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Review

Crossroads of hallmarks in aging and cancer: Anti-aging and anti-cancer target pathways can be shared?

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ABSTRACT

Most of the hallmarks proposed in cancer and aging are shared in terms of genetic pathways and biochemical processes. The dissection of the interconnection of the candidate hallmarks between cancer and aging could identify shared targets for improving human health. Here, we will focus on the 7 characteristic hallmarks both in cancer and aging, namely genetic instability, sustained proliferative signaling/loss of proteostasis, evading anti-growth signaling/epigenetic alteration, enabling replicative immortality and resisting programmed cell death/telomere attrition and cellular senescence, deregulating cellular energies/deregulated nutrient sensing and mitochondrial dysfunction, tumor promoting inflammation and avoiding immune destruction/altered intercellular communication, and tumor microenvironment/stem cell exhaustion. The current review identifies that most prominent targets are blocking NF-κB, inhibiting mTOR (mammalian target of rapamycin), IGF-1 (insulin-like growth factor 1) and PI3P (Phosphatidylinositol 3,4,5-trisphosphate)/Akt pathways, and these targets could cover all hallmarks shared by both anti-cancer and anti-aging properties. Based on this result, we will propose the possible approaches to target these pathways in order to achieve better health by reducing the risks of cancer and aging.

KEYWORDS: cancer, aging, hallmarks, genetic pathways, phytochemicals

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Introduction

Aging is one of the most recognizable characteristics of biology in all creatures including humans, but our understanding on the mechanisms of the aging process is still incomplete. Recent studies have shown that aging is defined as a progressive loss of physiological integrity accompanied by a diminished capacity to adequately maintain tissue homeostasis or to repair tissue after the damage. Aging is marked at least by a progressive decline in the function of multiple aspects including proliferation, differentiation and regeneration abilities at cellular, organ and tissue levels. During the aging process, gradual loss of function or degeneration occurs at the molecular, cellular, tissue and organismal levels. Age-related loss of function is a feature shared by almost all organisms, ranging from single-celled creatures to large, complex animals like us.

Among multicellular organisms with reparable or regenerative tissues, aging also entails another feature, that is changes in gain of function that allow cells to proliferate inappropriately, and then acquire phenotypes that increase their ability to proliferate, migrate, colonize and survive in ectopic sites, and evade attacks by immune surveillance system of the host. Thus, aging is one of the major drivers of malignant transformation. These phenotypes are depicted in the landmark papers of Hanahan and Weinberg (2000) [1] as the hallmarks of cancer, which originally consisted of 6 categories, and then expanded to ten (eleven, including tumor microenvironment) (2011) [2].

On the other hand, Serrano *et al.* in 2013 proposed that the tentative hallmarks of aging consisted of nine categories [3], and pointed out the common origin of both cancer development and aging process, although cancer and aging may seem to be opposite processes, i.e. cancer is characterized by an aberrant gain in cellular fitness, whereas aging is a loss of fitness. In this regard, cancer is no different from the other diseases related to aging, despite very different manifestation. In the process of aging and cancer development, a stress response termed 'cellular senescence' may link to multiple pathogenesis of both degenerative and hyperplastic diseases. The term 'senescence' is defined as a distinct change of the cellular phenotype that shows irreversible arrest of cell growth. In this regard, senescence is basically considered to be a potent anti-carcinogenic program, and hyperplastic or neoplastic transformation possibly involves a series of events that bypass the senescence process [4-7]. Although many aspects of hallmarks between cancers and aging are overlapped, there might be a crossroad that will divide the way to senescence/aging or to cancer development (Figure 1).

Recent advances in anti-aging medicine revealed that several mechanisms involved in aging process might be restored by chemicals, hormones, nutrient factors including vitamins and minerals and physical exercise. For instance, anti-oxidants such as several vitamins (C, D and E) and flavonoids might prevent aging, or several hormones including human growth hormone such as dehydroepiandrosterone might restore the aging process. On the other hand, a number of senescence induction therapies against various cancers have been proposed as targeting telomerase [8], p53-p21, Rb-p16 and CDKs (cyclin-dependent kinase) [9]. Different classes of chemotherapeutic agents and ionizing radiation could also induce senescence in human cancer cell lines as well as *in vivo* xenografted tumors through the up-regulation of p53-p21 and telomere shortening [9-13]. Aside from cytotoxic agents or irradiation, 'differentiating agents' such as retinoids could also induce senescence in several cancer cells and this also partly involves p21 [10, 14]. In this review, we describe each counterpart, both with different and shared features, in the hallmarks of aging and cancer to depict the crossroad between them, except for cancer–specific hallmarks of angiogenesis and metastasis.

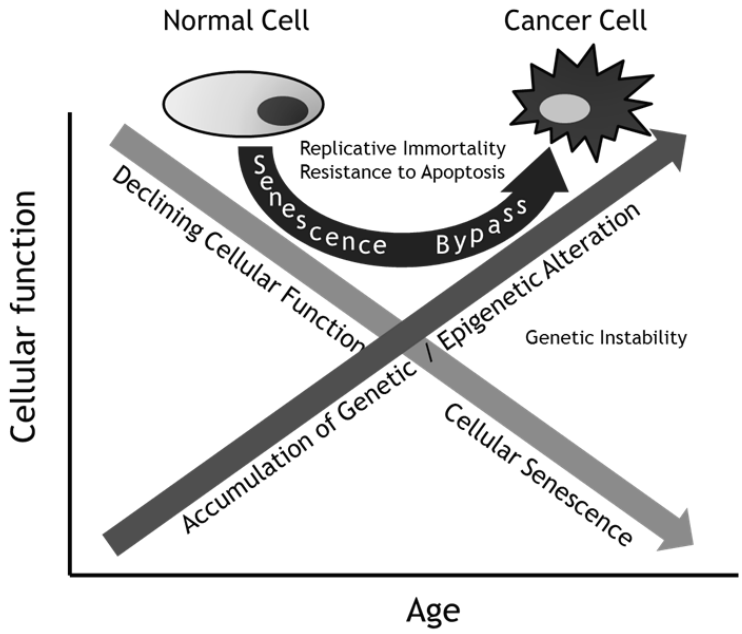

Figure 1. Cells crossing the junction in the direction of aging and cancer. Cellular functions decline during aging. Gain of malfunction occurs during cancer development in part as a result of impairment in normal aging process such as senescence bypass.

Then, we will discuss about how the shared targets and approaches by both anti-aging and anti-carcinogenic strategies work in either complementary or contrary manners.

Hallmarks in cancer and their counterparts in aging: an overview

Table 1 summarizes hallmarks of cancer and aging, and many of them are conceptually overlapped with each other as depicted. In this review, we will discuss each one of them to identify the possible shared targets and approaches against aging and cancer.

