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Biological and Molecular Diversity in Telomerase: Characteristics of hTERT in Human, Vertebrates and Yeast

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Abstract

hTERT (human telomerase reverse transcriptase) is the catalytic subunit of telomerase enzyme, and is essential for its functions. The aim of this review was to compare the TERT in human and other species including microorganism, vertebrates and mammals, in terms of its functions and regulation. According to literature, the catalytic subunit of telomerase in animals contains many conserved domains and residues, which have crucial roles in its functions. Moreover, the structure and biology of human telomerase seem to be more similar to that of dog compared other animals. Thus interestingly, unlike the mouse that is seemingly not a proper model for evaluation of telomerase activity and its regulation, dog may be an appropriate model for the experimental investigations of telomerase function and therapeutic strategies in cancer studies.

Keywords: Telomerase; hTERT; Human; Vertebrate; Yeast

Introduction

Telomere consists of 6 nucleotide sequences (GGATTT) at the terminal region of the eukaryotic chromosomes. During chromosome replication, DNA polymerase cannot replicate the ends of chromosomes at somatic level, and gradual loss of telomeres occurs after each round of replication [1-3]. Somatic cells have a limited capacity for proliferation known as the Hayflick limit, which is due to this loss of chromosome ends, and the number of replication beyond this limitation leads to apoptosis. Telomerase is a ribonucleoprotein enzyme that is responsible for maintaining the chromosome integrity in proliferative cells, by providing specific replication machinery at the chromosome ends [4,5]. It has essential roles in cell immortalization, tumorigenesis and progression of most cancers, as it is shown that telomerase has a high activity in 70-90% of malignant human tissues and many immortalized cell lines [6-9].

Telomerase is a multi-subunit enzyme, composed of RNA and proteins including Telomerase reverse transcriptase enzyme (TERT), Telomerase RNA (TER), ES1P catalytic subunit ES3P, KU heterodimers, Dyskerin and TEP that are required for assembly and maturation of telomerase. In human, TERT is known as hTERT, which is catalytic subunit of telomerase and is characterized by having reverse transcription (RT) activities. Also, TER subunit in human is known as hTER, which acts as a template for reverse transcription [10-14].

Telomerase is tightly regulated in several levels, including transcriptional and post-transactional. On one side, alternative splicing has an essential role in the regulation of hTERT mRNA expression [13,15], and on the other side, studies have shown that telomerase function is regulated by post-translational regulation in serine/threonine or tyrosine residue of hTERT [16]. In addition, several factors including p53, c-myc, AKT kinase, sp1, WT1, NF1, c-myb, AP1, and C-Ets2 regulate the catalytic subunits of telomerase [17-22].

It is demonstrated that human telomerase components are largely conserved in different species among mammals, and vertebrates, due to very important function of this enzyme [23-26]. Moreover, an association between regulatory factors in human telomerase and other species is stated [27,28]. Considering the numerous studies in this field, our aim in this review was to explore the relationship between human telomerase activity and functional hTERT with some candidate species. We compared function and sequences of hTERT with several species of mammals, vertebrates and microorganisms, in order to be able to suggest the best possible animal model for telomerase studies.

Telomerase Reverse Transcriptase (TERT) in Microorganisms

Yeast

Yeast telomerase is a ribonucleoproteins complex, composed of TERT (catalytic subunit), RNA template and protein subunits, however, its structure is not yet well known. In *saccharomyces cerevisiae*, there are a number of known subunits including Est1p, Est3p, Sm and Est2p (TERT) proteins in [29]. The comparison of TERT in yeast, compared to vertebrates, mammals and humans shows fundamental conserved residues in among species (Figure 1), which are essential for telomerase function. However, there are few regions in yeast telomerase which show specificity to this organism. The only less conserved in yeast can be considered as "nonconserved region" (N- region) of TERT, which seems to be species-specific characteristics. These regions are essential for maintaining telomerase and its performance, so the deletion based mutation in these regions affects the assembly of telomerase complex. On the other hand, deletion of the entire yeast TERT C-terminal does not interfere with the enzyme functions, but significantly reduces enzyme processivity.

In yeast, N-region proximal to GQ domains is an essential package for the telomerase processing and exhibiting the binding capability of nucleic acid. However, in human this package has important role in enzymatic processing. Furthermore, the domain of dissociation activities of telomerase is mapped to amino acid residues 69 to 134 in hTERT" and has a key role in elongation of telomere *in vivo* [27]. In addition, RT motif in yeast is highly conserved (includes 200-300 amino acids). Based on studies done in yeast and humans, a similar TERT and RT structure implies a similar function.

