Di Pietro *et al. Biology Direct* (2024) 19:119
https://doi.org/10.1186/s13062-024-00558-y

Biology Direct

REVIEW

Open Access

Telomeres: an organized string linking plants and mammals

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Abstract

Telomeres are pivotal determinants of cell stemness, organismal aging, and lifespan. Herein, we examined similarities in telomeres of *Arabidopsis thaliana*, mice, and humans. We report the common traits, which include their composition in multimers of TTAGGG sequences and their protection by specialized proteins. Moreover, given the link between telomeres, on the one hand, and cell proliferation and stemness on the other, we discuss the counterintuitive convergence between plants and mammals in this regard, focusing on the impact of niches on cell stemness. Finally, we suggest that tackling the study of telomere function and cell stemness by taking into consideration both plants and mammals can aid in the understanding of interconnections and contribute to research focusing on aging and organismal lifespan determinants.

Keywords Telomeres, Stem cells, Niche, Shelterin, Aging, Lifespan, Mice, Humans, Plants, Epigenetics

Background

Telomeres play a crucial role in determining cell stemness, organismal aging, and lifespan. In this study, we investigated the similarities in telomeres among *Arabidopsis thaliana*, mice, and humans. Our findings reveal common features, including their composition in multimers of TTAGGG sequences and their protection by specialized proteins. Furthermore, we explore the unexpected convergence between plants and mammals regarding the relationship between telomeres, cell proliferation, and stemness, emphasizing the influence of niches on these processes.

By considering both plant and mammalian systems, we propose that studying telomere function and cell stemness can enhance our understanding of interconnected mechanisms and contribute to research on aging and lifespan determination in organisms.

Life span is a key factor of all organism's lives and can depend on both intrinsic and extrinsic inputs. The life of vascular plants can span from several weeks as in ephemeral plants or as in the annual plant *Arabidopsis thaliana* to thousands of years as in Sequoia trees. In contrast, in eumetazoan, the lifespan can vary from 1 day as in mayflies to a maximum of two hundred years as in giant turtles or rough-eye rockfish. This difference in lifespan between animals and plants largely depends on distinct strategies of development. In plants most of the body organs are produced post-embryonically thanks to sets of pluripotent stem cells that are maintained for all the plant life. In mammals, pluripotent stem cells are linked with the embryonic stage, while in adult tissues subsets of

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adult stem cells confer only partial ability of tissue regeneration. In light of this, differential developmental strategies underpin the possibility of molecular and cellular differences in hallmarks associated with aging among the two kingdoms. In this review, we examined the properties of telomeres and stem cells. We considered the similarities and differences in mammals and plants, focusing on humans and mice on one hand, and on *Arabidopsis thaliana*, on the other. We reported on the characteristics of telomeric DNA, telomere-associated proteins, telomere-encoded RNA, stem cell subpopulations and specification, and the link between telomeres and stem cells.

Mammalian telomeres

Telomeric DNA

Mammalian telomeric DNA consists of tandem repeats of a specific nucleotide sequence, typically found at the ends of linear chromosomes. Mostly, telomeres contain a C- and G-rich strand and terminate with a 3' overhang made of single stranded DNA. In mammals, including humans, the telomere sequence consists of -TTAGGG repeats. The number of repetitions varies across species, as well as among different tissues and cell types (P. [106, 107],P. M. [106, 107]). Structurally, mammalian telomeres are organized into t-loops that form when the 3' telomeric overhang invades the double stranded portion of telomeric DNA [78, 195]. Telomeres are also organized into G-quadruplets in which four guanines form a structure stabilized by non-canonical base pairing [57]. Telomeric chromatin shows unusual features such as high mobility and short length of nucleosome repeats. Structural analyses propose a columnar model that contributes to conferring a compact chromatin structure and facilitating end protection [191, 191, 192, 192]. Mammalian telomeric and subtelomeric regions display epigenetic modifications and factors that are common to pericentric heterochromatin. These features encompass trimethylation of lysine 9 of histone H3, hypoacetylation of histones H3 and H4, the presence of HP1 (Heterochromatin Protein 1), and the abundant methylation of subtelomeric regions [23]. However, there are differences between pericentric and telomeric heterochromatin. For example, the deposition of H3K9me3 mark at telomeres was proposed to be dependent on SETDB1 (SET Domain Bifurcated 1) histone methyltransferase rather than on SUV39H1. Indeed, in cells depending mainly on ALT mechanism for the elongation of their telomeres (see Telomeres and mammalian stem cells section), SETDB1 was found enriched at telomeres and its loss disrupts telomeric heterochromatin influencing their ability to be elongated [69]. An important feature of human telomeric chromatin organization, is the coexistence of both active and repressive histone marks. Indeed, by Chip-seq experiment human telomeres were found to be enriched in in the euchromatic H4K20me1 and H3K27ac marks [41]. Chromatin organization of telomeric and subtelomeric regions impacts on telomere function and maintenance and are subjected to modification in physiological and pathological conditions [164]. Despite the high similarities between murine and human telomeres some differences are present and is important to take them in account in the translation of results obtained in mice as model systems to human. An important difference, for instance, regards the epigenetic status of human and murine subtelomeric regions. Indeed, it was found that while human subtelomeres are enriched in CpG dinucleotides, mouse subtelomeres are relatively CpG poor, and their methylation impacts differently in human and murine cells on the maintenance of telomeres, in particular through the regulation of TERRA transcription [208] (for further details see below Telomeric repeat–containing RNA section).

Telomeric proteins

In addition to these factors, the organization of telomeric chromatin in mammals is indeed influenced by both the telomeric sequence and a spectrum of epigenetic modifications, as we mention. Crucially, telomeric proteins actively engage with telomeric DNA, facilitating its folding and ensuring its functionality. These specialized proteins effectively create a protective barrier around telomeres, thwarting the initiation of a DNA damage response at chromosomal termini. These include the shelterins, which are, in human and mouse, TRF1 (Telomeric Repeat Binding Factor 1), TRF2 (Telomeric Repeat Binding Factor 2), RAP1 (Repressor/activator protein 1), POT1 (Protection of Telomeres 1; in mouse POT1A and POT1B), TIN2 (TRF-interacting nuclear factor 2), and TPP1 (also known as ACD, Adrenocortical Dysplasia

(See figure on next page.)

Fig. 1 Telomeres organization in mammals: (**A**) Human and (**B**) mouse shelterin shares a similar composition and organization, with six-proteins forming the complex (TRF1, TRF2, TIN2, TPP1, RAP1 and POT1) that binds to telomeric 5'-TTAGGG-3' repetitions. Unlike humans, mouse shelterin is composed of two POT1 proteins. (**C**-**D**) Mammalian shelterins are composed of proteins containing a Myb-domain (TRFs) that bind telomeric dsDNA, and containing OBs-folds (POT1), that bind telomeric ssDNA. (**E**) Human telomerase is composed of an enzymatic (TERT) and an RNA-template (TR) subunits. Mammalian telomeres possess both euchromatic and heterochromatic epigenetic marks

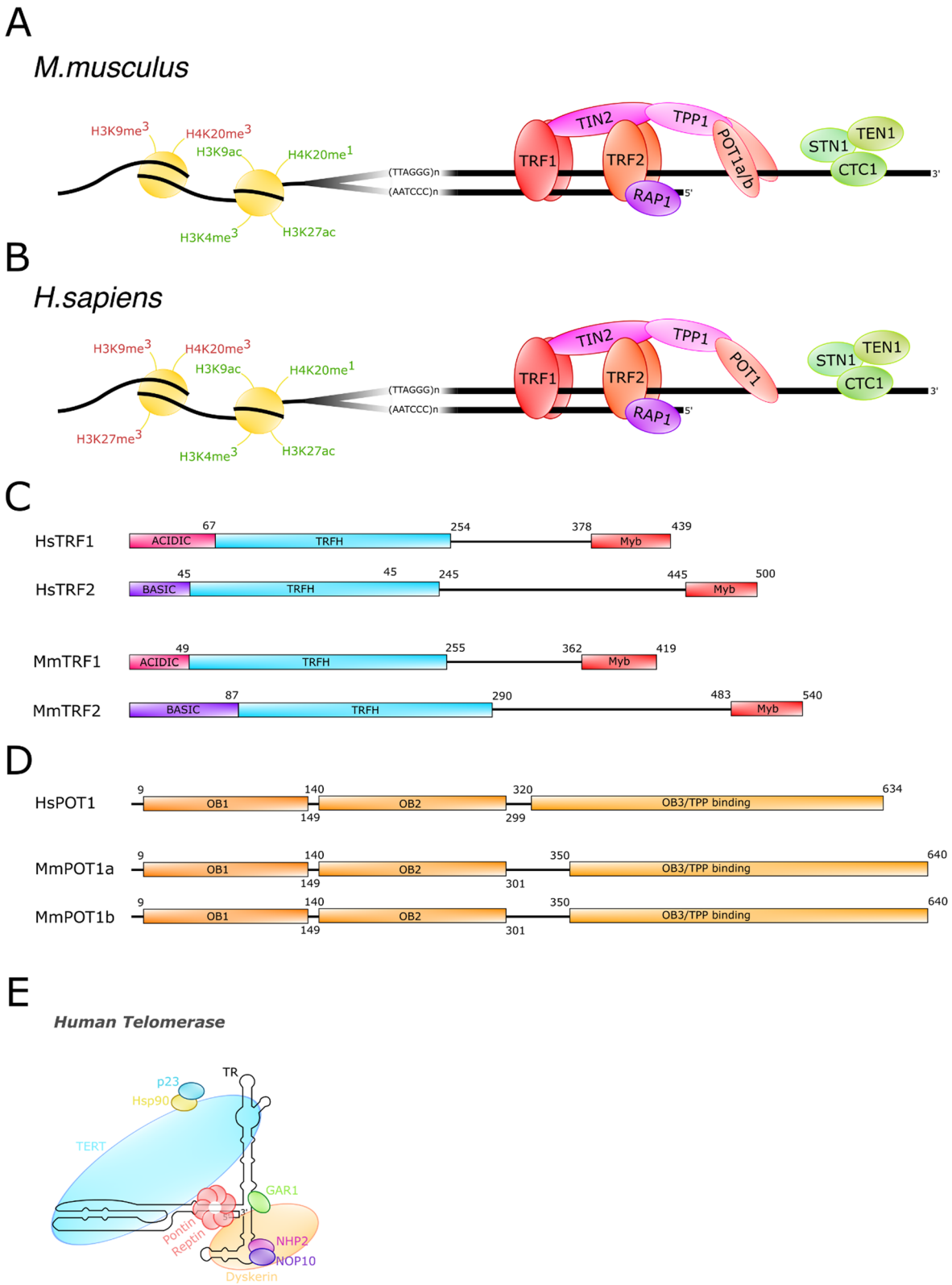

Fig. 1 (See legend on previous page.)

