. Genes oppositely expressed in cancer and aging

Apoptosis/Growth arrest				
Gene	**Protein function**	**In cancer cells**	**In aging cells**	**In aging organisms**
p53	Induces cellular apoptosis/ growth arrest; tumor suppressor	Downregulated in most human cancers (14, 6)	Elevated expression (17, 18)	Upregulating mutation is associated with early aging phenotype and lower cancer risk in mice (19, 20)
fas *(CD95)*	"Death" receptor of apoptotic signal	Decreased expression (27)	Higher expression on lymphocytes from adults compared with newborns (30)	Proportion of cells expressing CD95 is higher in older individuals (29)
bcl-2	Anti-apoptotic protein; proto-oncogen	Overexpressed in some cancers (31)	Decreased levels (63, 32)	Decreased expression in lymphocytes from older individuals (29)

Growth signal transduction				
Gene	**Function**	**In cancer cells**	**In aging cells**	**In aging organisms**
myc	Transcription factor; proto-oncogen	Overexpressed in many cancers (32)	Expression is lower in senescent cells (35, 32). Sustained expression rescues embryo cells from senescence (34).	Aging diminishes the *myc* expression including that in response to stress (66)
ras	Signal transducer; proto- oncogen	Activated in some cancers (36)	Decreased expression in senescent cells (38)	Activity is lower in old rats (37). Controlled expression extends the reproductive life span in yeast (39)
tyrosine kinase receptors	Growth factor receptors (e.g. erb-B, TRK); proto-oncogenes	Overexpressed in some cancers (32)	Receptor density and mitogenic response decrease with donor age (41, 42)	Overexpression of tkr-1 increases longevity in nematodes (44)

3. OPPOSITE MANIFESTATION OF COMMON SIGNALING PATHWAYS IN CANCER AND AGING

3.1. Apoptosis/growth arrest

3.1.1. P53

The potential immortality of cancer cells results from their ability to avoid apoptosis. The unlimited growth and proliferation of cancer cells are linked to their ability to avoid irreversible growth arrest (2, 4). Both these qualities require the suppression of *p53* tumor suppressor gene (6, 10, 11). The latter codes a transcription factor that induces apoptosis or cell circle arrest at the G1-S phase. It may also promote cell differentiation. P53 protein influences expression of many target genes, such as *fas, bax, bcl-2,* and *p21* (12, 13) (Figure 1)

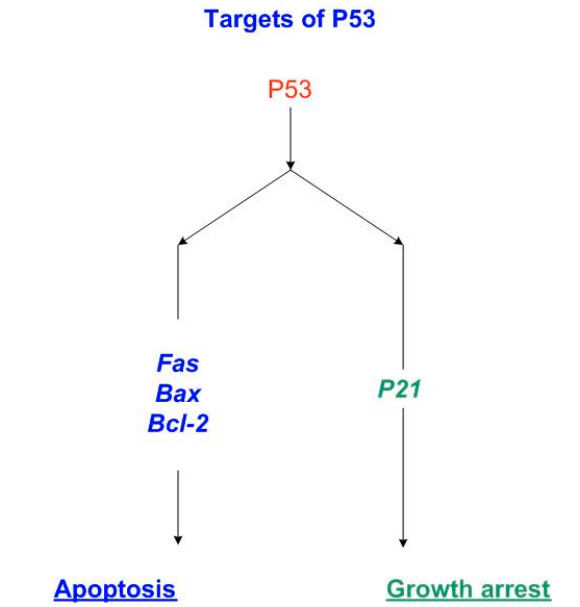

Figure 1. Selected genetic targets of P53 (Sources: 15, 28, 64).