The main characteristic of yeast telomerase is an inability to synthesize long extension product. In yeast and human, the synthesis of

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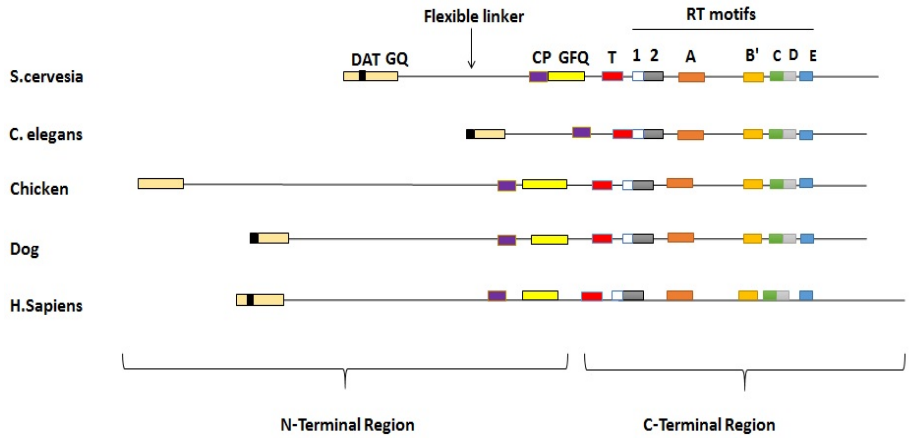

Figure 1: Schematic of sizes and relative locations of TERT protein motifs in human and some species.

3' telomeric DNA terminus is with the help of RNA template and short primers. DNA synthesis stops repeatedly during replication of template, therefore the majority of yeast telomerase products are inefficient, which suggests that yeast telomerase is inefficient not only at the 5' end of template but also in all templates areas [27,29] (Figure 1).

C-terminal region is highly conserved in human and other species. Note the flexible linker of chicken is longer than that of the mammalian species. In addition structure of TERT between human and dog are more conserved compared to other species.

Telomerase Reverse Transcriptase (TERT) in Vertebrates

TERT in fishes

Among fishes, TERT is well-studied in the zebrafish and pufferfish.

Zebrafish (*Danio rerio*): The length of Telomere in zebrafish is similar to that of human. Zebrafish telomerase reverse transcriptase (zfTERT) cDNA is 126 KD, and the range of other cDNAs is between 103 to 133 KD. Amino acid sequence that is coded by zfTERT is 36% identical to human and 32% to mouse. In addition, zfTERT contains 7 RT motifs and T motif which is especially found in TERT but not in other reverse transcriptase. Unlike mammalians, the zebrafish has a very high telomerase activity in somatic tissues. For this reason, the organs of adult zebrafish grow throughout the life. Telomere lengths are different in several different organs and tissues in zebrafish lifelong, alternative lengthening of telomeres (ALT), mechanism may be involved in this case in order to maintain telomeres in the absence of telomerase [26].

In mouse and *c.elegans*, mutation in either of the telomerase components including TERT and TR does not affect the phenotype in the first generation, but after several generations defects and chromosomal instability appear. However, because telomeres of zebrafish and humans are shorter than mouse, defects that result from mutation in each of telomerase component appears in the first generation. The TERT-/- zebra fishes show their phenotypes after first generation and stop cell proliferation in many tissues, such as gut and testis, which is controlled by p53 [26].

Pufferfish (fugue): The N-terminal region in pufferfish, recognized as fTERT, contains three regions with functional capacity known as motifs GQ, CP and QFP. The motifs CP and QFP, are accompanied by T- motif locating at the center of TERT, which are capable to mediate, and distinguish the binding of telomerase RNA in human, yeast and tetrahymena. The fTERT promoter contains Transcription Factor Binding Sites which are also traceable in the hTERT promoter including E2F-1, c-Myc, Mad 1, estrogen. In addition, Sp1 and USF are notable as well; and transcription factors play roles in the regulation of hTERT. However, the common transcriptional role of TFBSs in the hTERT and fTERT promoters may reflect the sharing mechanisms in mammalian and fish as two diverse species. Surprisingly, it is reported that TERT has a "single canonical E-box" within the promoters which locates at "position _68 to _72, relative to the TSS" in variety of species including mouse (mTERT), chicken (cTERT) and pufferfish (fTERT) Besides, the Sp1 is capable to cooperate with c-Myc and activate the hTERT transcription. Imperatively, the hTERT promoter including its two response elements lead to bind estrogen to its receptor through which the transcription of hTERT would be enhanced. Furthermore, the Sp1 and estrogen binding have role in the fTERT promoter [30].

Comparison of fTERT between human, chicken, mouse, and hamster showed lack of TATA box in fTERT promoter .However, promoters of fTERT and cTERT, by having the CCAAT box may characterize "TATA-less promoters" with an initiating role. Although the fTERT promoter has no CpG islands, but the human-TERT promoters and chicken seem to be GC-rich [31].