Protein Homolog). As depicted in Fig. 1, TRF1 and TRF2 bind double stranded telomeric DNA repeats. RAP1 interacts with TRF2, while POT1 interacts with the single stranded telomeric overhangs. TPP1 interacts with POT1 while TIN2 simultaneously interacts with TPP1, TRF1 and TRF2 and together hinge and stabilize the complex [143, 230]. Another protein complex sitting at telomeres is CST. This is formed in mammals by Ctc1 (Conserved Telomere Capping Protein 1), Stn1 (Suppressor of Cdc13 homolog), and Ten1 (homolog of telomerase capping complex subunit homolog) (Fig. 1A-B).

Structurally, TRF1 and TRF2 are similar (Fig. 1C). Both have a TRFH domain (Telomeric Repeat Binding Factor Homology domain), which is necessary to form homodimers, and a C-terminal Myb domain that is essential for interaction with double-stranded DNA [55, 80]. TRF1 and TRF2 differ in their N-terminal portions, which is acidic in TRF1 and basic in TRF2 (Fig. 1C). This portion is responsible for the interaction with other telomeric proteins and has a regulatory function [70].

TRF2 is the master shelterin factor: its depletion or the expression of a dominant negative form of TRF2, lacking the Myb and basic domains, trigger telomere end-to-end fusions. These chromosomal structures are a consequence of the activity of the DNA ligase IV and of the Non-Homologous End Joining pathway on the unprotected telomeric ends. The presence of telomeric fusions induces genome instability, cell senescence, or apoptosis [212]. TRF2 interacts with factors involved in sensing and repair of DNA damage, such as ATM (Ataxia Telangiectasia Mutated), MRN (Mre11-Rad50-Nbs1 complex), Ku70/Ku80, Apollo, and WRN (Werner Syndrome mutated RecQ Like Helicase), PARP (Poly (ADP-ribose) Polymerase) 1 and 2. TRF2 inhibits ATM activation. However, in case of telomere uncapping for excessive telomere shortening and/or for the loss of TRF2, ATM recruitment at telomeres is needed for a rapid activation of a DNA damage response, which inhibits cell cycle progression with damaged telomeres, potentially inducing cancerous transformation [45, 94].

Telomeres devoid of TRF1 show impairment in their replication, a process that is controlled by TRF1 in conjunction with the helicases RTEL1 (Regulator of Telomere elongation helicase 1) and BLM, together with other factors such as nuclear lamina associated protein AKTIP (AKT interacting protein) [27, 183].

POT1 binds to single stranded telomeric DNA thanks to the presence of two OB-Fold domains at its N-terminus (Fig. 1D). POT1 and its interactor TPP1 control the 3' overhang length and the sequence of the very terminal end of the chromosomes. POT1 is also an inhibitor of the DNA damage sensor ATR (Ataxia Telangiectasia and Rad3 related). In fact, loss of ATR triggers rapid telomere elongation, telomere length heterogeneity, and branched telomeric DNA structures. These aberrant telomeres derive from the activation of Homology Directed Repair (HDR) [71, 94]. Differently from human, murine shelterin contains equal levels of two functionally different Pot1 proteins, Pot1a and Pot1b. They likely derive from a recent event of gene duplication followed by divergence and the full protection and maintenance of murine telomeres requires both of them. Pot1a is mainly involved in telomere protection from being recognized as damaged DNA. Its absence results in early embryonic lethality and in the activation of an ATR dependent DNA damage response at telomeres leading to HDR dependent fusions [88, 144]. Pot1b accounts for correct maintenance and processing of 3' overhang. Its absence results in mice premature death due to bone marrow failure caused by accelerated telomeres shortening [83, 79].

The CST complex, initially discovered in yeast, binds single stranded DNA including, but not exclusively, telomeric overhangs, and is involved in replication and maintenance of telomeres. The depletion of CST components induces 3' overhang lengthening due to the failure of CST mediated recruitment of primase alpha [34, 160].

In this recruitment, POT 1 plays an important regulative function. Indeed, the analysis of Cryo-EM CST-POT1/TPP1 complexes structure revealed that CST-primase recruitment to shelterin requires POT 1 phosphorylation. POT 1 dephosphorylation is then needed to release CST-primase complex allowing its activation. This ensures the temporal coupling between the telomeres synthesis by replication machinery, the end resection processing, the telomerase activity and the fill in action of primase alpha guaranteeing the maintenance of telomeres [29].

If shelterins and the CST complex influence telomere maintenance, the main player regulating telomere length is telomerase, a complex which counteracts the shortening of telomeres by adding repetitive DNA sequences to the ends of chromosomes [22, 176]. Telomerase consists of an RNA template and a catalytic protein called telomerase reverse transcriptase (TERT; Fig. 1E). The RNA template guides TERT to synthesize and add DNA repeats onto the ends of chromosomes, replenishing the telomere sequences lost during each cell division [176]. While the RNA component is expressed ubiquitously in all cell types, the expression of TERT is limited to specific mammalian cell types, including embryonic cells, and in adult in germ cells, adult stem cells, T-and B-lymphocytes, while it is silent in the majority of other somatic cells from early human development [112, 129, 137, 222]. TERT expression is also aberrantly reactivated in most human cancers. This step is essential to let cancer cells to avoid senescence induction ensuring chromosomal

stability by maintaining telomere length. Cancer cells reactivate TERT expression by different mechanisms including TERT gene rearrangements, epigenetic alterations, somatic mutations in TERT gene promoter, or alteration in regulatory pathways [1, 30, 52, 114].

Shelterins regulate telomerase activity. TRF1, for example, is a negative regulator, via a mechanism which is common to other shelterins and links the functional activity of telomerase to the amount of TRF1 bound to telomeric sequences [190].

Telomeric repeat–containing RNA

For a long time, telomeres have been considered transcriptionally inactive. However, in 2007 it was discovered that telomeres are transcribed into long non-coding RNA molecules named telomeric repeat–containing RNA (TERRA) [12]. TERRA is transcribed by RNA polymerase II starting from different subtelomeric regions [177]. TERRA transcription is regulated during the cell cycle, with a peak in G1 and a decrease during the S-phase [18, 151]. DNA methylation and histone trimethylation have a repressive effect on TERRA expression, whereas histone acetylation promotes it [9, 11, 151]. Despite the high level of conservation of TERRA presence and features in the organisms studied to date, the mechanisms of TERRA regulation are not fully conserved between species. Indeed, for instance, it was discovered that human and mouse subtelomeres differ for the abundance of CpG dinucleotides, and their methylation levels correlate with TERRA transcription in human but not in murine cells [164, 208]. TERRA molecules are detected in the nucleoplasm associated mainly, but not exclusively, with telomeric repeats and with TRF1 and TRF2 [46, 104, 105, 117, 118]. The interaction between shelterin and TERRA has important consequences on TERRA distribution influencing also important processes as transcription and cell fate. Indeed, for example, it was demonstrated that TRF1, regulating TERRA levels, modulates the recruitment of polycomb complex to pluripotency and differentiation genes, influencing their expression [124]. TERRA is involved in telomere maintenance via its interaction with HP1 and SUV39H1 and in telomere replication and lengthening through telomerase recruitment [18, 46]. In this context, it was demonstrated that TERRA negatively regulates telomerase activity in human cells and TERRA transcripts preferentially locate at longer telomeres, letting the elongation of the shorter telomeres [156–19]. Alterations in TERRA trigger telomeric aberrations [18, 46, 118]. Growing evidence moreover outline the link between TERRA and ageing. For example, elevated levels of TERRA were observed in cells from patients with different type of premature ageing syndromes. These increased levels could be linked to the decrease in heterochromatic marker, observed during aging and could be important for the activation of a DNA damage response at telomeres to induce senescence [4, 5, 9, 231]. Moreover, considering the inhibitor effect of TERRA on telomeres activity, it's reasonable to speculate that the increased level of TERRA could impair telomerase activity in aged and prematurely aged stem cells contributing to the inhibition of tissue renewal [19].