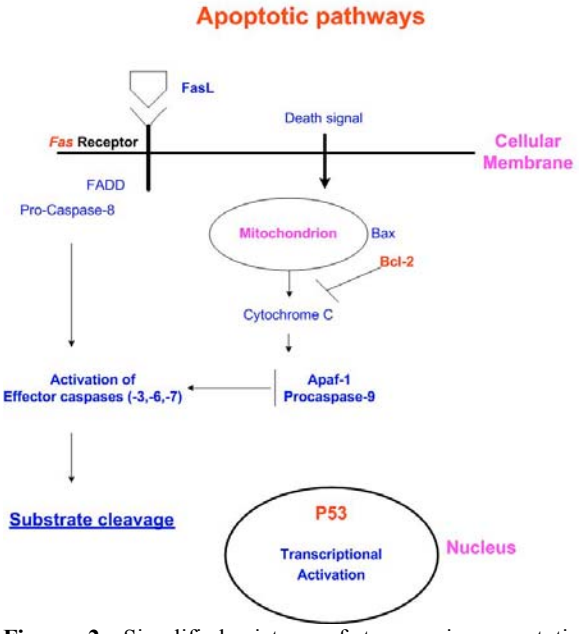

Figure 2. Simplified picture of two major apoptotic pathways: via "Death" receptor (Fas), and via mitochondrion (Sources: 15, 28, 65).

P53 is a key tumour suppressor. Mutations that downregulate or completely knock out this gene are found in all major histogenetic groups of cancer, such as colon (~60% cases), lung (~70% cases), brain (~40% cases), and esophagus (~60% cases) cancers. It is estimated that *p53* mutations are the most frequent genetic event in human cancer cells (14). Even if *p53* is not mutated, it is still downregulated in most human cancers (11, 15).

As for aging, *p53* is permanently expressed in senescent cells (9, 10, 16). *P53* gene expression increased significantly in aged rat brain (17). Elevated P53 protein is found to be associated with aging in human diploid fibroblasts (18). Mice carrying the *p53* mutation with a phenotypic effect analogous to the upregulation of this gene display an early aging phenotype along with a lower risk of cancer development (19, 20). Long-living mutant mice, $p66^{Shc-/-}$, have shown an impaired *p53* apoptotic response (21). Introducing the null *p53* allele has protected $Ku80^{-/-}$ and $mTR^{-/-}$ mice from premature aging (22, 23), indicating that the senescence phenotypes were *p53*-dependent (24). Recently, Van Heemst (2003) demonstrated that individuals with the Pro/Pro genotype of *p53* (corresponding to reduced apoptosis in cell) significantly increased both survival rates and the proportion of deaths from cancer at oldest old ages (85+) (25).

Thus, it follows that the upregulation of the *p53* tumor suppressor gene is required for both cellular and organismic aging, while its downregulation may have an anti-aging effect on cells and (at least in some cases) on organisms (Table 3).

3.1.2. Fas

One apoptotic pathway involves the transduction of a signal from outside Fas-ligand (FasL) to the "death" receptor, CD95 (or Fas), on the cellular membrane. This signal activates a cascade of caspases, which are intracellular enzymes destroying cell proteins (Figure 2).

The expression of CD95 is weaker on cancer cells. Cancer cells may avoid apoptosis when, for instance, Fas receptor is in soluble form (26) or when its expression to cell surface is decreased (27). This, together with increased expression of FasL, may help cancer cells to avoid immune surveillance because FasL is able to counterattack host lymphocytes. The decreased expression of CD95 in cancer cells can be directly related to downregulation of *p53* because the latter has the ability to induce transport of CD95 from the golgi apparatus to the cell surface (28).

As regards aging, the susceptibility of cells to Fas-mediated apoptosis was shown to increase with the age of the donor (29). The proportion of CD4+ and CD8+ lymphocytes expressing the Fas receptor was significantly higher in serum taken from old compared to that from young individuals (45% vs. 29%). It was possible to induce an *in vitro* apoptosis in 55 % of the CD4+ cells of old (65-95) donors, while it was possible in only 26% of the cells of young (20-29) donors. A similar relationship was observed for CD8+ cells (29). Other studies show that the Fas receptor is weakly expressed on the lymphocytes of newborns; however, its expression progressively increases in adulthood (30).