TERT in birds

Chicken: Among birds, TERT is well-studied in the chicken. The chicken telomerase reverse transcriptase (chTERT) proteins have 45% similarity to humans. The chTERT property can be distinguished from hTERT and other vertebrates by larger sizes of chTERT proteins due to greater linker region in N-terminal domain (144 amino acid greater than human). The chTERT genes are located at 2q2, near the telomere. Amongst many transcription factors, those binding to 5' UTR or promoter of chTERT are similar to human (Table 1). In spite of this fact, there are binding site of p53, WT1 and c-Ets2 in hTERT promoter that not present in chTERT promoters. Exclusively there are many binding site for c-myb in 5' UTR of chTERT. However, there is only one E-box in -264 of chTERT promoters but two E-box in -34 and -242 of hTERT [24].

Moreover there is CCAAT motifs in chTERT but is not found in hTERT promoter. This motif is essential for transcription initiation of TATA poor promoters, which usually is adjacent to transcription start site. Both hTERT and chTERT have many CpG Island in 5' UTR and

Factors Species	P53	c-myc	AP1	NF1	WT1	C-Ets2	SP1	c-myb
Human	Rep	Act	Act	Act	Rep	Act	Act	Act
Dog	Rep	Act	Act	Act	Rep	Act	Act	Act
Mouse	Rep	No effect						
Chicken	_		Act	Act			Act	Act
Zebrafish	Rep							
Pufferfish	-	-	Act	Act	-	-	Act	Act

Table 1: The comparison of factors binding to hTERT promoters in different species.

coding region, this shows that their function is regulated by methylation mechanism [23,24,28]. It could be concluded that regulation of chTERT and hTERT expression is similar but they have apparently different structures (Table 1).

TERT in mammalians

Telomerase structure and biology has been studied in several mammalian species include pig and dog.

Pig: Telomere sequences in pig is revealed to be TTAGGG which is similar to human, although its length in pigs is 10-30 KD which is longer than humans'. Lymph node, lung, and kidney tissues of male and female have high telomerase activities, but male pigs unlike females display no or very low levels of telomerase activity in the liver. In contrast, the telomerase activity of spleen in female pigs is higher than males. Moreover telomerase activity is low in ovary of female pigs. In contrast the humans, telomerase activity in ovary is associated to proliferation of endometrial tissue during the menstrual. The pig telomerase biology is more similar to mouse and rat rather than other animals and human [32].

Dog: The dog TERT protein composed of 1123 amino acids with a molecular weight of -124 kDa. Dog telomere length is 12-23 kb. Comparing the dog TERT with other mammals, it seems that the dog TERT have highest level of similarities to human TERT. Besides, telomerase activity in canine cell line is similar to human.

TERT in many eukaryotes such as yeast, ciliates, plants and mammals, is a large catalytic protein domain, which composed of several RT motifs, including 1, 2, A, B, C, D, and E which are essential for catalytic activity. TERT specific motif that is called T-motif, is located at the center of dog TERT proteins. The comparison of canine TERT with vertebrates revealed that the sequences of TERT N-terminal in this species are very similar [33,34]. The hTERT are more closely resembles to dog TERT rather than other mammals. Only Minor differences exist between human and dog sequences and we tried to refer to some of them; the core promoter of hTERT located at 300 bp upstream of start codon (ATG), but in dog TERT core promoter is located 314 bp away from start codon. Besides, there are several Sp1 binding sites located within this region and there is one MZF2 (zinc finger 2 protein) binding site in-605 of canine TERT promoter. MZF2 inhibits the expression of TERT promoters, and several MZF2 binding site exist in the hTERT promoter, four of which located at 200 bp upstream of hTERT core promoter.

In canine TERT there is an E-box at -1397; whilst, two E-boxes present in hTERT promoter. WT1 binding site located in the core promoter region of canine hTERT but in -358 bp of hTERT promoter. Telomerase levels are undetectable or low in both canine and human somatic tissues, and telomere gets shorter through each division. At a glance, differences and similarities between telomerase expressions in various tissues of humans are compared with several species in Table 2. Considering these facts that the dog physiology has many similarities with human [25,35,36] and that telomerase is highly expressed in most canine cancers (up to 90%), it seems that regulation of the dog telomerase catalytic subunits is very similar to humans (Table 2).

Mouse: The biology of telomerase in humans and mice are very different. Human telomeres are much shorter than that of mice. Telomere shortening has a pivotal role in tumor growth in humans but has limited role in mouse. Most mouse somatic cells, unlike human, gain telomerase activity and express hTERT [25,37]. Transcriptional activity of the hTERT promoter is much less than the TERT promoter in mouse that may be due to no conserved CG-box regions in hTERT promoter which are responsible for this suppression. So cis-regulation has been suggested to be important for regulation of the TERT transcription in tissue-specific manner [38]. By considering these facts, regulation of telomerase function in mouse and humans are highly different. However, mouse TERT (mTERT) promoter like hTERT has two E-boxes and also has p53 binding site. Mutations in E-box reinforce both hTERT and mTERT promoter expression; in fact, the hTERT promoter is activated by c-myc and deactivated by p53 while the mTERT promoter does not respond to either of them [39].