Plant telomeres

Telomeric DNA

Similarly to animals, plant telomeres can end with G-rich DNA repeats that terminate in a 16–200 single stranded 3′G overhang (Fig. 2A). Plant telomeric DNA is mostly characterized by repetitions of the general minisatellite oligonucleotide motif 5'-TmAGn-3' (m: 2–4, n: 3), that is useful for recognition of telomeres by telomeric proteins present on both blunt and 3' G overhang ending telomeres [201]. This sequence is conserved in most eukaryotes, and even in some protozoa, and it is thus considered the ancestral one. In most plants, including *Arabidopsis thaliana*, this sequence is characterized by the heptanucleotide 5'-TTTAGGG-3' (Arabidopsis-type motif). The Arabidopsis-type motif was the ancestral one, and a mutation in the template region of telomerase could give rise to other telomeric motifs, including the human-type motif 5-'TTAGGG-3' [167, 201]. However, several independent evolutionary events in telomerase or the telomerase RNA template enriched the range of telomeric repetition sequences causing the formation of shorter repetitions such as in the Asparagales and longer repetitions such as in *Allium* [56, 148, 149, 167, 225].

(See figure on next page.)

Fig. 2 Telomeres organization in plants: (**A**) *Arabidopsis* telomeres are coated by a smaller number of proteins representing the mammalian orthologue of TRFs and POTs proteins (TRB1, TRB2, TRB3, POT1a and POT1b) binding the 5'-TTTAGGG-3' repeats. CST complex (CTC1-STN1-TEN1) is conserved among mammals and plants. (**B**) Ku70/Ku80 heterodimer binds blunt-ended chromosome termini. (**C**-**D**) *Arabidopsis* shelterins-like TRBs are composed of proteins containing a Myb-domain, that bind telomeric dsDNA, and containing OBs-folds (POT1s), that bind telomeric ssDNA. About TRF/TRB proteins, only the Myb-domain (red) appear to be conserved in both mammals and plants. About POT1 proteins, both OB1- and OB2-folds (orange) appear to be shared among mammals and plants. Both mammals and plant telomeres possess both euchromatic and heterochromatic epigenetic marks. (**E**) *Arabidopsis* RuvBLs proteins are tethered to telomerase complex by association with TRBs, differently from the human ones in which Pontin/Reptin associate with TERT and Dyskerin

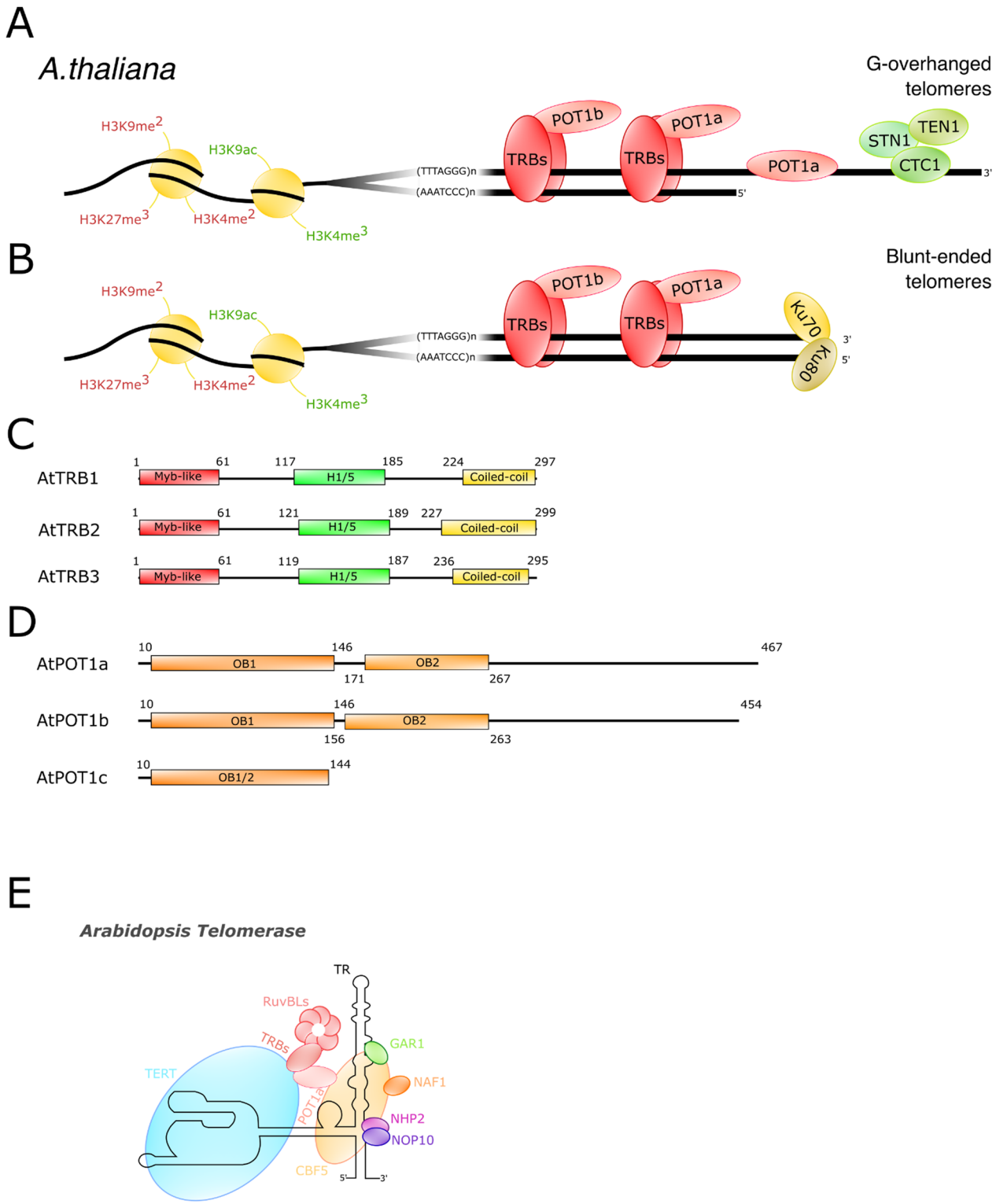

Fig. 2 (See legend on previous page.)

One of the major differences between mammals and plant telomeres resides in their ends. About 50% of chromosome ends in plants show short 3' G-overhangs (1–3 nucleotides) or even blunt ends [138, 211, 232]. It has been proposed that these blunt telomeres do not undergo post-replicative 3' end resection that is essential to create the G-overhang. These short overhangs cannot form t-loop and/or cannot bind single stranded telomeric proteins; such telomere ends are protected by the non-homologous DNA repair factors KU70/KU80 (Fig. 2B). The association of KU70/KU80 with 1–3 nucleotide long 3' G overhangs or with blunt ends is key to maintaining this architecture since *ku* loss of function mutants show formation of 3' G overhangs on both sides of the chromosome [162, 211, 232]. It is interesting to note that blunt ended telomeres evolved only recently in plants, since mosses such as *Physcomitrella patens* show only chromosomes ending with 3' G-overhangs [61]. The evolutionary advantage given by blunted chromosomes in plants is still not clear; one theory supports the idea that blunt ended telomeres might provide high genome stability to plants given that telomeres ending with G-overhangs are subjected to telomere rapid deletion that leads to the loss of large telomere sections [138].

Arabidopsis telomeres possess a mix of both euchromatic and heterochromatic marks, making these structures close enough to avoid recombination and open enough to allow transcription. Consistent with this, they present the mark of constitutive heterochromatin H3K9me2 [216] and the facultative heterochromatin mark H3K27me3 [214]. *Arabidopsis* telomeres show also euchromatic modifications, and include the presence of the H3K4me3 [217] and H3K9Ac [214]. Interestingly, *Arabidopsis* telomeres present a H3K4me2 modification [214] that, in contrast to mammals where it is a euchromatic mark, plays a repressive role in plants. Indeed, studies have shown that this modification is associated with telomere silencing, causing repression of gene expression in these regions in contrast with its function in mammals (Fig. 2A-B) [113].

Telomeric proteins

Both blunt and 3' G-overhang telomeres are bound and coated by a complex containing shelterin-like proteins such as TRBs (Telomere Repeat Binding), and POT1s (Protection Of Telomere) (Fig. 2A-D). In analogy, with mammalian shelterins, these protein complexes allow for the proper metabolism and protection of chromosome termini.

In *Arabidopsis* there are five members of the TRB family (TRB1-5), but only TRB1, 2, and 3 are involved in telomere metabolism [102]. These proteins possess a myb-like domain at the N-terminus through which they can bind telomeric double stranded DNA (Fig. 2C). Thanks to a histone-like domain (H1/5), the different members of the TRB family can homo- or hetero-dimerize to bind telomeric double stranded DNA and can interact with other key telomere factors, including telomerase (Fig. 2C) [135]. *trb1* mutants are characterized by telomere shortening indicating its function at telomeres [180]. Beyond their localization at telomeres and their binding to telomeric repeats TRB proteins can associate also to promoters of different genes containing a telo-box motif linked to Polycomb complex proteins [234]. Here TRBs proteins are involved in the silencing of their target loci by diminishing chromatin accessibility via deposition of the repressive H3K27me3 mark mediated by PRC2 (Polycomb repressive complex 2) [235] and the removal of the activating H3K4me3 mark mediated by JMJ14 (Jumojini14) (M. [220, 221]). Indeed, *trb1 trb2 trb3* triple mutants show loss of H3K27me3 [235] and an enrichment in H3K4me3 over TRB (and JMJ14) binding sites (M. [220, 221]). As TRBs are also found in the PWWPs-EPCRs-ARIDs-TRBs (PEAT) complex, it is conceivable that a further level of chromatin compaction mediated by TRBs involves histone deacetylation [108, 204]. Moreover, the identification of a role of the linker histone H1 in limiting H3K27me3 deposition by antagonizing TRBs-mediated PRC2 activity at telomeric loci suggest a safeguard mechanism to avoid the formation of excessively large H2K27me3 blocks at telomeric regions [206]. In *Arabidopsis*, there are other proteins containing Myb domain and able to bind telomeric DNA, at least in vitro, as TRFL1 proteins family, but their single or multiple abrogation do not alter telomere length or generate phenotypes associated with telomere dysfunction, so they are not considered to have telomeric functions [64, 98].