All cancer types share eleven common hallmark characteristics as described in the literature by Hanahan and Weinberg [2], and they are summarized below:

1. Genetic instability: The cells in cancer have become genetically unstable.
2. Sustained proliferative signaling: Cancer cells are growing uncontrollably.
3. Evading anti-growth signaling: Cancer cells are able to avoid/ignore anti-growth signaling.
4. Enabled replicative immortality: Cancer cells have bypassed a replication limit that is not functioning properly.
5. Resisting programmed cell death (apoptosis): The cells have a self-destruct mechanism that is not functioning properly.
6. Deregulated metabolism: The metabolic machinery with the cancer cells is not functioning normally.
7. Angiogenesis: Cells that are oxygen-deprived within a tumor will signal for new blood flow.
8. Tumor promoting inflammation: Cancer cells are frequently found in an inflammatory environment.
9. Evading immune destruction: The cancerous cells are able to evade immune system surveillance.
10. Tissue invasion and metastasis: Malignant cancerous cells invade nearby tissues, and ultimately enter the blood stream or lymph system, which allows them to spread and colonize in other parts of the body.
11. Tumor microenvironment: Cancer cells can create the microenvironment that specifically fits them.

Aging is characterized by a progressive loss of physiological integrity that is defined as the time-dependent functional decline, and this deterioration shows a strong relationship with major human pathologies including cancers. Cancer and aging may seem to be opposite processes; however these can be regarded as two different manifestations of the same underlying process, the accumulation of cellular damage. In this context, besides hallmarks of cancer described above, Lópes-Otin and Serrano *et al.* proposed nine tentative hallmarks of aging [3].

1. Genetic instability: One common denominator of aging is the accumulation of genetic damage throughout life that results in genetic instability.

Table 1. Relationship of hallmarks between cancer and aging.

Cancer	Aging
1. Genome instability and mutation	1. Genomic instability
2. Sustained proliferative signaling	2. Loss of proteostasis
3. Evading anti-growth signaling	3. Epigenetic alteration
4-a. Enabling replicative immortality	4-a. Telomere attrition
4-b. Resisting programmed cell death	4-b. Cellular senescence
5. Deregulating cellular energies	5-a. Deregulated nutrient sensing
	5-b. Mitochondrial dysfunction
6-a. Tumor promoting inflammation	6. Altered intercellular communication
6-b. Avoiding immune destruction	
7. Tumor microenvironment	7. Stem cell exhaustion
8. Inducing angiogenesis	-
9. Activating invasion & metastasis	-

2. Loss of proteostasis: Aging and some aging-related diseases are linked to impaired protein homeostasis or proteostasis.
3. Epigenetic alteration: A variety of epigenetic alterations affects all cells and tissues throughout the life.
4. Telomere attrition: Telomere exhaustion limits the proliferative capacity that causes replicative senescence.
5. Cellular senescence: Many aging-associated stimuli trigger cell senescence.
6. Mitochondrial dysfunction: As cells and organisms age, the efficacy of the respiratory chain tends to diminish.
7. Deregulated nutrient sensing: The metabolic machinery will not be functioning properly with aging.
8. Altered intercellular communication: Beyond cell-autonomous alterations, aging involves changes at the level of intercellular communication that are affected by inflammation and other endocrine/paracrine signaling.
9. Stem cell exhaustion: The decline in the regenerative potential of tissues is one of the most obvious characteristics of aging.

These holistic frameworks of hallmarks in both cancer and aging appear relatively straightforward, but it belies the underlying complexity of the disease or aging. A single gene or a single pathway cannot change the entire process of pathology of the disease or the aging process. There is actually a great variety of aberrant genetic pathways that can be used to achieve each of these hallmarks, and these different pathways can vary significantly in the cells within any types of cancer or instances of cancer and aging. The idea of these hallmarks provides us much more nuanced understanding of the biology of cancer and aging.

Figure 2 illustrates the overlaps in the hallmarks of cancer and aging. Outer circle depicts the hallmarks of cancer and inner circle depicts the hallmarks of aging. As described above, most of the hallmarks proposed in cancer and aging are

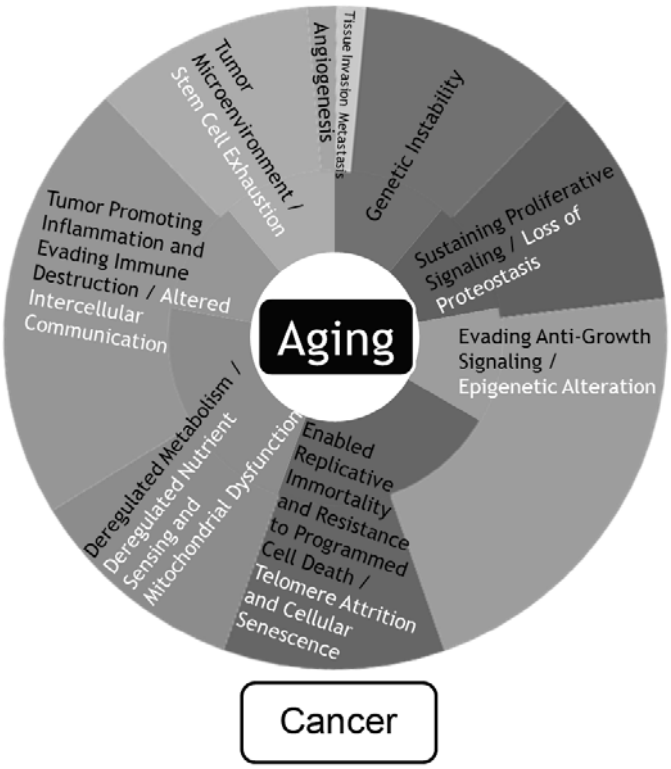

Figure 2. Common hallmarks of cancer and aging. Many hallmarks are overlapped between cancer and aging except for cancer-specific hallmarks namely angiogenesis and invasion/metastasis.

shared in terms of genetic pathways and biochemical processes, although these are not completely overlapped. The dissection of the interconnection of the candidate hallmarks between cancer and aging could identify shared targets for improving human health. Here, we will focus on the 7 characteristic hallmarks both in cancer and aging, except for cancer-specific characteristics of angiogenesis and tissue invasion/metastasis which do not have their direct counterpart hallmarks in aging.

1. Targeting genetic instability in both cancer and aging

DNA is always attacked by exogenous and endogenous threats such as physical, chemical and biological stresses including reactive oxygen species (ROS) causing replication errors. These errors result in DNA damages including mutations and chromosomal translocations leading to functional gains and losses [15]. Accumulation of somatic mutation, chromosomal aneuploidies and copy number variations both in nuclear DNA and mitochondrial DNA has been found to be associated with aging [16, 17]. DNA repair mechanisms are strongly affected by ROS, p53 and NF-κB signaling pathways, and are involved in genetic instability during the aging process, suggesting that these pathways could be the possible targets for anti-aging medicine. During the aging process, functional decline of organs and tissues occurs by mutations and epimutations as a result of failure in DNA repair mechanisms [18]. Failure of DNA repair mechanisms could lead to both accelerated aging process and cancer development. Thus, the restoration of DNA repair mechanisms could be a good candidate for both anti-aging and anti-cancer strategies. However, increased level of p16INK4a and activation of p53 are involved in cellular senescence that may work to restrain potentially tumorigenic transformation [19, 20]. This suggests that these proteins possess anti-tumor and pro-aging functions, and may serve as examples of antagonistic pleiotropy. In contrast, blocking the NF-κB pathway and elimination of ROS would have a better chance to benefit both anti-aging and anti-cancer strategies [21], although exogenous antioxidants may possibly help cancer cells to survive just as much as they may help normal cells [22].