Studies on human ovarian epithelial cells, vascular endothelial cells, and breast cancer cells suggested that an Estrogen receptor Responsive Element (ERE) exists in the promoter region of hTERT, but there is not in the mouse TERT promoter [40]. In another study on MEF and HEK cell lines, it was determined that the hTERT promoter

Tissue Species	Ovary	Testis	Respiratory system	Lymphocyte	Heart	Kidney	Spleen	Liver	Gastro enteral system
Human	High	High	-	Low	-	-	Low	-	Low
Mouse	-	High	Moderate	Moderate	-	-	Moderate	High	High
Zebrafish	High	High	Very high		Low	High			
Pig	Low	High	Very high	Very high		Very high			
Dog		High	Low	Moderate		Low	Moderate	-	
Cat		High	Low	Moderate		Low	Moderate		
Chicken	High	High			low		Very high	High	High
Pufferfish	High	High	High		moderate		moderate		moderate

Table 2: Comparison of telomerase expression in human, mammalians and vertebrates tissues.

was inhibited by p53, p63 and p73. Although p53 inhibit the hTERT expression through inhibition of c-myc, in mouse cells inhibit the TERT expression via Ebox/E2F pathway [41]. There are 12 CpG Island at 615bp upstream of the transcription start site in mTERT promoter; these regions are hypomethylated (30% in adult liver, 20.8% in fertilized egg). This could be a potential explanation of higher telomerase activity in mice compared to human. Thus, methylation plays significant role in regulation of mTERT expression [42,43]. Finally as an overview, the key characteristics of TERT in different species are provided which is reflective of common behavior and diversity as well (Table 3).

It worth's to highlight the facts of similarity in specific physiologic and anatomic pattern for vertebrates regarding the selected biological characteristics (Table 4).

In spite of the similarities and the differentiae facts amongst these species, the main leading conclusion relies on' development and evolution'. However, our aim was to achieve the applicability of one of the mentioned animals as experimental tool in human in purpose of modeling the telomerase biological pattern and drug innovation.

Findings	References	Findings	References
Human		**Dog**	
TGF-beta treatment of MCF-7 cells_ repressed the hTERT promoter activity in a dose-dependent manner.	Yang et al. [1]	Molecular targets, telomerase biology and tumor genetics in dogs, cats and humans.	Pang, et al. [33]
hTERT promoter is GC-rich, lacks TATA and CAAT boxes_ contains binding sites for several transcription factors		TERT mRNA expression is associated with telomerase activity in dogs	Nasir, et al. [34]
hTERT expression subject to multiple levels of control_ regulated by different factors		Multiple transcription factor binding sites to the canine TERT promoters_E-box, Sp1, AP1, MZF-2 and ER/Sp1 binding sites_ similar to hTERT	Long, et al. [25]
The hTERT expression is partly regulated by atypical alternative splicing	Wong, et al. [15]	Dog telomere biology is similar to that in humans	Nasir, et al. [36]
		Yeast	
Re-amplification of the products could help the investigators to determine the majority of telomerase-positive samples.	Mehdipour [16]	Utility of budding to identify a large multi-subunit RNP enzyme (383 kDa, including hTERT-Cdc13 and hTR.	Wong, et al. [29]
Regulatory regions of the hTERT promoter _positive and negative regulation of telomerase	Horikawa, et al. [19]	Structure of the core telomerase components_RNA and telomerase reverse transcriptase subunit	Neal, et al. [27]
		Zebrafish	
Telomerase repressed in normal human somatic tissues but reactivated in cancer	Kim, et al. [6]	Zebrafish is effective model for the discovery of new drugs able to reactivate telomerase in dyskeratosis congenital DC patients.	Anchelin, et al. [26]
Mutations in sporadic melanoma cases at two positions in the TERT promoter _generated binding motifs for Ets/TCF transcription factors.	Horn, et al. [13]		
		Chicken	
The hTERT protein plays a key role in the activation of telomerase in cancer cells	Nakayama, et al. [11]	Several transcription factor binding motifs in the 5' flanking/promoter region of chTERT _similar to hTERT (E-box, Ik1, MAZ, Sp1 sites)_several c-Myb sites in chTERT only	Delany, et al. [24]
Shelterin protein interacts with hTERT and recruits hTERT onto the telomeres_ novel function of hTERT adds a new element to the molecular model of telomere length maintenance.	Zheng, et al. [3]	Telomerase activity in chickens similar to mice.	Venkatesan, et al. [3]
Association between hTR expression and telomerase activity	Hosseini-Asl, et al. [44]	TERT and TR transcript levels correlate with telomerase activity_TR is the rate-limiting factor in telomerase-negative tissues.	O'Hare, et al. [28]
		Mouse	
Expression of hTR and hTERT may be independent of tumors' stage.	Hosseini-Asl, et al. [44]	Essential role for telomerase and telomeres, in the maintenance of genomic integrity and viability of high-renewal organ systems.	Lee, et al. [37]
Several enzymes are necessary for telomerase functioning that facilitate new approaches for inhibit the telomerase in treating cancer.	Holysz, et al. [5]	The condensed chromatin environment of hTERT locus was crucial to its silencing during cell differentiation.	Wang, et al. [38]
Progression of malignancy is dependent on activation of telomerase	Counter, et al. [7]	large body mass presents an increased telomerase activity and cancer risk	Gorbunova, et al. [45]
		Pufferfish	
Activation of telomerase is an event that starts mostly at low grades of brain including meningioma and astrocytoma tumors.	Kheirollahi [9]	The level of fTERT expression was found to be higher in actively dividing cells and reduced at inactivity cell cycle regulate TERT and possibly telomerase activity.	Yap, et al. [30]
		Pig	
Importance of using hTERT genes FISH probes for cases with cancer cervix	Eid, et al. [22]	Somatic pig tissues levels of telomerase activity more similar to mouse and contrasts with humans and dog.	Fradiani, et al. [32]