Interestingly, in *Arabidopsis* the H1/5 domain is fundamental for interacting with the shelterin-like proteins POT1a, b homologous of the mammals POT1 proteins. Most organisms, including plants, possess a single copy of POT1, but in angiosperms POT1 has been duplicated [99, 100]. In *Arabidopsis,* there are three POT1-like loci, POT1a, POT1b and POT1c. Among those, POT1c is expressed at an extremely low level in vivo, and plants harboring mutation in this gene have a wild type phenotype, suggesting that this protein is not involved in telomere metabolism [99, 100]. The two active POT1 proteins, POT1a and b, derive from a recent gene duplication and contains two OB-fold domain, homologous to the two OB-folds of human POT1 (Fig. 2D). As in mammals, POT1a can interact with the single stranded telomeric DNA, but it accumulates at telomeres only transiently mainly in S-phase, likely as part of telomerase

complex. This protein positively regulates telomerase addition of telomeric repeats, increasing telomerase processivity [10, 193, 200]. In line with functions of POT1a, *pot1a* mutants show a reduced telomerase activity and a progressive telomere shortening [36, 186]. Intriguingly, POT1a is not needed to recruit telomerase to telomeres and it is not essential for chromosomes end protection, indicating a distinct role for POT1 proteins in mammals [159]. POT1b shows a complementary function in the negative regulation of telomerase and its overexpression results in several developmental defects [36]. It has been demonstrated that overexpression of a dominant-negative allele of POT1b results in telomere shortening and end-to-end chromosome fusions, supporting the idea that POT1b is involved in chromosome end protection [186]. *POT1b* expression is developmentally regulated and it is detectable only in root tips, seeds, and flowers. Moreover, POT1b expression is induced by oxidative stress to which telomeres are highly sensitive due to their elevated content in G [31, 184]. These observations provide ground to speculate a role for telomere metabolism in plant plastic development.

Plant telomeric DNA is bound by the CST (CTC1-STN1-TEN1) complex (Fig. 2A). The *Arabidopsis* CST complex is structurally analogous to the mammalian one and plays a role in protection of chromosome ends. In fact, the depletion of each of CST subunit elicits telomere shortening and fusions and long G-overhangs. Despite being viable, mutants null for CST proteins show defects in cell proliferation and morphological defects [74, 109, 199]. The CST complex interacts with the shelterin-like proteins thanks to the STN1 subunit. Namely, STN1 interacts with POT1a and TEN1 in a mutually exclusive manner, with the former positively regulating the telomerase, and with the latter negatively regulating it [10, 159]. Telomerase acts on telomeres lacking CTC1 or STN1 to partially alleviate defects derived from their depletion [159], indicating that the CST complex is not required for telomerase recruitment to telomeres. Moreover, the CST complex cooperates with ATR (ataxia telangiectasia and Rad3-related) kinase in maintenance of telomeric DNA [24, 152].

As in mammals, telomere length depends on a dynamic balance between mechanisms that shorten and elongate telomeres. Telomere length is highly variable among different plant species and ecotypes. In the *Arabidopsis Columbia* ecotype telomere length is about 2.5–5 kb, whereas in other ecotypes, such as *Wassilewskija*, telomere length ranges from 3.5 to 8 kb [185]. Both extra-long and extra-short telomeres are disadvantageous for plants. Mutations in CST proteins cause telomere shortening, resulting in chromosomal fusions [84, 199]. In contrast, mutations in *KU* genes cause ultra-long telomeres that are subject to random trimming, thus generating genome instability [163, 223]. It has been demonstrated that the minimal functional length for Arabidopsis telomeres is approximately 400 bp, when the telomeres overcome this threshold, the shortened telomeres exhibit chromosome end-to-end fusions and genome instability [224].Interestingly, presence of t-loops in plants was firstly demonstrated in *P.sativum*, suggesting that this structure could occur in higher plants [32]. Considering that in vitro studies have demonstrated that the minimal length for telomeric DNA to form t-loop is around 500 bp, it was suggested that the minimal length observed for Arabidopsis telomeres could be the length needed to form t-loop, suggesting that this structure could be important for end protection [78, 224]. How and whether species and ecotype specific telomere length is related to blunted end telomeres is still a matter of discussion.

Telomerase in *Arabidopsis* is composed, as in mammals, of an enzymatic (TERT) and an RNA- subunit (Fig. 2E). As in mice and humans, Arabidopsis TERT associates with an RNA template (AtTR) that guides TERT to synthesize and add DNA repeats onto the ends of chromosomes [56]. Differently from most human cells, in which the expression of TERT is highly regulated whereas the RNA subunit is quite ubiquitously expressed, the levels of AtTR show a tissue-specific pattern that resembles the one observed for TERT [179].

As in mammals, plant telomerase complex includes not only AtTR and TERT, but also other proteins with a regulative function as CBF5 (the Arabidopsis orthologue of Dyskerin in animals), or plant RubvL proteins (Fig. 2E). TRB proteins were implicated in the recruitment of telomerase complex at telomeres thanks to their interaction with TERT itself, but also with CBF5 and POT1a [92, 150, 178, 180].

It keeps on being intriguing to understand the mechanisms through which chromosome ending replication occurs in blunt or short plant telomeres and whether and how telomerase is recruited on such telomeres. It has been proposed that restricted access both exonucleases and telomerase at blunt or short telomere ending causes low telomere length variations [139]. It has also been shown that telomerase inactivation results in only 250 nucleotides shorter telomere across each plant generation [161]. Considering this results, it has been proposed that telomere length stability might be desirable for plants but not for animals where the stability of blunt-ended telomeres may be deleterious and results metastatic cancer. Further molecular, genetic and ecological studies will permit to enlighten this point.

Telomeric repeat–containing RNA

The overall organization of plant telomeres allows transcription from telomeric and subtelomeric regions of the lncRNA TERRA, which is involved in facilitating the deposition of heterochromatic modification on telomeres, in a similar fashion to animals [217]. However other than TERRA, the transcription of both telomeric strands produces another lncRNAs named ARRET (antisense telomeric transcript). TERRA and ARRET generate a dsRNA that is processed by the RNA-processing enzymes of the RdDM (RNA-dependent DNA methylation) pathway such as RNA-dependent RNA polymerase 2 (RDR2) and DICER-like 3 (DCL3) to generate telomeric siRNA [54, 217]. These siRNAs are involved in the methylation of specific DNA sequences mediated by small RNAs. RDR2 is required for additional RNA-dependent RNA synthesis after TERRA and ARRET annealing and DCL3 then cleaves the newly generated dsRNA into a 24 nt small RNAs that appear to be specifically held by Argonaute 4 (AGO4) to mediate siRNA-mediated DNA methylation of asymmetric cytosines in telomeric sequences [217].

Despite several advances in understanding the role of lncRNAs in the plant kingdom, their function in development still remains vague. TERRA and ARRET are paradigmatic examples of lncRNAs that are transcribed in plants, but their functions has not been thoroughly characterized. Accordingly, whether or not TERRA and ARRET play a role in the maintenance of stem cell activity is still unknown. Future studies will help to clarify their roles.

Stem cell plasticity in mammals and plants

Stem cells in mammals

Mammalian stem cell subpopulations

Stem cells are characterized by their extraordinary ability to undergo asymmetric division, wherein one daughter cell is programmed to acquire a specialized fate while the other retains its stem cell identity. The asymmetry of mammalian stem cells has been, in most cases, established during embryogenesis. Embryonic stem cells are pluripotent, i.e. can produce all three germ layers, ectoderm, endoderm, and mesoderm, while adult stem cells are not and, in principle regenerate only the tissue of origin.

Embryonic stem cells are derived from the inner cell mass of the blastocyst, which is an early-stage embryo typically formed within the first few days after fertilization. Pluripotency of embryonic stem cells has been shown by in vitro differentiation experiments, and, more conclusively, by chimeric mice created via embryonic stem cell implant in mouse blastocysts [25, 53].

Mammalian adult stem cells are categorized into multiple types and can be found in several tissues and organs, including bone, brain, skeletal muscle, and hair follicle [38](Fig. 3A).

The best characterized adult stem cells are hematopoietic stem cells. The presence of stem cells in blood—anticipated by the success of bone marrow transplants in humans- was demonstrated by experiments of serial transplants of mouse hematopoietic stem cells in sublethally irradiated mice. The latter experiments were used to show not only that adult blood contains progenitors, but also to demonstrate that these progenitors can regenerate themselves [13, 207]. The molecular tools used to isolate, enrich, and define mammalian blood stem cells are cell surface markers, conceptually exploiting immunology and hematology studies on surface receptors. These include Lin (bone marrow-derived lineage-negative), which must be down-regulated, while CD34 (Cluster of Differentiation 34), CD38, CD45RA, CD90, and CD49f must be up-regulated [123, 142, 165, 236] (Fig. 3A). Even though the list of such molecules is in continuous expansion, with an extreme level of superdefinition with the advent of single cell transcriptomics, the CD34 remains a paradigmatic marker of hematopoietic stem cells, also based on its pivotal role in the switch from bench to bedside of stem cell research [7, 81, 93, 188].