3.1.3. Bcl-2

Another apoptotic pathway involves the release of Cytochrome C from mitochondria and following activation of effector caspases. The Bcl-2 protein blocks this apoptotic activity of mitochondria (see Figure 2). The *bcl-2* is known as a proto-oncogen overexpressed in some cancers (31). As for aging, the density of this protein is

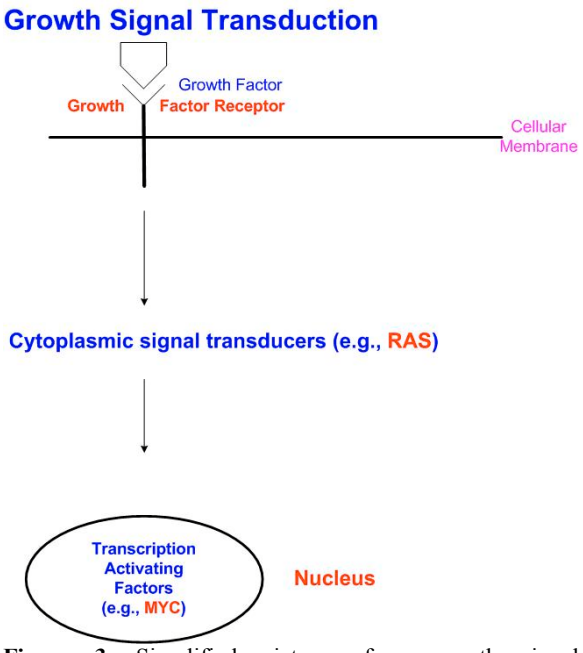

Figure 3. Simplified picture of a growth signal transduction pathway (Sources: 31, 32).

lower in aging cells and in lymphocytes taken from old individuals compared to young ones (32, 29).

Thus, available evidence indicates that key genes contributing to apoptosis/growth arrest signalling pathways are oppositely expressed in cancer and aging cells (Table 3). There is also evidence - although limited - that the downregulation of the *p53* tumor suppressor gene may have an anti-aging effect on cells and organisms.

3.2. The Growth Signal Transduction

The proliferation, the growth signal autonomy and the de-differentiation of cancer cells are all associated with the upregulation of the growth signal transduction pathway. This typical pathway involves the transmission of a signal from an external growth factor to the growth factor receptor on a cellular membrane (such as tyrosine kinase receptor), and from there to cytoplasmic proteins (e.g., GSP and RAS), passing the signal to a nucleus transcription factor such as *myc* (Figure 3). Myc has the ability to induce cell division and suppress cell differentiation (32, 33).

The majority of known proto-oncogenes normally participate in the growth signal transduction pathway in cells (31). Among these, *ras, myc* and *tyrosine kinase receptors* are particularly involved in both aging and cancer.

3.2.1. Myc

Elevated *myc* transcription is found in many human cancers (32, 33). However, it is expressed at much higher levels - not only in cancer, but also in normal young proliferating cells - when compared to terminally differentiated non-dividing ones (32). The sustained expression of the *myc* rescued rat embryo cells from senescence (34). At the same time, significantly decreased levels of *c-myc* transcription have been found in late passage human fibroblasts compared to early passage cells (35).

3.2.2. Ras

Ras is a proto-oncogen activated in many cancers (36). As for aging, Ras activity has been found to be lower in cells isolated from old rats compared to those from young ones (37). Ras expression decreased during *in vitro* senescence of human fibroblasts (38). At the same time, the controlled overexpression of the v-Ha-ras has extended reproductive life span in yeast nearly two-fold (39).

3.2.3. Tyrosine kinase receptors

Expression of these receptors is elevated in some human cancers (32, 31, 40). As for aging, human fibroblasts express fewer epidermal growth factor receptors and display a weaker mitogenic response to the growth factor with increasing donor age (41, 42, 43). It has been demonstrated that upregulation of a tyrosine kinase receptor may increase both longevity and stress resistance in nematodes. The overexpression of tkr-1 has significantly improved their survival (average 65%) and resistance to heat and ultraviolet irradiation (44).