As described, aging and cancer are linked by DNA damage and its erroneous processing by genome maintenance systems. Hypothetically, various endogenous and exogenous factors cause DNA damage in stem cells too. Apoptosis and senescence are the major cellular responses that lead to the attrition of stem cell populations that cause organ aging, while DNA repair is another response that may lead to errors for increase of cancer risks. DNA maintenance machinery, sometimes referred to as ‘care takers’, has been documented and mostly behaves as tumor suppressors, and is represented by p53 that takes a central role as the ‘guardian of the genome’ [23, 24].

To target the genomic instability, prevention of DNA damage, enhancement of DNA repair and blocking of centrosome amplification could be the potential targets for anti-aging as well as prevention of cancer development. However, every target may lead to unwanted side effects because of the multiple roles for cellular function such as DNA repair mechanism that may contribute not only to anti-aging programs but also to drug resistance in cancer cells. These targets also will not be sufficient to change the whole sequences of the disease. For instance, aiming for the activation of p53 pathway could be a good candidate for cancer treatment target. Activation of p53 function will generate the increase of gene expression that controls mitochondrial ROS production, causing ROS-induced cell death. However, such ROS generation might work contradictory against aging, possibly accelerating aging process.

2. Targeting sustained proliferative signaling in cancer and loss of proteostasis in aging

The ability of cancer cells to proliferate is an important character in cancer development and progression. Unlike normal cells that carefully control their cell growth and division cycle, cancer cells sustain the proliferative signaling pathways that are deregulated in terms of a homeostasis of cell number and function. Sustaining proliferative signaling involves numerous pathways such as HIF-1 (hypoxia inducible factor-1), NF-κβ (nuclear factor-*kappa B*), PI3K-Akt, wnt-β-catenin, IGFR1 (insulin-like growth factor-1), CDKs, and androgen and estrogen signaling. These pathways are initially involved in the adaptation of cancer initiating

cells/cancer stem cells to their microenvironment during the very early stage of cancer development [25], and then the continued selection of cells with sustained proliferative signaling further promotes tumor heterogeneity that gives not only growth advantages but also capacity of migration into surrounding tissues and eventually metastasis to distant sites.

Activation or excessive expression of oncogenes usually results in correspondingly increased cancer cell growth advantages. However, excessively elevated signaling by oncoproteins including RAS, MYC and RAF also can provoke induction of senescence and/or apoptosis [26]. In this paradoxical context, it can be assumed that certain types of cancer cells may adapt to high levels of oncogenic signaling pressures by disabling their senescence- or apoptosis-inducing circuitry to obtain their growth advantages. In addition, normal homeostatic regulation is considered to be operated in part through the negative feedback loop that involves PI3K/Akt/mTOR signaling pathway [27]. Disruption of these negative feedback mechanisms is also capable of enhancing proliferative signaling.

Proteostasis has been demonstrated for its alteration with aging [28], and the development of some age-related pathogenesis is in conjunction with chronic expression of unfolded, misfolded or aggregated proteins. Aging cells accumulate the damaged and misfolded proteins through a functional decline in their protein homeostasis governed by proteostasis machinery that leads to reduced cellular viability. The proteostasis machinery is modulated by metabolic signaling pathways mediated by many means, mainly IGF-1 and mTOR/AMPK (adenosine monophosphate-activated protein kinase) signaling axes.

The insulin/IGF-1 signaling pathway has been shown to be involved in lifespan extension. Reduced IGF-1 signaling activity extends lifespan in many species [29]. IGF-1 signaling acts through the recruitment of PI3K AGE-1 (PtdIns-3-kinase *age-1*) and activates AKT kinase with localization of transcription factors in cytosol, and eventually suppresses the transcription for lifespan extending factors [30]. Thus, reduced activity of IGF-1 signaling elevates the transcription of lifespan extending factors, and will promote lifespan extension.

Dietary restriction has been shown to extend the lifespan in multiple species [31]. Like IGF-1 signaling, dietary restriction pathways also affect transcription/translation rates. Protein synthesis is reduced under dietary restriction, possibly through reduced activation of the mTOR kinase [32]. Indeed, reducing translation rates alone is sufficient to extend lifespan. Thus, reducing mTOR signaling function directly increases longevity in multiple species in part by reduced translation rates [33, 34].

Several stress responses such as heat shock response (HSR) and hypoxia response also affect the lifespan through the HSF-1 (Heat shock factor-1) and HIF-1. Over-expression of HSF-1 enhances the folding of proteins and stabilizes proteins to activate specific target genes in relation to longevity, leading to the extension of lifespan such that animal age would be accelerated without the HSR [35]. The contribution of hypoxia response, another stress response besides HSR, is controversial to the lifespan extension. The hypoxia response is regulated by HIF-1 transcription factor that is involved in proteosomal degradation. Hypoxia-HIF-1 pathway seems to influence lifespan; however, several reports indicated that activation or over-expression of HIF-1 extend lifespan, but other reports suggested its loss of function would extend lifespan, suggesting that complex interactions may exist among this stress response pathways [36, 37].

Autophagy, especially the most studied macroautophagy, is required for lifespan extension, and interactions of the signaling networks involving SIRT1 (sirtuin-1), mTOR, FoxO3 (forkhead box O3) and NF-κB regulate the process of autophagy [38]. Inhibition of mTOR signaling significantly increased longevity [39] and longevity genes such as FoxOs and SIRT1 inhibit NF-κB activation through PI3K/Akt signaling [40], suggesting that inhibition of PI3K/Akt/NF-κB pathway will contribute to extending lifespan.

Taken together, pathways of IGF-1, PI3K/Akt/mTOR/NF-κB and HIF-1 involved in both sustaining proliferative signaling and proteostasis can be simultaneously targeted to accomplish both anti-cancer and anti-aging effects.

3. Targeting the evasion of anti-growth signaling in cancer and epigenetic alteration in aging

Normal cells have the internal programs to oppose limitless growth governed by anti-growth signaling,

and these programs are mediated by the activation of tumor suppressor genes that govern the restriction of cell growth and proliferation. In contrast, cancer cells possess the capability of evading these programs through their characteristic inactivation of tumor suppressors by genetic and epigenetic mechanisms.

The most investigated and prototypical tumor suppressors in numerous animal and human cancers are p53 and Rb. They mainly play a role for regulating cell cycle machinery with the interaction of other factors such as CDKs and CDKIs (cyclin-dependent kinase inhibitors), and activate senescence and apoptotic programs. Both p53 and Rb genes are frequently deleted or mutated in many types of cancers [41, 42]. Other frequently mutated tumor suppressor genes are phosphatase and tensin homolog (PTEN), adenomatous polyposis coli (APC), ataxia teleangiectasia mutated (ATM), BRCA1 and 2, von Hippel-Lindau tumor suppressor (VHL), cyclin-dependent kinase inhibitor 2A (CDKN2A) and Wilms tumor protein 1 (WT1).