Table 3: Exploration of Key facts in TERT territory in different species at a glance.

Characteristics	Key similarities to humans	Key differences
Zebrafish and Pufferfish		
Lifespan		Lifespan of 3-5 years; generation time of 3 months
Anatomy	Vertebrate body plan	Fishes; Aquatic adaptations include streamlined body plan and different locomotor strategies
Diet and metabolism	Omnivorous	Poikilothermic, grows optimally at 28.5°C
Reproductive system	Molecular and embryological biology of germ-cell development; cellular anatomy of germ-cell organs, the testis and ovary	No sex chromosomes; fertilization is ex vivo (that is, no uterus or the related internal female reproductive organs); oocytes are surrounded by a chorion, not the zona pellucida, which must be penetrated by sperm; non-lactating; no breast equivalent
Gastrointestinal system	Major organs: liver, exocrine and endocrine pancreas, gall bladder; zonal specializations along the length of the absorptive alimentary tract; immune cells in lamina propria	Lack an acidified digestive organ; have an intestinal bulb rather than stomach; intestinal Paneth cell not present
Respiratory system	Cellular gas exchange; oxygenation is dependent on circulation and hemoglobin carriage	Respiration occurs in gills, not lungs; no pulmonary circulation; possess an endoderm-derived swim bladder (functioning as a variable buoyancy device), which corresponds embryologically but not functionally to the lungs
Cardiovascular system	Multi-chamber heart with an atrium and ventricle; circulation within arteries and veins; separate lymphatic circulation	Has left–right distinctions in cardiac anatomy, but does not have separate left–right circulations, that is, the heart has only two chambers; so far no evidence for secondary heart field derivatives; lymph nodes have not been described
Chicken		
Lifespan		Life span of 8 year: generation time of 6 months
Anatomy	Vertebrate body plan	Bird; light skeletal system and light but powerful musculature; have more cervical (neck) vertebrae;
Diet and metabolism	Omnivorous; homeothermic	The average body temperature of a chicken is 41-45°C;
Reproductive system	Males have two testes	Females have two ovaries; right testes are also smaller than the left; egg-laying; have no phallus; sperm is stored in the seminal glomera.
Gastrointestinal system		Small intestine; chicken has crop; gizzard
Respiratory system	Have lungs	Do not have a diaphragm; the gas exchange occurs in the walls of microscopic tubules, called 'air capillaries; transferring more oxygen with each breath.'
Cardiovascular system	Four chamber heart, a right atrium and ventricle which receive deoxygenated blood from the body and send it to the lungs and a left atrium and ventricle which receive oxygenated blood from the lungs and send it to the body.	Has to work much harder than a human heart, the inside walls of the atria and ventricles are much smoother than those of the human. And the valves, though present, are much simpler. The ventricles of the bird heart have more muscle mass and less chamber space than those of a human; faster heart rate
Mouse		
Lifespan		Life span of 2-3 year: generation time of 8-9 week
Anatomy	Vertebrate body plan; mammals	Size; skull and tail morphology and in the shape and orientation of shoulder and pelvic girdle bones; Articular cartilage is thinner in mice and the subchondral bone plate more variable in thickness; cortex mostly comprises circumferential lamellae; structure of the dentition
Diet and metabolism	Omnivorous; the average body temperature is 36.9°C; homeothermic	Gnawer
Reproductive system	Similar ovaries, fallopian tubes, uteri, and placentation; histologic appearance and basic functions;	There are several structural and functional differences; prostate is divided into four lobes, where each lobe is histologically distinct; contains additional accessory sex glands that are not found in the human
Gastrointestinal system	Abundant bacterial flora within the colon; smooth muscle–enveloped tube with innermost mucosa (barrier epithelium, lamina propria, and muscularis mucosae), submucosa, muscularis propria, and variable serosa or adventitia	The morphologic appearance of the different sections of the upper digestive tract
Respiratory system	Both have two lungs; diaphragm is present; trachea has cartilage rings.	Anatomy and histology of the lungs; higher basal metabolic rate and more rapid respiratory rate in mice. The relative size of airway lumens of mice is larger; Mouse has smaller lungs, and branching occurs after bronchiole levels; Fungus seen in mouse lung
Cardiovascular system	Four-chambered hearts: left and right atria, a dominant left ventricle, and a thinner-walled right ventricle; the ratio of heart to body weight	Mouse heart is far smaller than the human heart; thinner walls of mouse arteries and the prominent presence of cardiomyocytes around mouse pulmonary veins
Pig		
Lifespan		Life span of 8 year: generation time of 12 month
Anatomy	Vertebrate body plan, mammals; major chest and abdominal muscles found in humans are present in the pig; dental anatomy	Different facial expression; bigger ears, a tail; different feet; position and number of toes on their feet; location of chest muscles that attach to the shoulder girdle; gluteal muscles
Diet and metabolism	Omnivorous; homeothermic	Average body temperature 38.8°C