If blood easily recalls a regenerating adult tissue that makes the presence of progenitors expected, other tissues in mammals regenerate and contain stem cells, including skeletal tissue and muscles [20] (Fig. 3A). Skeletal regeneration and skeletal stem cells were characterized starting with the work by Friedenstein who first described skeletal stem cells as stromal stem cells supporting a hematopoietic and lymphoid microenvironment [62]. In the following years, other studies underlined and further defined the role of skeletal stem cells in bone regeneration and in the organization of the bone marrow hematopoietic microenvironment [20, 21, 171, 172]. It was demonstrated early on that stromal cells, which fall into the group of osteoprogenitors/skeletal stem cells/mesenchymal stem cells, form adherent colonies *ex-vivo* [62, 63]. This phenotype is used to isolate skeletal stem cells from bone biopsies. Additionally, surface markers, in analogy with the approach applied to hematopoietic stem cells, have been identified to type skeletal stem cells. These include downregulated CD34 and CD45 and upregulated CD146 [171]. In depth analysis of cells of various origin with this marker phenotype has, however, highlighted that they cannot be an absolute guarantee of skeletal cell stemness [172]. Indeed, transcriptomic studies on cells identified not only in bone marrow, but also in other tissues as CD34 − /CD45 − /CD146 + have shown that the differentiation potential of these cells depends on the site of origin. This fact is further supported by

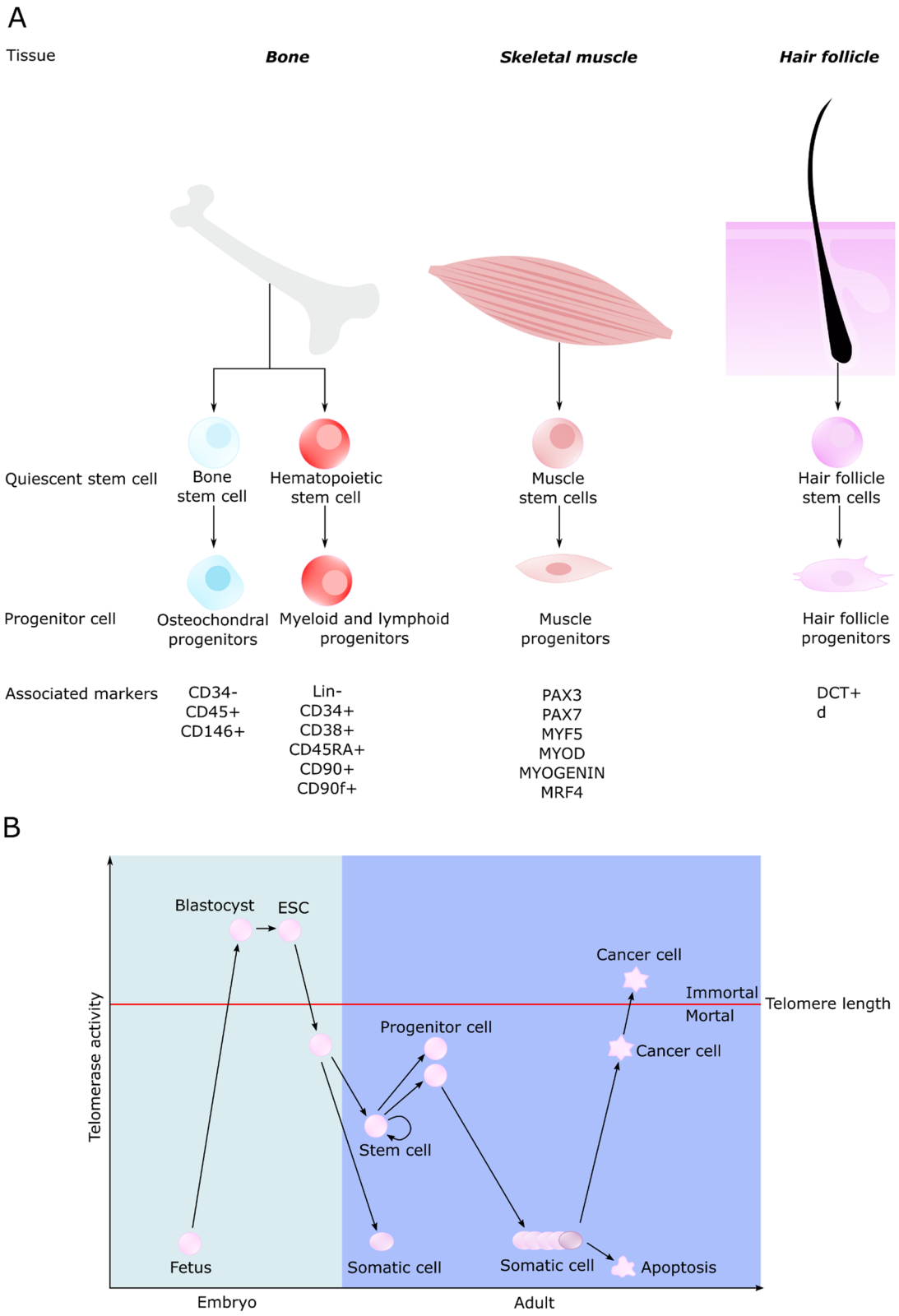

Fig. 3 Mammalian stem cells (**A**) Subpopulations of adult stem cells and their associated markers. (**B**) Telomerase expression in mammalian stem cells. Higher telomerase expression is found in embryonic stem cells (and cancer cells upon reactivation); it decreases in adult stem cells and is not detectable in most somatic cells

the observation that CD34 − /CD45 − /CD146 + cells of different origin have different transcriptomic signatures [172] (Fig. 3A). Taken together, the data suggest that the conclusive proof of stemness can be obtained only by performing functional in vitro and in vivo differentiation assays. In the case of skeletal stem cells, this translates in the ability of the cell sample to develop an ectopic functional ossicle upon transplantation in mice [21, 172].

A third class of adult stem cells in mammals are derived from skeletal muscle and were first identified by their morphology, which is flattened and relatively small compared to the mature myofibers, the post-mitotic syncytial cells that compose muscles [127] (Fig. 3A). Called satellite cells due to their anatomical location at the periphery of myofibers, they mostly stay quiescent but can transition into an actively dividing state following injury to regenerate skeletal muscle tissue and to replenish the reservoir of stem progenitors, on the other. The molecular definition of skeletal muscle stem cells is associated with PAX3 and PAX7 and with the so-called myogenic regulatory factors, MYF5, MYOD, MYOGENIN and MRF4 [158] (Fig. 3A). The renewal and properties of skeletal muscle stem cells is a dynamic process regulated by the microenvironment [68, 140].

Mammalian stem cell specification

Stem cell specification in mammals is controlled both by internal and external factors. A recent intriguing example of stem cell determination in mammals concerns melanocyte stem cells. This subpopulation of stem cells controls hair color; its exhaustion leads to hair graying and is present in its undifferentiated state in the hair follicle niche [141]. Recent data show that these cells transit from an undifferentiated to a differentiated state by physical translocation [198]. In other words, cell mobility defines the stem or non-stem cell status. This latter observation supports the concept that stemness is not a fixed property, but rather a state that depends on the microenvironment or niche. In fact, the stem cell niche, which refers to the specialized microenvironment or anatomical location where stem cells reside within a tissue or organ, provides the necessary signals, support, and cues that regulate the behavior of stem cells, including their self-renewal, differentiation, and maintenance. It is a dynamic and complex environment that involves interactions between stem cells and surrounding cells, extracellular matrix components, and signaling molecules. These interactions play a crucial role in determining the fate of stem cells – whether they remain in a quiescent state, divide to generate more stem cells, or differentiate into specialized cell types to contribute to tissue regeneration and repair [33, 130, 131].

Bone represents a particularly intriguing example of stem cell niche since it hosts and controls two types of stem cells, namely hematopoietic and skeletal progenitor cells. This is clearly demonstrated by the histological organization of chimeric ossicles created in immunodeficient mice implanted subcutaneously with skeletal progenitor cells isolated from human bone marrow, which generate human osteoblasts, associate with sinusoids, self-renew into stromal cells, and, at the same time, organize hematopoietic niches for the creation of full mouse blood tissue [171]. Understanding the intricacies of the bone stem cell niche has significant implications for bone marrow transplantation, regenerative medicine, and treatments for disorders involving blood cell production, such as leukemia and other hematological diseases.

In addition to what is described above, the *fluidity* of the concept of stemness is supported by the discovery of induced pluripotent stem cells. These cells were generated by adding reprogramming factors – originally, Oct4 (octamer-binding transcription factor 4), Sox2 SRY-Box Transcription Factor 2), Klf4 (Kruppel like factor 4), and c-Myc (Myc: Master Regulator of Cell Cycle Entry and Proliferative Metabolism)-to adult differentiated cells, forcing them back into a pluripotent state, like embryonic stem cells [203]. This discovery dates to 2006 and was made first with mouse samples, and later with human and other animal derived cells [202, 203]. Beyond being a proof that the modulation of the intranuclear microenvironment imposed by the addition of specific factors recreates stemness in differentiated mammalian cells, reinforcing the idea that stemness is an inducible state, the discovery of induced pluripotent stem cells has significant implications in applied science. In fact, induced pluripotent stem cells offer, in principle, an alternative to embryonic stem cells for research and potential therapies, they can be generated from a patient's own cells, minimizing the risk of immune rejection in transplantation, and allowing for personalized medicine approaches. Moreover, they represent an up-to-date tool for the development of 3D organoids with human cells to simulate physiological and pathological paths in organ development [35, 66, 154, 196, 210, 213].