Cancer cells can also evade tumor suppressors by epigenetic silencing through DNA methylation, histone methylation and/or acetylation. These epigenetic modulations can give growth advantages to cancer cells by silencing the tumor suppressors. Unlike genetic alterations of deletion and mutation that are irreversible, epigenetic repressions are potentially reversible. Thus silenced tumor suppressors through epigenetic modulation could be restored by synthetic chemicals and/or natural compounds.

These epigenetic alterations affect normal cells as well throughout life [43]. The acetylation and methylation status of DNA and chromatins changes with age, and these modifications can alter the organismal longevity [44].

One of the epigenetic regulations occurs by direct methylation and demethylation of DNA bases. During the course of aging, DNAs become globally hypo-methylated; however certain loci corresponding to tumor suppressors and polycomb target genes are hyper-methylated [45]. Thus, these hyper-methylated DNAs could be the potential targets for extending the lifespan. DNA methyl transferases (DNMT) are key enzymes that regulate DNA-methylation, and inhibition of such enzymes will reactivate tumor suppressors and polycomb genes silenced by hypermethylation. However, the relationship between DNA methylation and aging is more complicated than the case of histone modification. Histones can be altered by a number of modifications with acetylation and methylation, and specific histone modifications are associated with gene expression and gene repression [46]. Histone acetylation is generally associated with gene expression, while histone methylation works in a pattern-specific manner; for instance, histone 3 trimethylated at lysine 4 (H3K4me3) plays a role in gene expression, while histone 3 trimethylated at lysine 27 (H3K27me3) takes a role in gene repression [47]. In this context, enzymes that modify DNA and histones such as methyltransferases, demethylases, acetyltransferases and deacetylases are the main players in central regulatory mechanisms [46]. Thus these enzymes could be the possible candidates for targets of anti-aging and anti-cancer approaches. Regarding aging, inactivation of H3K4 methylase subunits extends lifespan, whereas inactivation of a H3K4 demthylase shortens lifespan in worms [48]. Histone acetylation is strongly associated with gene activation such that histone deacetylation could be associated with gene repression. Sirtuin family of NAD+(nicotinamide adenine dinucleotide+)-dependent lysine deacetylases has been indicated in their association with control of longevity, considerably through silencing the pro-aging gene expression by deacetylation of histone, although the precise mechanisms remains to be elucidated [49]. Among sirtuin family in mammals, Sirt6 has been demonstrated for their anti-aging effects through the interaction with NF-κB subunit RelA[50] as well as for telomeric chromatin maintenance to promote replicative capacity [51].

Aged tissues express a set of pro-aging genes including p16INK4a at significant higher levels, and these pro-aging gene expressions are partly under the regulation of NF-κB signaling pathways [52]. Increased activation of mTOR pathway is also associated with pro-aging [39]. Therefore, inhibitions of NF-κB and mTOR pathways are essential for restoring some features of youthful cells. Several natural compounds like polyphenols that will be described in later section are involved in restoring the youthful phenotypes and extending lifespan, possibly through the inhibition of those

pathways. We will also discuss about tumor suppressors that are strongly related to the hallmark of replicative immortality in the next section.

4. Targeting the enablement of replicative immortality/the resistance to programmed cell death in cancer and telomere attrition/cellular senescence in aging

Replicative immortality is the characteristic that cancer cells possess in contrast to the cells in most normal lineages. Normal cells, unlike normal germ cell and some somatic stem cell lineages that possess the ability to undergo continuous self-renewal, can divide and proliferate in only a limited number of cycles. Cellular senescence and crisis/apoptosis are the distinct barriers for this limitation.

Telomeres are centrally involved in replicative senescence and unlimited proliferation. Telomeres progressively shorten in non-immortalized cells *in vitro*, and the so-called replicative senescence or Hayflick limit [53] has been explained in association with telomere exhaustion. Telomerase, the specialized DNA polymerase that is able to add telomere repeat segments to the ends of telomeric DNA is absent in most of the unimmortalized mammalian somatic cells, but is expressed in immortalized cells represented by human cancer cells at functionally significant level. The presence of telomerase activity or enforced expression of this enzyme leads to a resistance to cellular senescence and crisis/apoptosis. Conversely, suppression of telomerase activity can lead to activation of these proliferative barriers. Therefore, telomerase is a possible target for cancer treatment that can induce senescence and apoptosis in cancer cells.

With regard to aging, a crucial link between telomere shortening and cellular senescence/ organismal aging has been reported [54]. Recent evidences indicate that shortened telomeres exhibit decreased lifespan, while lengthened telomeres exhibit increased lifespan, and aging can be reverted by telomerase activation [55, 56]. Thus, the strategies based on targeting telomere–telomerase would work in opposite ways in cancer and aging, i.e. telomerase suppression might work for anti-cancer but in a pro-aging fashion, i.e. accelerating aging.

DNA damage is an inducer of cellular senescence and apoptosis and also works as an initiator for neoplastic transformation, especially when mutations and epimutations accumulate in tumor suppressor genes. Senescence often involves convergent interdependent activation of tumor suppressors p53 and p16/pRb. Increased levels of p16 expression were observed during the aging process [19] and elevated p53 activity showed a reduced longevity and induced early onset of aging in spite of preventing the tumorigenic transformation [57]. Deficiency of p16, not only demonstrated higher regenerative capacity at older age, as evidenced by increased stem cell ability, but also demonstrated increased incidence of spontaneous and carcinogen-induced cancers [58]. Loss of p53 function may also delay the onset of age-related degeneration, but increases the frequency of tumorigenesis [59]. Thus, targeting p16 and p53 to restore their abilities to induce senescence/apoptosis in cancer therapy would work in counter action of senescence/ aging, especially in somatic/tissue stem cell functions.

The two barriers namely senescence and crisis/ apoptosis have been rationalized as a crucial cancer defense. On the other hand, telomere attrition causes cellular senescence and also genetic instability that could induce tumor formation. Thus, all of these taken together, the hallmarks of replicative immortality as well as anti-growth signaling evasion and resistance to apoptosis in cancer and their counterparts namely telomere attrition and cellular senescence in aging may represent an antagonistic pleiotropy; i.e. targeting these hallmarks may work in favor of anti-cancer but in a pro-aging manner.

5. Targeting the deregulation of cellular energies in cancer and the deregulation of nutrient sensing/mitochondrial dysfunction in aging

In normal cells, tricarboxylic acid cycle is the common energy metabolism under aerobic conditions, but glycolysis is favored under anaerobic conditions. Whereas in cancer cells, energy metabolism is re-wired as the so-called ‘Warburg effect’ [60, 61], which defines that their energy production largely depend on glycolysis even in the presence of oxygen and is termed as ‘aerobic glycolysis’. This reprogrammed energy metabolism in cancer cells has been shown to be associated

with activated oncogenes such as RAS, MYC [62, 63] and loss of tumor suppressors such as TP53 [64].