Reproductive system	Ovaries; testes; prostate gland	In female urogenital sinus is present; oviducts each leads to horn of the uterus; Uterus two horn. In male penis underneath the ventral skin surface, posterior to the umbilical cord;
Gastrointestinal system	Esophagus; stomach, small and large intestines. Mesenteries	Colon is spiral
Respiratory system	Multi-lobed lungs; bronchial tubes leading to the lungs	Lungs have thinner walls; alveoli are less densely packed; pigs don't have a diaphragm. Instead, they use muscles in their throat sacs to help draw in air and push it back into the lungs; they don't breathe through their mouths; use muscles beneath their jaws to help move air
Cardiovascular system	Size; the heart is in the same place between the lungs, the liver and gall bladder	Aortic-mitral fibrous continuity was reduced in the outlet component of the porcine left ventricle, with approximately two-thirds of the aortic valve being supported by left ventricular musculature; the arterial duct (ductus arteriosus) leads directly from the pulmonary trunk to the aorta.
Dog		
Lifespan		Life span of 13 year: generation time of 3 year
Anatomy	Vertebrate body plan, mammals; Dog anatomy includes the same internal structures that are in humans; brain have dedicated voice areas; brains, are also sensitive to acoustic cues of emotion;	have disconnected shoulder bones (lacking the collar bone of the human skeleton); The olfactory bulb in dogs is roughly forty times bigger than the olfactory bulb in humans, The teeth are designed to crush dense objects;
Diet and metabolism	The average body temperature is 37-39°C; homeothermic	Carnivorous
Reproductive system	In the female, the reproductive system is composed of the ovaries, oviducts, uterus, cervix, and vagina; the ovaries are the site of production of the unfertilized eggs; the eggs pass from the ovaries into the oviducts; The developing embryos mature within the uterus, attached to its walls by the placenta which also surrounds them; uterus of the dog is Y-shaped. In the male Testicles, ductus or vas deferens, prostate gland, and penis. Sperm production and storage occurs within the testicles.	The epididymis is comparatively large;
Gastrointestinal system	Physiology of stomach; small intestine; large intestine; esophagus trace	Stomach is more acidic; Digestive tract is a lot smaller
Respiratory system	Have right and left lungs; diaphragm muscle; trachea has cartilage rings; the body's carbon dioxide is replaced with oxygen	It is also a unique cooling system
Cardiovascular system	heart has 4 chambers; The chambers on the right side are completely separate from the chambers on the left side; two arteria and two ventricle; a dominant left ventricle, and a thinner-walled right ventricle ; coronary arteries; coronary sinus remains similar in size to humans	Smooth inner lining of the ventricle; dog heart smaller than human hearts.

Table 4: Similarities and difference facts between human and some vertebrate animals.

Conclusion

As a complementary insight, some regions of N-terminus and C-terminal of TERT that have essential roles in telomerase activity are conserved in human and other species, while some other regions in N-terminus of hTERT, that have critical roles in telomere maintenance and the ability of telomerase process, are not conserved.

Although the structure of the yeast TERT gene is very similar to hTERT, its performance is different due to the extra regulatory proteins in human telomerase. On the other side, the regulation of expression in chicken TERT and hTERT are similar but their structure is different. The hTERT and mouse TERT sequences are similar but remarkable differences in regulation of their functions may be due to the extra proteins in human telomerase structures and its' different transregulation. Notably, the structure of the catalytic subunit, the regulation of expression and telomerase function in dog is more similar to humans compared to other animals.