Telomeres and mammalian stem cells

The activity of telomerase is abundant in embryonic stem cells and is also detected in lymphocytes and in adult stem cells as hematopoietic, epithelial, and mesenchymal stem cells [60, 87, 119, 132, 166, 182](Fig. 3B). Proof of the role played by telomerase activity and telomere length in cell proliferation potential, which does not necessarily coincide with stemness, derives from studies of diseases such as cancer and dyskeratosis congenita [14, 76, 97]. In cancer, telomere elongation is needed for the

indefinite proliferative activity of cancer cells. This forced telomere elongation is obtained either by reactivation of telomerase or by alternative telomerase-independent elongation (ALT), a mechanism based on recombination and replication activity [121, 189, 233]. On the other end, in dyskeratosis congenita, a syndrome of premature aging linked to mutations in several genes including *DKC1 (dyskerin pseudouridine synthase 1), TERC, TERT, NOP10 (Nucleolar Protein Family A Member 3), NHP2 (Nucleolar Protein Family A Member 2), and TIN2*, telomeres and telomerase defects are drivers of the disorder which includes bone marrow failure and stem cell dysfunction [8, 85, 97, 126, 175, 209, 218, 219].

The response to telomere de-protection is, interestingly, different in stem cells compared to non-stem cells. Specifically, mouse embryonic stem cells and human pluripotent stem cells display an altered response to critically short telomeres including impaired activation of senescence, extended proliferation, and DNA synthesis [39, 153]. At the molecular level, these phenotypes have been associated with a different role played by the shelterin TRF2 in pluripotent stem cells compared to somatic cells [125, 145, 168]. Moreover, an intrinsic link also exists between critically short or TRF1 depleted telomeres and pluripotency genes. These are likely caused by epigenetic mechanisms involving Polycomb Repressive Complex 2 activity, possibly depending on TERRA [39, 124].

Plant stem cells

Plant stem cells subpopulations

Plant stem cells are defined, partly as mammalian stem cells, by their structural association with their niches. In plants, stem cell niches are in special structures called meristems [15, 16, 49, 174], (Fig. 4). In the niches, an organizer center maintains the stemness of contacting cells via local signals [49, 174]. Meristems are maintained for the entire life of the plant, ensuring continuous tissue and organ replacement and growth [49]. Two main meristems are generated during embryogenesis and maintained post-embryonically; the shoot apical meristem that gives rise to all the shoot organs such as leaves and flowers, and the root apical meristem from which all root tissues originate [174] (Fig. 4). Given that plant cell position determines cell fate, plant stem cells are multipotent. Shoot apical meristem and root apical meristem can originate additional meristems called secondary meristem that give rise post-embryonically to additional organs such as flowers, lateral roots, and cambium [174].

Shoot apical meristem and root apical meristem show distinct organization. The shoot apical meristem is a dome structure compound by two outer layers called tunica and an inner corpus (Fig. 4A). The shoot apical meristem can be divided in different zones by cell activity: the central zone, where stem cells are positioned over an organizing center, the peripheral zone where stem cell daughters proliferate, and the rib zone comprising stem cells positioned under the organizing center and stem cell daughters that ensure stem growth [174]. In the tunica, a large pool of stem cells is present whose number increases until the plant reaches the reproductive phase [174]. In the corpus, a pool of cells acts as an organizing center to maintain stemness of the outer neighboring cells. The asymmetric cell divisions occurring in the stem cells of the central zone displace the stem cell daughters in the peripheral zone and after several rounds of cell divisions will be primed and give rise to lateral organs such as leaves or new meristems such as floral meristems [174] (Fig. 4B).

Given the function of the root, namely a continuously growing organ specialized in penetrating soil that grows from the proximal area (the shoot to root junction) to the distal one (the root tip), the root apical meristem has a dynamic structure that is dissimilar from the shoot apical meristem [49, 173] (Fig. 4B). The root apical meristem has a dynamic structure that ensures continuous growth of the root organ [49], [173]) (Fig. 4B). From the distal tip to the proximal area, the root apical meristem can be divided in three different developmental zones; the stem cell niche, the division zone, and the transition zone [49, 173]. The most distal zone of the root apical meristem is the stem cell niche, where a set of stem cells divide asymmetrically to continuously produce daughter cells. In the stem cell niche, stem cells surround an organizer center (the Quiescent Center, QC) that maintains stemness of the contacting cells [49, 173]. The stem

(See figure on next page.)

Fig. 4 Plant meristem organization: (**A**-**B**) Shoot Apical Meristem (SAM). Schematic representation of *Arabidopsis* SAM. Tissues are depicted in false colors. Stem cell niche (SCN) function relies on the activity of WUS and STM to determine a cytokinin maximum in the Organizing Centre (OC) and on the induction of CLV3 by WUS that in turn represses WUS. Cell from SCN generate daughter cells composing the peripheral zone before differentiation and incorporation in lateral organs. (**C**-**D**) Root Apical Meristem (RAM): Schematic representation of *Arabidopsis* RAM. Tissues are depicted in false colors. All root tissues originate from stem cell niches (SCN, red line). SCN is patterned and maintained thanks to the formation of an auxin maximum in SCN (green gradient) and the activity of PLETHORA (PLTs) transcription factors. Along with SHR and SCR transcription factors, these mechanisms maintain stem cell function and counteract cytokinin activity, allowing for a predominance of cell division over cell differentiation in the meristematic zone

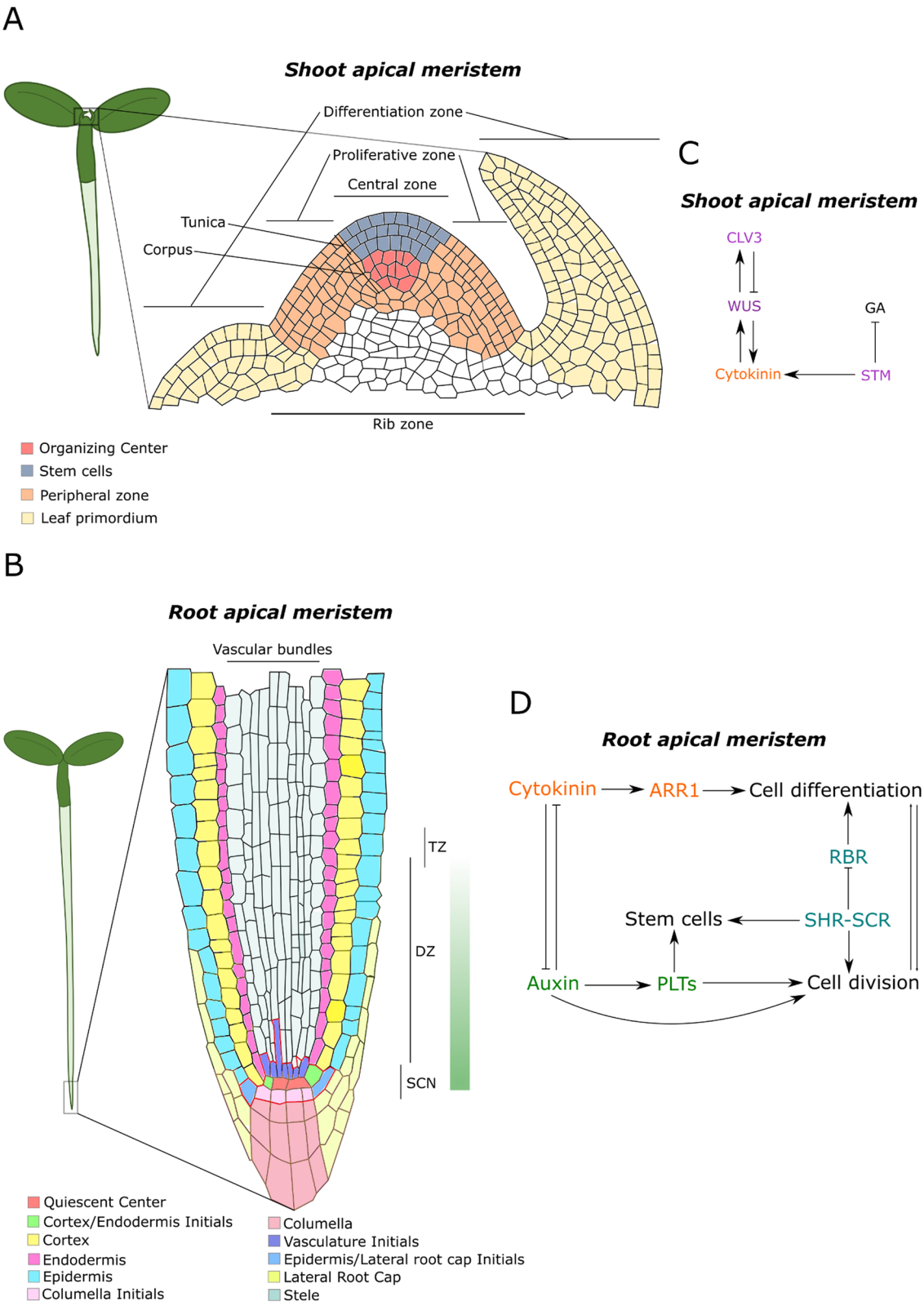

Fig. 4 (See legend on previous page.)

cells divide asymmetrically to continuously produce daughter cells that lose the contact the quiescent center and start to divide symmetrically to acquire properties of transit amplifying cells and compose the division zone. The transit amplifying cells divide a discrete number of times prior to reaching a boundary transition zone where cells stop to divide and start to elongate and differentiate, exiting from the meristem. Since after exiting from the meristem cells start to elongate along the proximal distal axis, the stem cell niche is moved distally along with the root tip [49, 173]. A peculiar case is given by the distal stem cells that give rise to the columella, a tissue required to aid root penetration, perceive gravitropic stimuli, and protect the stem cells from mechanical stresses. As the last file of columella continuously detaches from the root tip, this set of stem cells do not produce transit amplifying cells but originate daughters that directly acquire differentiation properties such as starch granules [49, 173].