Several components of glucose and glutamine metabolism have emerged as important regulators of metabolism in cancer. The overall goal in cancer metabolism is to over-spill the glycolytic pathway thereby providing metabolites that can be used for cellular growth advantages. In glucose metabolism, Hexokinase 2 (HK2), 6-Phosphofructo-2-Kinase/Fructose-2, 6-Biphosphatase 3 (PFKFB3) and Pyruvate kinase isoform M2 (PKM2) all regulate glycolytic flux. Both HK2 and PFKFB3 are regulators that fill up glycolytic metabolites i.e. providing metabolites and accelerating glycolytic process; conversely, PKM2 regulates the drainage of metabolites. Thus, identifying therapeutic strategies to 'turn off the glycolysis flux' is very important in limiting cellular growth in cancer. Recent studies have also identified an important role for glutaminolysis in proliferating cancer cells. Glutamine oxidation can provide carbons for cellular growth, nitrogens for generating hexosamines and nucleotides as well as can provide metabolic energy through the exchange and reduction of equivalents of ions and electrons. Thus, glutaminonlysis is also an attractive therapeutic target in cancer.

Association between mutations in enzymes directly involved in metabolic pathways and development of several types of cancer has been reported [65]. Aberrant metabolism now has a pro-oncogenic role and has led to the redefinition of some metabolites as 'oncometabolites' that could be powerful influencers of epigenetics, and are also positioned as new therapeutic angles in certain types of cancer.

As previously described, hypoxia response system in cancer tissues plays an important role in accelerating tumor progression through transcription factors of hypoxia-inducible factors (HIF) that upregulate many genes including glycolytic pathway-related factors [66], thereby acting as the primary driver of 'metabolic reprogramming'. The hypoxic conditions in cancer tissues can upregulate glycolysis by increased levels of HIFs. Therefore, HIFs also could be potential targets for abnormal metabolic pathways in cancer.

The metabolic alterations in the hallmarks of aging are composed of two major mechanisms: deregulated nutrient sensing and mitochondrial dysfunction. The insulin–IGF-1 signaling pathway, AMPK/mTOR and sirtuin pathways are playing the central roles in deregulated nutrient sensing systems. The IGF-1 pathway is participating in glucose sensing, while mTOR is sensing high amino acid concentrations; AMPK senses low-energy state by detecting high AMP levels. Down-regulation of IGF-1 pathway and mTOR pathway extends lifespan as previously described, and this could be achieved by minimizing cellular metabolism and growth [67]. Moreover, knockdown of both these pathways extends lifespan synergistically due to the crosstalk between the IGF-1 and the mTOR pathways via increased AMPK [68]. These collective evidences support that these pathways could be the potential targets for extending longevity through decreased nutrient signaling responses.

Progressive mitochondrial dysfunction occurs with age, and this results in increased production of ROS causing global cellular damages as well as further deterioration of mitochondria. However, several reports have indicated that conflicting evidences exist for the contribution of ROS to aging process as either pro-, or anti-, or none of them [69, 70]. The contribution of dysfunctional mitochondria to aging may have alternative ways rather than ROS generation, including activation of cellular signaling in stress responses and induction of cell death [71, 72].

The mitochondrial dysfunction can be caused by inadequate expression of mitochondrial DNA genes that are required for mitochondrial electron transport. When mitochondrial electron transport cannot occur adequately, cells will develop Warburg-type metabolism that generate ATP via aerobic glycolysis as described above. Specifically, low levels of nuclear NAD+ can produce a state of 'pseudohypoxia' inducing high levels of HIF-1α that inhibits the adequate expression of mitochondrial DNA and fails in appropriate electron transport. Thus, supplementation with NAD+ precursor could reverse this mitochondrial dysfunction and 'Warburg-type' metabolic state [73].

In this scenario, inhibition of aerobic glycolysis, i.e. 'turn off the glycolysis flux' could be the most potentiated strategy in targeting metabolism regulation for both anti-carcinogenic and anti-aging therapy. Therefore, inhibition of Hexokinase 2 (HK2) or 6-Phosphofructo-2-Kinase/Fructose-2, 6-Biphosphatase 3 (PFKFB3), and activation of Pyruvate kinase isoform M2 (PKM2) or Pyruvate dehydrogenase could be the potential targets to inhibit aerobic glycolysis. Several molecules show the potential efficacy on inhibitory actions on aerobic glycolysis, such as 3-bromopyruvate and 1-(4-pyridinyl)-3-(2-quinolinyl)-2-propen-1-one (PFK15) that inhibit HK2 and PFKFB3, respectively, and TEPP-46 and dichloroacetate that activate PKM2 and pyruvate dehydrogenase, respectively. 3-bromopyruvate is a dual inhibitor of HK2 as well as oxidative phosphorylation and is specifically effective against cancer cells [74]. Another hexokinase inhibitor 2-deoxyglucose can block glycolysis and it works better when combined with inhibitors of ATP-generating oxidative phosphorylation such as the mitochondrial targeting drug Mito Q [75]. Metformin, a blocker of stage 2 oxidative phosphorylation could also show potential as anti-cancer agent, especially against p53-/- cells applied with chemotherapeutic agents [76]. The physiological interventions such as fasting, calorie restriction and physical exercise also might influence cancer metabolism such that they possibly manipulate the aging process too. Further studies testing the effects of such interventions to manipulate deregulated metabolism will be an important and exciting new area of cancer biology as well as aging process.

6. Targeting tumor promoting inflammation/avoidance of immune destruction in cancer and altered intercellular communication in aging

The linkage between cancer progression and inflammatory responses has been demonstrated since Virchow first proposed the role of inflammation in cancer [77]. The presence of infiltrated immune cells or immune responses in cancerous tissues could be considered as an attempt to eradicate tumor cells; however numerous evidences support that inflammatory milieu mostly promotes carcinogenesis [78]. Chronic inflammation is linked to various hallmark capabilities in cancers, including sustained proliferative signaling, evasion from cell death, angiogenesis, invasion and metastasis through supplying bioactive molecules such as growth factors, chemokines and extracellular matrix-modifying enzymes [79]. Inflammation also can contribute to carcinogenesis through the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) that could damage DNA and induce gene mutation and/or post-translational modification of proteins related to carcinogenesis [80]. Thus, the inflammatory responses including responsible immune cells or molecules could be potential targets for anti-cancer therapy. Specifically, macrophage migration inhibitory factor, COX-2, NF-κB, TNF-α, iNOS, protein kinase B (AKT) and CXC chemokines could be the strong candidates for targeting cancer-associated inflammation.