According to previously conducted studies (Table 3), telomere length and telomerase function is associated to body size. Since dogs have a size larger than other studied animals, and also that human and dog have lots in common regarding anatomy, metabolism, alimentary tract, reproductive-e, respiratory- and cardiovascular system (Table 4), it is probably why the structure and biology of human telomerase is more similar to dog than other animals (Figures S1 and S2). Tumor development mechanism and also similar cancer stem cells are conserved between humans and dogs, as well (Table 3). Due to the biological similarities, we can predict similar response to treatment in cancers. These results suggest that dog can be an excellent model for exploring telomerase and diseases related to its abnormal activity.

References

1. Weinrich SL, Pruzan R, Ma L, Ouellette M, Tesmer VM, et al. (1997) Reconstitution of human telomerase with the template RNA component hTR and the catalytic protein subunit hTRT. Nat Genet 17: 498-502.
2. Yang H, Kyo S, Takatura M, Sun L (2001) Autocrine transformation growth factor_suppresses telomerase activity and transcription of human telomerase reverse transcriptase in human cancer cells. Cell Growth Differ 12: 119-127.
3. Zheng YL, Zhang F, Sun B, Du J, Sun C, et al. (2014) Telomerase enzymatic component hTERT shortens long telomeres in human cells. Cell Cycle 13: 1765-1776.
4. Cohen SB, Graham ME, Lovrecz GO, Bache N, Robinson PJ, et al. (2007) Protein composition of catalytically active human telomerase from immortal cells. Science 315: 1850-1853.
5. Holysz H, Lipinska N, Paszel-Jaworska A, Rubis B (2013) Telomerase as a useful target in cancer fighting-the breast cancer case. Tumour Biol 34: 1371-1380.
6. Kim NW, Piatyszek MA, Prowse KR, Harley CB, West MD, et al. (1994) Specific association of human telomerase activity with immortal cells and cancer. Science 266: 2011-2015.
7. Counter CM, Hirte HW, Bacchetti S, Harley CB (1994) Telomerase activity in human ovarian carcinoma. Proc Natl Acad Sci U S A 91: 2900-2904.

8. Shay JW, Bacchetti S (1997) A survey of telomerase activity in human cancer. Eur J Cancer 33: 787-791.

9. Kheirollahi M, Mehrazin M, Kamalian N, Mohammadi-asl J, Mehdipour P (2013) Telomerase activity in human brain tumors: astrocytoma and meningioma. Cell Mol Neurobiol 33: 569-574.

10. Meyerson M, Counter CM, Eaton EN, Ellisen LW, Steiner P, et al. (1997) hEST2, the putative human telomerase catalytic subunit gene, is upregulated in tumor cells and during immortalization. Cell 90: 785-795.

11. Nakayama J, Tahara H, Tahara E, Saito M, Ito K, et al. (1998) Telomerase activation by hTRT in human normal fibroblasts and hepatocellular carcinomas. Nat Genet 18: 65-68.

12. Hosseini-Asl S, Atri M, Modarressi MH, Salhab M, Mokbel K, et al. (2006) The expression of hTR and hTERT in human breast cancer: correlation with clinico-pathological parameters. Int Semin Surg Oncol 3: 20.

13. Horn S, Figl A, Rachakonda PS, Fischer C, Sucker A, et al. (2013) TERT promoter mutations in familial and sporadic melanoma. Science 339: 959-961.

14. Wrighton KH (2015) Telomeres: Chaperonin' telomerase. Nat Rev Mol Cell Biol 16: 4.

15. Wong MS, Wright WE, Shay JW (2014) Alternative splicing regulation of telomerase: a new paradigm? Trends Genet 30: 430-438.

16. Hosseini-Asl SP, Mehdipour (2013) Detection of Telomerase Activity: A New Strategy for Detecting Low Activity of Telomerase. In: Telomere territory and Cancer. Parvin Mehdipour (Ed.), Springer, Netherland.

17. Cong YS, Wen J, Bacchetti S (1999) The human telomerase catalytic subunit hTERT: organization of the gene and characterization of the promoter. Hum Mol Genet 8: 137-142.

18. Holt SE, Aisner DL, Baur J, Tesmer VM, Dy M, et al. (1999) Functional requirement of p23 and Hsp90 in telomerase complexes. Genes Dev 13: 817-826.

19. Horikawa I, Cable PL, Afshari C, Barrett JC (1999) Cloning and characterization of the promoter region of human telomerase reverse transcriptase gene. Cancer Res 59: 826-830.

20. Papanikolaou V, Athanassiou E, Dubos S, Dimou I, Papathanasiou I, et al. (2011) hTERT regulation by NF-ÎºB and c-myc in irradiated HER2-positive breast cancer cells. Int J Radiat Biol 87: 609-621.

21. Cifuentes-Rojas C, Shippen DE (2012) Telomerase regulation. Mutat Res 730: 20-27.

22. Eid MM, Nossair HM, Ismael MT, Amira G, Hosney MM, et al. (2011) Clinical significance of hTERC and C-Myc genes amplification in a group of Egyptian patients with cancer cervix. Gulf J Oncolog 1: 18-26.