Plant stem cell specification

Over the past few decades, significant progress has been made in unraveling the molecular mechanisms governing stem cells. Much like in the animal kingdom, where specific transcription factors exert control over pluripotency, the plant kingdom relies on transcription factors to specify and maintain stem cells. Within the shoot apical meristem, the homeodomain transcription factors WUSCHEL (WUS) and SHOOT MERISTEMLESS (STM) take center stage in regulating the activity of the stem cell niche and the shoot apical meristem [115, 128], (Fig. 4C). WUS, an evolutionarily conserved homeobox gene, is expressed in the organizing center of the shoot apical meristem and is pivotal in determining the stemness of neighboring stem cells [128]. Mutations leading to the loss of WUS function result in a meristem devoid of stem cells [128]. WUS governs stem cell activity by regulating the plant hormone cytokinin [75, 110]. WUS plays a pivotal role in maintaining the homeostasis of stem cells within the shoot apical meristem by regulating their quantity. Research has shown that WUS has the capacity to move from the organizing center to the outer layers of the tunica through plasmodesmata [42, 227]. This movement results in the dilution of WUS from one layer to another, a crucial process for proper regulation of stem cell homeostasis [42, 120, 228]. In the outer tunica layers, WUS stimulates the expression of the CLAVATA3 (CLV3) peptide [26, 228]. CLV3, in turn, restricts WUS expression in the organizing center by binding to the CLAVATA1 and CLAVATA2 receptor kinases, repressing WUS expression in tunica cells [26, 37, 59, 155]. This is substantiated by the observation that clv mutants exhibit a broader WUS domain, accompanied by an expanded stem cell pool [59]. DNA modifications, particularly methylation of the WUS promoter by the methyltransferase MET1, are responsible for the repression of WUS expression in tunica cells [17, 103, 111]. However, the precise spatial dynamics of the WUS/CLV feedback system continue to be a subject of ongoing debate.

SHOOTMERISTEMLESS (STM), a KNOTTED1 LIKE HOMEOBOX, is expressed throughout the shoot apical meristem and is indispensable for stem cell activity. Loss-of-function mutants of *STM* fail to develop a shoot apical meristem [115]. STM prevents cell differentiation by repressing the expression of genes involved in meristem exit, such as the MYB transcription factor ASYMMETRIC LEAVES 1 (AS1), while also influencing the metabolism of the plant hormone Gibberellin, a hormone implicated in shoot cell differentiation [28, 82, 91]. STM regulates the expression of cytokinin biosynthesis genes, such as *ISOPENTENYLTRANSFERASE (IPT)*, and it has been proposed that this regulation is both necessary and sufficient for STM to promote apical meristem activity in shoots [91]. Cytokinin, in addition to promoting WUS expression, induces the expression of cell cycle regulators, such as CYCLIN D3;1, thus promoting transit amplifying cell activity [181, 205]. Notably, STM and WUS are intricately connected, with STM enhancing WUS activity and vice versa [197], implying a dynamic interplay in control of stem cell programming. Meristematic cells that accumulate high levels of the plant hormone auxin lose their meristematic activity and are directed towards the formation of lateral organ primordia.

In the root apical meristem, the formation of an auxin maximum is fundamental to pattern and position the stem cell niche [48, 169], [174]) (Fig. 4D). Auxin as acts as a morphogen, and its distribution within the root meristem is orchestrated by the activity of PIN proteins [47, 77, 173, [229]. The PIN-FORMED (PIN) protein family, comprised of eight secondary transporters [2], including PIN1, 2, 3, 4, and 7, are polarly and asymmetrically localized on the cell plasma membrane, governing polar auxin transport in the root [47, 77, 173, 229]. The activity of PINs is required to create an auxin gradient along the meristem, culminating in an auxin maximum within the stem cell niche, which plays a critical role in providing and sustaining stem cell identity. This auxin maximum promotes the expression of *PLETHORAs (PLT)*, a family of AP2 transcription factors [6]. Mutant combinations of PLTs, such as *plt1* and *plt2* loss-of-function mutations, lead to reduced stem cell function and a differentiated root apical meristem. Furthermore, in cases of multiple *plt1*, *plt2*, *plt3*, and *plt4* loss-of-function mutants, no root is formed, since the stem cell niche fails to develop [6]. The distribution of *PLT* mRNAs mirrors that of auxin, exhibiting a maximum within the stem cell niche and a decline at the transition zone [122]. PLTs also play a role

in regulating auxin distribution, influencing the expression of PINs and auxin biosynthesis [77, 122]. The interplay between auxin and PLT in defining stem cell activity remains a topic of ongoing discussion. However, it is evident that auxin and PLT gradients produce similar outcomes: high levels of PLTs and auxin specify the stem cell niche, whereas lower levels of auxin and PLT promote cell division [47, 173]. Interestingly, a minimum threshold of both auxin and PLT is required to induce cell differentiation at the transition zone [47, 173]. A combination of wet and in silico experiments has provided evidence that cytokinin functions as a master regulator in the establishment and positioning of these thresholds. At the transition zone, cytokinin modulates the expression of the auxin signaling repressor *SHORTHYPOCOTYL2* (*SHY2*) and the auxin catabolic gene *GRETCHEN HAGEN 17* (*GH3.17*) by binding to the receptor AHK3, which activates the ARR1 type B response regulator (Dello [43],Dello [44, 47, 50, 174]. This regulation is adequate to generate an auxin minimum at the transition zone, triggering meristematic cells to undergo differentiation.

In the context of stem cell function, the activity of GRAS transcription factors, SHORTROOT (SHR) and SCARECROW (SCR), is essential [15, 86, 170]. SHR is primarily expressed in vascular cells, and its protein moves through plasmodesmata, targeting the endodermis and the quiescent center [51, 67, 86, 136, 170, 215]. In these tissues, SHR physically interacts with its target SCR, initiating the transcription of genes responsible for defining the quiescent center's function [116]. Loss-of-function mutants for both SHR and SCR result in an inactive quiescent center, leading to decreased stem cell activity and a diminished population of transit-amplifying cells [170]. The combined and independent actions of the auxin/PLT and the SHR/SCR modules are critical in triggering stem cell function, implying that these two modules act on partially distinct targets to promote stemness. It is worth noting that SHR and SCR are capable of repressing ARR1 expression in the quiescent center [133, 134]. This regulation is fundamental to control the quantity of auxin synthesis in the stem cell niche. Recent research has demonstrated the importance of PLTs in excluding ARR1 expression in the stem cell niche. In these cells, PLTs promote the expression of *KISSMEDEADLY1* and *2* (KMD2) F-BOX proteins, leading to the degradation of ARR1 and ARR12 [96, 187]. The auxin/PLT and SHR/SCR modules likely interact within the stem cell niche to establish a distinct domain where inputs for cell differentiation are eliminated, ultimately promoting stem cell identity.

Similar to animals, the RETINOBLASTOMA RELATED PROTEIN (RBR) plays a crucial role in balancing cell division and cell differentiation within the root stem cell niche [40, 147, 226]. RBR maintains quiescence in the quiescent center by interacting with SCR. Targeted reduction of RBR expression in the quiescent center triggers additional asymmetric cell divisions, while transient overexpression of RBR promotes stem cell differentiation. [226]. This data establishes RBR as a master regulator of quiescent center identity, although it also suggests that RBR is primarily involved in controlling the cell differentiation program. Further analysis is necessary to fully comprehend the role of RBR in regulating stem cell identity and functions. RBR has also been implicated in maintenance of genome integrity in root meristem cells. Plant roots are exposed to various environmental factors that can result in DNA damage. To counteract the consequences of DNA breaks, plants, and animals have evolved DNA Damage Response (DDR) pathways [72, 90]. RBR, in conjunction with E2FA, is recruited to sites of DNA damage in an ATM- and ATR-dependent manner. The precise role of RBR in DDR is not fully understood, but may be involved in the recruitment of DDR proteins, regulation of DDR factor transcription, cell cycle arrest, or a combination of these possibilities. Nonetheless, these results highlight the crucial need to maintain genome integrity within the stem cell niche. Additionally, it has been observed that auxin accumulation in the stem cell niche is pivotal in preserving genome integrity in response to environmental stresses such as cold. Roots respond to cold stress (< 4 °C) enhancing auxin accumulation in the stem cell niche by triggering the programmed cell death of columella stem cells [65, 89]. Furthermore, recent studies suggest that this process is mediated by the upregulation of specific cold-responsive genes and the activation of stress signaling pathways, which collectively contribute to the plant's adaptive response to low temperatures. The cold-induced factor CBF3 plays a crucial role in mediating these responses. CBF3 not only regulates root stem cell activity but also influences regeneration and developmental processes in response to cold [146].

The programmed cell death of these cells leads to a lack of auxin redistribution within the meristem, resulting in cell cycle arrest in the meristem and the accumulation of auxin in the stem cell niche. The precise mechanism by which auxin promotes genome integrity is not yet understood, but one possibility is that this hormone influences chromatin accessibility (Fig. 4D).