The immune system operates as a significant barrier to cancer formation and progression, and several evidences support the fact that the immune system is able to contribute to immune surveillance that possibly links to tumor eradication [81, 82]. In this context, the ability of cancer cells to evade immune attacks is another hallmark in conjunction with the generation of immune regulatory cells and their secretions [81, 82], as well as induction of immune suppressive mediators [83, 84]. One of the most important aspects in cancer is the intra-tumoral heterogeneity that considerably provides the genetic, epigenetic and phenotypic plasticity to cancer tissues and this aspect could contribute to the evasion of immune surveillance. Considerable targets in enhancing the immune attacks against cancer cells are to promote the activities of cytotoxic lymphocytes, NK cells and macrophages, to induce IL-12 as well as inhibit Treg lymphocytes. Among specific molecules that can increase cytotoxic T-lymphocytes, immunomodulatory antibodies to cytotoxic T-lymphocytes-associated protein-4 (CTLA-4) and programed cell death protein-1 (PD-1) have been approved for clinical use in certain types of cancers such as melanoma, lung and renal cell cancers [87, 88]. A number of non-specific immunomodulatory approaches including vaccination using peptide, dendritic cells and phytochemicals also have been explored [89, 90], but further study will be required to approve them as the blockades of immune surveillance evasion.

Aging involves changes at the level of intercellular communication including the increase of inflammatory reactions and the decline of immune surveillance against pathogens as well as pre-malignant cells. The so called 'inflammaging' is a prominent aging-associated alteration in intercellular communication [91]. 'Inflammaging' is caused by dysfunctional immune system with secretion of pro-inflammatory cytokines, enhanced activation of NF-κB and defective autophagy responses, leading to the increased production of IL-1β, tumor necrosis factor and interferons [71]. Inhibition of NF-κB signaling pathway that is over-activated as a result of inflammatory response with aging can rejuvenate the old-aged phenotype of tissues and restore the young-aged phenotype [92]. Several studies have indicated that sirtuins such as SIRT1, 2 and 6 can down-regulate the inflammatory response through deacetylayion of NF-κB subunits and that this possibly results in lifespan extension through the repression of inflammation-related genes.

Systemic chemokine levels increase with age and some of them such as CCL11/eotaxin are closely associated with functional decline that underlie the aging process [93, 94]. The anti-inflammatory approaches could achieve the extending lifespan in part through cancer prevention and in part through tissue/organ rejuvenation [95].

Another mechanism underlying the altered intercellular communication during aging process is the so-called 'immunosenescence' that leads to the decline in immune function represented by a failure to wipe out the infectious organisms and infected or malignant-transformed cells [96]. The decline in immune functions involve both innate and adaptive immune cells such as decreased cytotoxicity of NK cells and dendritic cells as well as activation of cytotoxic T-cells. Thus, restoring the declined immune functions along with aging could be the alternative way to the anti-aging approach.

Taken together, both inhibition of inflammatory responses and activation of immune surveillance system will potentially act in anti-carcinogenic and anti-aging fashion. Among the many factors and pathways, NF-κB signaling pathway is most widely involved in both carcinogenic and aging process through the inflammatory responses. However, NF-κB plays an important role in the maintenance of host defense responses under normal conditions. For example, a prolonged inhibition of NF-κB activity resulted in animals that were more susceptible to bacterial infection [97]. Thus, the strategy that inhibits NF-κB will need to be carefully monitored to avoid broad suppression of innate immunity. This unwanted side effect is shared not only by NF-κB inhibition, but also by inflammatory response suppression through the inhibition of macrophage inhibitory factor and TNF-α.

In this regard, the rejuvenation of immuno-senescence could be more practical than the suppression of inflammatory responses. Among the means of rejuvenation of immunosenescence, the depletion of regulatory T cells (Tregs) has been found to be an effective strategy to enhance the immune response, and PI3K-Akt pathway inhibitors selectively inhibit Tregs with minimal effect on conventional T cells and *in vivo* treatment with these inhibitors result in a significant and selective reduction in Tregs in both naïve and tumor-bearing mice with a significant therapeutic antitumor effect. Thus, PI3K-Akt pathway inhibitors that deplete Tregs appear to represent one of the promising agents in both anti-cancer and anti-aging therapy [98].

7. Targeting tumor microenvironment in cancer and stem cell exhaustion in aging

The regenerative potential of tissue or organ is declining along with aging. As described above, immunosenescence that defines the diminished production of immune cells is one of the examples of attrition of regenerative function with aging. Further, the regenerative function in other tissues such as brain, bone and muscle also diminishes with age. These functional declines are considered to be primarily caused by the exhaustion of stem cells themselves in their corresponding tissues. Stem cell exhaustion is induced by several mechanisms such as accumulation of DNA damages and increased expression of cell cycle inhibitory factors like *p16* and *p21*.

Along with these cell-intrinsic pathways, cell-extrinsic pathways also play an important role in the decline of stem cell function during aging. For instance, an increase of FGF2 (fibroblast growth

factor 2) signaling in the muscle stem cell niche could accelerate depletion of stem cell and diminish regenerative capacity [99]. Furthermore, parabiosis experiments revealed that some systemic factors can rejuvenate the declined neural and muscle stem cell functions in old mice [94].

In this regard, stem cell rejuvenation could reverse the organismal aging phenotype, and this could be achieved by the inhibition of FGF2 [99], mTORC1 (mammalian target of rapamycin complex 1) [100], GTPase (guanosine triphosphatase) and CDC42 [101].

When considering tumors as organs, tumors are composed of tumor cells and tumor stromal cells with extracellular matrices where tumor cells exist, i.e. 'tumor microenvironments'. This microenvironment is a cause and consequence of tumorigenesis that consists of cancer cells and host cells coevolving dynamically through both direct and indirect cellular interactions with the production of metabolites and secreted factors. In turn, this environment regulates the ability of a cancer to grow and survive via multi-scale effects on many biological programs through tumor cell-matrix interaction for cellular proliferation, growth and metabolism, as well as inter-cellular communications for angiogenesis, and innate and adaptive immunity.

Tumors are commonly very diverse and contain various heterogeneous regions in terms of the degree of proliferation, differentiation, vascularity and invasiveness. Although concrete evidences have not been established, a hypothesis that the existence of subclass cell population within tumors can give rise to intra-tumor heterogeneity has emerged in recent years, originally for the hematopoietic malignancies, and then for several solid tumors as well [102-104]. These subclasses of cell population termed as the so-called 'cancer stem cells (CSCs)' have been identified by several means such as Hoechst dye side-population, ability of sphere colony formation, presence of aldehyde dehydrogenase and some surface markers. CSCs are also proposed as the primary tumorigenic cells, i.e. 'tumor-initiating cells (TICs)'. They share several features with normal counterpart stem cell characteristics and contribute to chemo- and radio-resistance as well as plasticity (recurrence) and metastatic process. Stem cells require the specific microenvironment, i.e. 'stem cell niche' to maintain their characteristics, and CSCs might require its counterpart, i.e. the so-called 'cancer stem cell niche' to maintain their specific phenotypes including dormant and drug resistance capacity.