23. Venkatesan RN, Price C (1998) Telomerase expression in chickens: constitutive activity in somatic tissues and down-regulation in culture. Proc Natl Acad Sci U S A 95: 14763-14768.

24. Delany ME, Daniels LM (2004) The chicken telomerase reverse transcriptase (chTERT): molecular and cytogenetic characterization with a comparative analysis. Gene 339: 61-69.

25. Long S, Argyle DJ, Gault EA, Campbell S, Nasir L (2005) The canine telomerase catalytic subunit (dogTERT): characterization of the gene promoter and identification of proximal core sequences necessary for specific transcriptional activity in canine telomerase positive cell lines. Gene 358: 111-120.

26. Anchelin M, Alcaraz-Pérez F, Martínez CM, Bernabé-García M, Mulero V, et al. (2013) Premature aging in telomerase-deficient zebrafish. Dis Model Mech 6: 1101-1112.

27. Neal FL (2000) Yeast Telomerases: Structure, Mechanisms and Regulation. Madame Curie Bioscience Database, Austin.

28. O'Hare TH, Delany ME (2005) Telomerase gene expression in the chicken: Telomerase RNA (TR) and reverse transcriptase (TERT) transcript profiles are tissue-specific and correlate with telomerase activity. Age (Dordr) 27: 257-266.

29. Wong LH, Unciti-Broceta A, Spitzer M, White R, Tyers M, et al. (2013) A yeast chemical genetic screen identifies inhibitors of human telomerase. Chem Biol 20: 333-340.

30. Yap WH, Yeoh E, Brenner S, Venkatesh B (2005) Cloning and expression of the reverse transcriptase component of pufferfish (*Fugu rubripes*) telomerase. Gene 353: 207-217.

31. Liu L, Lai S, Andrews LG, Tollefsbol TO (2004) Genetic and epigenetics modulation of telomerase activity in development and disease. Gene 340: 1-10.

32. Fradiani PA, Ascenzioni F, Lavitrano M, Donini P (2004) Telomeres and telomerase activity in pig tissues. Biochimie 86: 7-12.

33. Pang LY, Argyle DJ (2009) Using naturally occurring tumours in dogs and cats to study telomerase and cancer stem cell biology. Biochim Biophys Acta 1792: 380-391.

34. Nasir L, Gault E, Campbell S, Veeramalai M, Gilbert D, et al. (2004) Isolation and expression of the reverse transcriptase component of the Canis familiaris telomerase ribonucleoprotein (dogTERT). Gene 336: 105-113.

35. Dressman JB (1986) Comparison of canine and human gastrointestinal physiology. Pharm Res 3: 123-131.

36. Nasir L, Devlin P, Mckevitt T, Rutteman G, Argyle DJ (2001) Telomere lengths and telomerase activity in dog tissues: a potential model system to study human telomere and telomerase biology. Neoplasia 3: 351-359.

37. Lee HW, Blasco MA, Gottlieb GJ, Horner JW 2nd, Greider CW, et al. (1998) Essential role of mouse telomerase in highly proliferative organs. Nature 392: 569-574.

38. Wang S, Zhao Y, Hu C, Zhu J (2009) Differential repression of human and mouse TERT genes during cell differentiation. Nucleic Acids Res 37: 2618-2629.

39. Fujiki T, Udono M, Kadooka K, Yamashita S, Miura T, et al. (2010) Regulatory mechanisms of human and mouse telomerase reverse transcriptase gene transcription: distinct dependency on c-Myc. Cyto 62: 333-339.

40. Misiti S, Nanni S, Fontemaggi G, Cong YS, Wen J, et al. (2000) Induction of hTERT expression and telomerase activity by estrogens in human ovary epithelium cells. Mol Cell Biol 20: 3764-3771.

41. Yao Y, Bellon M, Shelton SN, Nicot C (2012) Tumor suppressors p53, p63TAα, p63TAy, p73α, and p73β use distinct pathways to repress telomerase expression. J Biol Chem 287: 20737-20747.

42. Horikawa I, Chiang YJ, Patterson T, Feigenbaum L, Leem SH, et al. (2005) Differential cis-regulation of human versus mouse TERT gene expression in vivo: identification of a human-specific repressive element. Proc Natl Acad Sci U S A 102: 18437-18442.

43. Pang LY, Argyle DJ (2009) Using naturally occurring tumours in dogs and cats to study telomerase and cancer stem cell biology. Biochim Biophys Acta 1792: 380-391.

44. Hosseini-Asl S, Modarressi MH, Atri M, Salhab M, Mokbel K, et al. (2006) The association between telomerase activity and expression of its RNA component (hTR) in breast cancer patients: the importance of DNase treatment. J Carcinog 5: 17.

45. Gorbunova V, Seluanov A (2009) Coevolution of telomerase activity and body mass in mammals: from mice to beavers. Mech Ageing Dev 130: 3-9.