Thus, there is strong evidence that proto-oncogenes participating in growth signal transduction pathway are oppositely expressed in cancer and aging cells. There is also limited evidence that controlled activation of some of these proto-oncogenes may have an anti-aging effect on cells and organisms (Table 3).

One should notice that growth signal transduction pathway has been intensively studied last years in relation to aging (45, 46). This pathway has been proposed to be a conserved regulator of aging in different species (see e.g., 47, 48, 49, 50). Mutations of many relevant genes (e.g., *daf-2* and *age-1* in *C. elegans*) have been found to increase longevity in experimental animals (51, 52, 53, 54). However, only few such mutations manifested themselves in the *activation* or *overexpression* of a known proto-oncogene (44). Thus, additional studies are needed to explore the effect of the controlled "cancer-like" upregulation of proto-oncogenes involved in growth signalling pathways on aging and longevity.

4. APPLICATION TO ANTI-CANCER TREATMENT

The fact that cancer cells do not "age" suggests that these cells have high competitive ability in environment of aging host cells. The proportion of aging cells increases with age, and proliferative and survival advantage of cancer cells increases in an old organism, too, in part providing an increase in cancer risk with age (55). In this situation, "rejuvenation" of normal host cells surrounding the tumor could be a prospective anti-cancer treatment. One such method may involve grafting young proliferating cells (e.g., embryonic stem cells) in the area near a malignant tumor. Such therapy would help to supplant cancer cells, rather than to kill them.

There are data - although limited - supporting this

view. Neural stem cells (NSC) have shown a potential to hunt malignant cells (when implanted into intracranial gliomas in adult rodents *in vivo*). NSC surrounded the tumor and expanded aggressively advancing tumor cells (56). Yip *et al*., (2003) suggested using this property of NSC for targeted drug delivery during cancer treatment (57). Earlier, Barnea *et al*., (1996) found that fractions derived from human embryonal neural tissue extracts significantly suppress the proliferation of human breast cancer cells. Significant inhibition of proliferation of osteosarcoma and fibrosarcoma was also obtained (58). Joshi *et al*., (2000) revealed significant increase in the survival of leukemia as well as breast cancer bearing mice that received *in vitro* IL-2-activated peripheral blood stem cells after tumor transplantation compared with untreated mice (59).

After this manuscript had already been written, additional evidence on the possibility of supplanting malignant cells with normal young proliferating cells came to light. During the recent 2nd Congress of the International Society of Stem Cell Research (ISSCR), Staflin *et al*., (2004) demonstrated that neural progenitor cells can inhibit malignant glioma growth *in vivo* (60). Glioma cells were co-inoculated with neural progenitor cells (embryonic as well as adult) into a rat's CNS. Embryonic (but not adult) neural progenitor cells inhibited glioma cell division and induced glioma cell apoptosis. Complete tumor remission occurred about 20% of the animals. The importance of this study is that authors have compared outcomes of treatments with adult versus embryonic progenitor cells and have proved that only embryonic (i.e., the youngest) cells have an effect on these tumors.

5. CONCLUDING REMARKS

Comparative analysis shows that phenotypes of cancer and aging are, in many instances, opposite. Cancer cells do not "age"; their metabolic and growth characteristics are opposite to those observed in cellular aging (both replicative and functional). That is, cancer manifests itself as local uncontrolled "rejuvenation" in an organism (1).

Available data indicate that the opposite phenotypic features of aging and cancer results from the opposite manifestation of common genes participating in apoptosis/growth arrest or growth signal transduction pathways. Genes normally managing cellular aging promote cancer when contrarily expressed.

Understanding the opposition between cancer and aging has practical application to developing new anti-aging and anti-cancer interventions. The controlled overexpression of proto-oncogenes as well as the downregulation of tumor suppressors might produce an anti-aging effect in cells and organisms. This, however, needs further and careful investigation in life-term experiments. Application to cancer therapy seems more realistic for today. Rejuvenation of normal host cells surrounding the tumor could be a prospective anti-cancer treatment. One such method may involve grafting young proliferating cells (e.g., embryonic stem cells) in the area near a malignant tumor.

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