Cancer cells can interact with tumor stromal cells such as endothelial cells, pericytes, inflammatory cells and cancer-associated fibroblasts that construct the tumor microenvironment through numerous cytokines and growth factors. Endothelial cells are involved in tumor-associated angiogenesis that is regulated by complex signaling pathways such as VEGF (vascular endothelial growth factor), angiopoietin and FGF signaling [105]. Endothelial cells are also stimulated by pericytes, another important cell population for angiogenesis, through the secretion of Ang-1 and VEGF, and collaborate with pericytes to synthesize the vascular basement membrane, an important component of tumor vasculature. Immune inflammatory cells can infiltrate into tumor tissues as if tumor tissues are recognized as the sites of chronic inflammation. Their presence in tumor microenvironment is associated with various tumor pathologies in both antagonizing and promoting fashions. Unlike tumor-antagonizing CTLs and NK cells, macrophages, mast cells, neutrophils and T and B lymphocytes can act as tumor-promoting inflammatory cells as previously described [76]. These inflammatory cells effect tumor-promoting action through the secretion of various signaling molecules such as growth factors of EGF (epidermal growth factor), VEGF, FGFs, chemokines and cytokines as well as enzymes such as MMPs (matrix metalloproteinases), cathepsin proteases and heparanases, and then facilitate tumor cell proliferation, angiogenesis, tissue invasion and metastasis [106]. In addition to tumor-promoting effects, a class of tumor-infiltrating myeloid cells suppresses CTLs and NK cells to afford evasion of immune destruction.

Fibroblasts, often termed as 'cancer-associated fibroblast', are another important population in tumor stroma that interact with the cancer cells, endothelial cells, pericytes and tumor-promoting inflammatory cells through a variety of secretory factors to support tissue structure and enhance tumor phenotype including cancer cell proliferation, angiogenesis, invasion and metastasis [107]. The

network of cancer-associated fibroblasts, pericytes and endothelial cells could contribute to tumor progression providing the so-called 'perivascular cancer stem cell niche' [108].

Specific biological programs could be exploited as targets that impact tumorigenesis and tumor microenvironment. These programs include the cytokine signaling, cholesterol metabolite synthesis, generation of reactive oxygen species and hypoxic condition, macrophage activation and conversion, regulation of dendritic cells, regulation of angiogenesis, and fibrosis. Many cytokines are involved in cell-cell interactions in the microenvironment. Among these cytokines, IL-6 has been found to play a significant role in the tumor microenvironment [109]. Macrophages, monocytes and T cells can produce IL-1α and IL-6, and activate JAK (Janus kinase) and the signal transducers and activators of transcription (JAK/STAT) activating STAT3 [110]. STAT3 leads to cancer cell survival, proliferation and metastasis, and it also promotes angiogenesis and expression of immune suppressive factors in the tumor microenvironment [110]. Activation of IL-6–STAT signaling induces fibroblast senescence and promotes tumorigenesis through autocrine and paracrine pathways in tumor microenvironment [111]. Inhibition of JAK-STAT pathway could rejuvenate some of stem cell functions [112, 113]. Therefore, inhibition of these pathways could be the possible targets for both anti-cancer and anti-aging approaches.

ROS and HIF are the potential targets for the modulation of microenvironment, and the anti-cancer/anti-aging effects of inhibition of these targets have been discussed in the previous sections.

Dendritic cells can regulate T cell functions via IDO (Indoleamine-pyrrole 2,3-dioxygenase), which degrades the essential amino acid tryptophan (TRP) and catalyzes the generation of kynurenine (KYN) [114, 115], that result in the inhibition of proliferation of T cells and NK cells, promotion of regulatory T cell (Treg) differentiation and inhibition of DC immunogenicity [114-116], as well as induction of anergy in CD8 cytotoxic T cells and promotion of CD4 differentiation towards Tregs [114, 115, 117]. Regardless of the source, IDO activation can induce immunosuppression leading to tumor growth, and therefore, IDO inhibitors may be useful to target tumor microenvironment for the treatment of cancer [118]. Hence, Treg activation and immunosenescence are closely related as previously described, and inhibition of IDO counteracting Treg activation possibly prevents immunosenescence and enhances immune responses against aging.

Organismal aging could be reversed by stem cell rejuvenation through inhibition of FGF2 and mTORC1 signaling, and inhibition of these pathways possibly suppresses tumor progression through inhibition of cell proliferation, angiogenesis and tumor-promoting inflammation. The disruption of stem cell niche network might play an anti-cancer role, but also could play a pro-aging role led by stem cell exhaustion; however the niche for cancer stem cells and normal tissue stem cells might be different. This issue must be elucidated in the future.

Conclusions and outlook: Targeting shared pathways in cancer and aging

Based on this review, the comprehensive results are summarized in table 2. We will attempt to propose shared targets for both anti-aging and anti-cancer approaches, as many targetable pathways are involved in both aging process and cancer development, excluding cancer-specific hallmarks of angiogenesis and invasion/metastasis. The results obviously showed that a number of targets are shared by both anti-aging and anti-cancer approaches. However, most of the pathways involved in cancer hallmarks of genetic instability, replicative immortality and evasion of apoptosis such as inhibition of DNA repair, activation and restoration of p53 and p16, and inhibition of telomerase, may act in a pro-aging fashion such that targeting these pathways will not be recommended for anti-aging purposes. Especially, all targets of replicative immortality and evasion of apoptosis possibly promote cellular senescence.

Most prominent targets shared by both anti-cancer and anti-aging properties are blocking NF-κB and inhibiting mTOR signaling. Targeting either of these two or both pathways will cover all of the cancer and aging hallmarks except for replicative immortality and evasion of apoptosis; also targeting

Table 2. Summary of shared targets between cancer and aging hallmarks.

Hallmarks	Possible shared target	Cancer	Aging
Genetic instability	inhibition of DNA reapir	A	P
	activation of p53	A	P
	increase of p16	A	P
	elimination of ROS	P	C
	blocking NF-κB	A	A
Sustained proliferative signaling - loss of proteostasis	inhibition of IGF-1	A	A
	increase of HSF-1	C	A
	inhibition of HIF-1	A	C
	blocking NF-κB	A	A
	inhibition of PI3K/Akt	A	A
	reducing mTOR	A	A
	inhibition of CDKs	A	A
Evading anti-Growth signaling - epigenetic alteration	inhibition of DNA methyl transferase 1	A	C
	Inhibition of H3K4 methylation	A	P
	histone acetylation	A	P
	activation of Sirtuin	C	A
	inhibition of NF-κB	A	A
	inhibition of mTOR	A	A
Enabling replicative immortality and resisting programmed cell death - telomere attrition and cellular senescence	inhibition of telomerase	A	P
	restore p53 function	A	P
	restore p16 function	A	P
Deregulating cellular energies - deregulated nutrient sensing and mitochondorial dysfunction	inhibition of HK2	A	P
	inhibition of PFKFB3	A	N
	activation of PKM2	A	N
	activation of AMPK	A	A
	inhibition of IGF-1	A	A
	inhibition of mTOR	A	A
	inhibition of HIF-1	A	C
	reverse mitochondrial dysfunction	A	A
Tumor promoting inflammation and avoiding immune destruction - altered intercellular communication	inhibition of NF-κB	A	A
	inhibition of PI3K-Akt	A	A
Tumor microenvironment - stem cell exhaustion	inhibition of FGF2	A	A
	inhibition of mTORC1	A	A
	inhibition of IL6	A	A
	inhibition of JAK signaling	A	A
	inhibition of IDO	A	A

A: Anti-action, P: Pro-action, C: Controversial, N: No relationship found.

these hallmarks in cancer might act in a pro-aging manner (Note that cancer-specific hallmarks of angiogenesis and invasion/metastasis are excluded in this review.).

Next possible targets are inhibition of IGF-1 and PI3K/Akt pathways, both of which also show anti-aging and anti-cancer properties. Inhibition of IGF-1 will cover the hallmarks of sustained proliferative signaling/loss of proteostasis and deregulated metabolism, and inhibition of PI3K/Akt will cover the hallmarks of sustained proliferative signaling/loss of proteostasis and inflammation/ altered intercellular communication in cancer and aging. Thus, these possible targets will be enough to cover all hallmarks shared by anti-cancer and anti-aging properties such that we will seek and discuss the approaches focusing on targeting these pathways for gaining human health by reducing the risks of aging and cancer.

Varieties of natural products such as phytochemicals, flavonoids or other plant extracts have shown their anti-cancer as well as anti-aging effects by targeting various pathways including NF-κB, mTOR, IGF-1 and PI3P/Akt pathways. Several nutrient factors can modify the underlying mechanisms that cause genetic instability. For instance, Vitamin B and D show protective role against DNA damage [119, 120], and selenium [121, 122] and carotenoid [123] show a role for enhancing the DNA repair, leading to both anti-aging and cancer prevention. In contrast, resveratrol shows an inhibitory effect on DNA repair that potentially enhances the effects of chemotherapeutic agents against cancer [124, 125]; however inhibition of DNA repair might work in accelerating aging process, although resveratrol has been suggested as showing) life expanding effect [126]. Anti-oxidants also have been suggested as showing life expanding effects, but they may cause more cancers than they could prevent [22]. Further investigation will be required on these issues.

On the other hand, polyphenols of resveratrol and curcumin and flavonoid of genistein could be the potential therapeutic agents targeting both sustaining proliferative signaling and proteostasis. Curcumin blocks cancer cell proliferation by targeting signaling pathways such as NF-κB, STAT3, PI3K/Akt [127] and mTOR [128]. Resveratrol also blocks PI3K/AKT signaling by down-regulating cdk2, cyclinD1 and proliferative cell nuclear antigen (PCNA), and also downregulates AKT-ERK (AKT-extracellular signal-regulated kinase) signaling [129] and IKK (I kappa B kinase)-mediated phosphorylation of IκB [130] thereby inhibiting NF-κB [131]. Genistein blocks NF-κB [132] and promotes apoptosis by altering polyamine metabolism [133], and exerts anti-proliferative activity by blocking EGF signaling through FoxO3 activity [134, 135]. These natural compounds possibly act in an anti-carcinogenic as well as anti-aging manner against the hallmarks of sustaining proliferative signaling and proteostasis.

A number of natural polyphenols acts as demethylating and deacetylating agents, and reactivates tumor suppressors to combat cancers. For instance, curcumin inhibits the expression of DNMT1 (DNA (cytosine-5)-methyltransferases 1) that subsequently reactivates the tumor suppressors of p15(INK4B) and RASSF1 (Ras association domain-containing protein 1) by promoter demethylation and induces cell cycle arrest and apoptosis [136, 137]. The green tea polyphenol EGCG (epigallocatechin gallate) reactivates tumor suppressors of p21 and p16INK4a by reducing DNA methylation and increasing histone acetylation, and also induces cell cycle arrest and apoptosis [138]. Demethylating activity of EGCG is associated with the inhibition of DNMT1 via hydrogen bonding. Resveratrol and genistein also inhibit DNA methylation in cell culture and human intervention studies, resulting in reactivation of tumor suppressors [139].

However, in this scenario, these effects by curcumin, resveratrol and EGCG may promote pro-aging processes in cellular levels, as reactivation of tumor suppressors usually leads to cellular senescence and apoptosis. Furthermore, these polyphenols are also well known for their anti-aging effects through various manifestations, and possibly show the effects on cancer prevention through the activation of tumor suppressors. For instance, depletion of H3K4me3 increases lifespan by demethylation as described above [48]. Therefore, the effects of epigenetic modification between carcinogenesis and aging crossover in a very complex manner.

Among the phytochemicals, secoiridoid polyphenols in extra virgin olive oil have shown their efficacy in anti-cancer and anti-aging activities through the activation of AMPK (AMP-activated protein kinase) and suppression of crucial genes involved in the 'Warburg effect', suggesting extra virgin olive oil secoiridoid could be a potential gerosuppressant and anti-cancer agent [140].

Many molecules of phytochemicals can inhibit NF-κB pathway thus suppressing the inflammatory responses [141]. Dietary spices such as turmeric (curcumin), red pepper (capsaicin), cloves (eugenol), ginger (gingerol), cumin, anise and fennel (anethol), basil and rosemary (ursolic acid), garlic (diallylsulfide, S-allylmercaptocysteine, ajoene), and pomegranate (ellagic acid) that contain these phytochemicals have shown their inhibitory effects on NF-κB signaling pathway [142]. Polyphenols of resveratrol and EGCG also have potential inhibitory effects on NF-κB signaling pathway [143, 144]. Inhibition of NF-κB signaling by these phytochemicals could suppress immune response and show anti-carcinogenic effects.

In addition to the inhibition of NF-κB signaling, curcumin could inhibit PI3P/Akt pathway resulting in anti-cancer effect through PTEN activation [143], and resveratrol could inhibit IGF-R1 (insulin-like growth factor receptor 1) signaling [145], and genistein could inhibit Akt pathway exhibiting the anti-cancer effects [143, 146]. Curcumin, resveratrol, gallic acid, epigallocatechin gallate (EGCC) and genistein also could inhibit the mTOR pathway [147]. For anti-aging purpose, these natural compounds may be favored compared to synthetic chemicals or molecules in terms of undesired or unknown adverse effects. Of course, there are possible adverse effects in natural products such as phytochemicals, but effective inhibition of multiple pathways of NF-κB, mTOR, IGF-1 and PI3P/Akt involved in cancer development as well as aging process can be achieved by appropriate combinations of these chemicals with minimal adverse effects.

There are several concerns to achieving the desired effects from these approaches using natural products. One of the most important concerns is their bioavailability. The downside to phytochemical or natural product therapy is their poor absorption, rapid metabolism and excretion. Also, appropriate concentration with non-toxicity and highest effectiveness must be determined.

Aging process is the loss or decline of cellular and organ functions and sometimes acts as the defense mechanism of cancer development, while cancer development is the gain of abnormal function at the cellular level, sometimes as the results of failure of aging/senescence process. Thus, cellular or organ functions cross the junction toward loss (aging) or gain (cancer) at some points in the life. Proposed targets described in this review will provide new insights into the means of combating both cancer and aging. Further studies will be required to confirm the most beneficial approaches for achieving further improvements in human health.

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CONFLICT OF INTEREST STATEMENT

All authors have no conflicts of interest to declare.

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