Telomeres and plant stem cells

As in mammals, plants employ telomerase to maintain and elongate their telomeres. In *Arabidopsis*, telomerase activity is tightly restricted to dividing tissues where

it correlates with transcription of TERT mRNA [58]. Moreover, differently from most human cells where the expression of telomerase RNA is quite ubiquitous, in *Arabidopsis* also the levels of AtTR is regulated and correlates with telomerase activity [179].

Telomerase is highly expressed and active in both meristems, where it is involved in maintaining meristem growth and ensuring stem cell renewal [74]. Indeed, *tert* mutants show progressive telomere shortening and aberrant shoot [161] and root [74] development, linking telomere length to meristem activity in plants [74]. A clear example of this link is given by roots; in this organ telomere length is tightly coupled with meristem activity and mutations that impair telomere length results in shorter roots and root meristems [3, 65, 74, 194, 199]. It is interesting to note that *tert* dependent reduction of root meristem activity grows worse from generation to generation, suggesting that DNA and telomeric damage accumulate in the stem cells in descendants lineages. Using of Quantitative Fluorescent In Situ Hybridization (Q FISH) in vivo, it has been shown that root stem cells have longer telomeres than transit amplifying and differentiating cells [74]. The link between telomere length and meristem activity was further supported by the finding that *plt1 plt2* double mutants show longer telomeres in the stem cells of the root [74]. A further support to the link between telomere maintenance and stem cells activity comes from the discovery of the effects on telomere factors expression in the roots of *scr* mutations. SCR is a key regulator of stem cell activity, partly by promoting the expression of *CTC1*, *STN1*, *TEN1*, and *TERT* components, which are crucial for maintaining telomeres and genome integrity in the stem cell niche (Wang, 2023). Remarkably, *scr* mutants exhibit longer telomeres, which appears counterintuitive. This could be due to the activation of an alternative telomere lengthening mechanism in response to damaged telomeres or a reduction in meristematic function in the roots of *scr* mutants. (B. [220, 221]).

Conclusions

The biological bases of the taxonomic classification of plants and mammals in two separate kingdoms are evident, which makes it surprising to find common elements in the organization of telomeres, which are pivotal in determining cell stemness and proliferation, organismal aging, and lifespan. We examined these elements herein, focusing on *Arabidopsis thaliana* for the plant and on mice and humans for the animal kingdom.

As detailed in Table 1, similar traits can be seen in the presence and characteristics of shelterins, in the presence of TERRA, and of the TERT complex in both kingdoms. Potential similarities in cell stemness are present in the two kingdoms, particularly when focusing on the concept of niches. In this latter perspective, a speculative parallel is that considering root apical meristem and mammalian bone progressive variation of local microenvironments is seen that accompanies progenitor differentiation and tissue specification (Fig. 5). Reasoning in this trans-kingdom perspective pushes the conceptualization of stemness as an inducible phenotype. This is demonstrated in mammals with the system of induced pluripotent stem cells and is present in *Arabidopsis* tissues.

Collectively, these aspects suggest that studying telomeres and stemness across both plants and mammals could be highly beneficial. This unconventional approach could lead to the discovery of new mechanisms involved in the control of stemness and telomere function, potentially impacting research on aging and lifespan determinants. Additionally, such an approach could be used to test the effects of plant hormones, and proteins on telomeres, stemness, and organismal outcomes in mammals. One promising example, with preliminary data available, is

Table 1 List of regulators of telomere metabolism in Arabidopis, mice and humans

	Arabidopsis thaliana	Mus musculus	Homo sapiens	References
Chromatin mark (-)	H3K9me2	H3K9me3	H3K9me3	[1, 2]
	–	H4K20me3	H4K20me3	[3, 4]
	H3K27me3	–	H3K27me3	[1, 5]
Chromatin mark (+)	H3K4me2	–	–	[6]
	H3K4me3	H3K4me3	H3K4me3	[2, 7]
	–	H4K20me1	H4K20me1	[2]
	H3K9ac	H3K9ac	H3K9ac	[6-8]
	–	H3K27ac	H3K27ac	[2]
Overhang	5′-TTTAGGG-3′	5′-TTAGGG-3′	5′-TTAGGG-3′	[9, 10]
	2,5-5 kb	~50 kb	5-15 kb	[11, 12]
Overhang binding proteins	STN1	STN1	STN1	[8]
	TEN1	TEN1	TEN1	
	CTC1	CTC1	CTC1	
Shelterin	TRB1, 2, 3	TRF1	TRF1	[10, 13]
	–	TRF2	TRF2	[10]
	POT1 a, b, c	POT1a/b	POT1	[10], [14–16]
	–	TIN2	TIN2	[10]
	–	TPP1	TPP1	
	–	RAP1	RAP1	
Telomerase composition	TERT	TERT	TERT	[96], [17–20]
	TER	TR	TR	
	CBF5	Dyskerin	Dyskerin	
	NHP2	NHP2	NHP2	
	NOP10	NOP10	NOP10	
	GAR1	GAR1	GAR1	
	NAF1	–	–	
	RuvBLs	Pontin/Reptin	Pontin/Reptin	
	–	Hsp90	Hsp90	
	–	p23	p23	
	TRBs	–	–	
	POT1a	–	–	
Telomerase expression	Pollen, seedling, young rosette leaves, siliques, SAM, RAM	Embryo, brain, thymus, hearth, lung, liver, spleen, kidney, intestine, muscle, skin, testis	Blastocyst, fetuses (no brain), hair follicle bulbs, basal cells of the gastrointestinal tract, basal keratinocytes of the skin lymphocytes, hematopoietic progenitors, stem cells, urothelium, prostate, endometrium, cancer cells	[21–32]

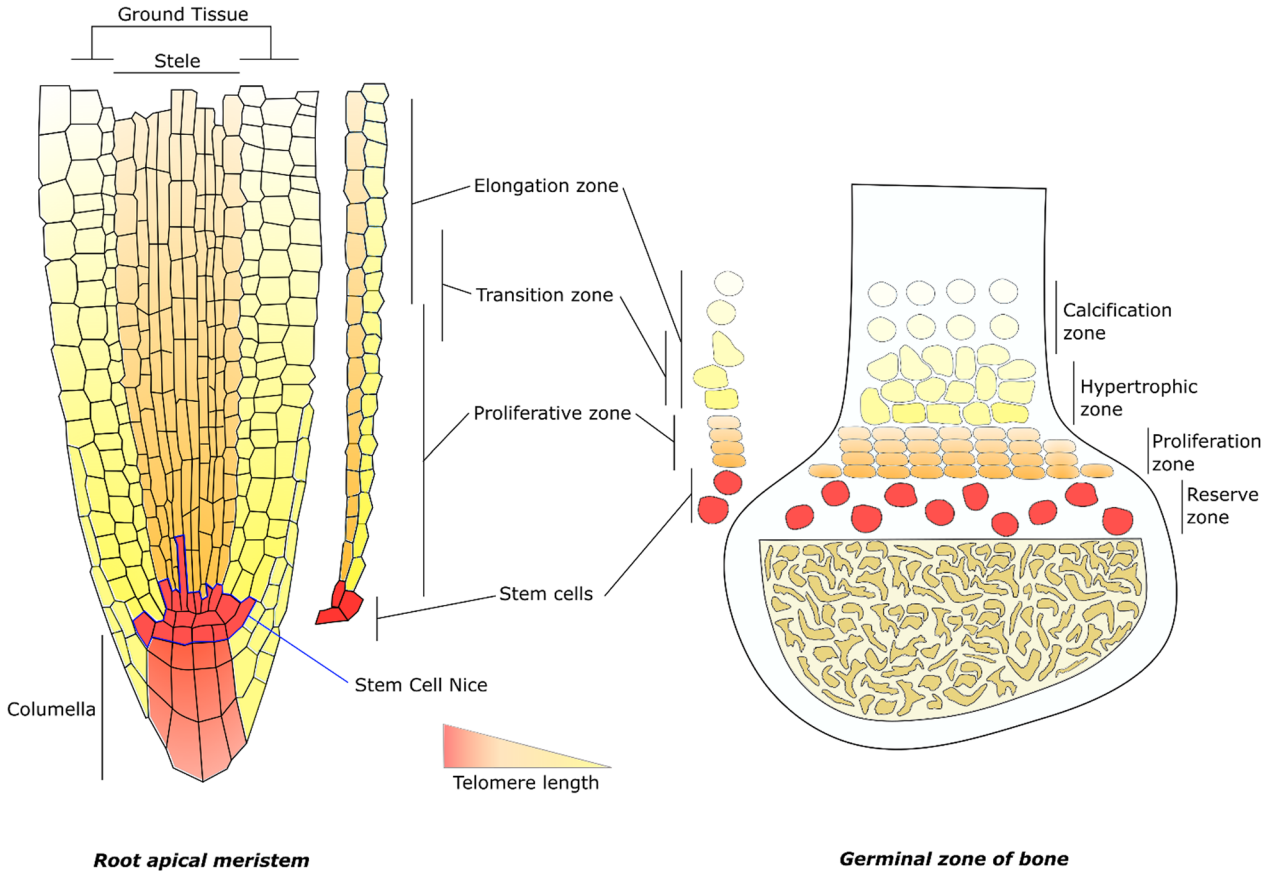

Fig. 5 Speculative parallels between plants and mammalian stem niches: (**A**) *Arabidopsis* root apical meristem and (**B**) mammalian germinal zone of bone. Stem cells (red) have longer telomeres than the committed ones (orange) and more differentiated cells (yellow), showing telomere shortening as cell differentiation progresses

auxin, whose effects on mammalian cells are beginning to be understood [73, 95, 101].

Acknowledgements
Acknowledgments The authors acknowledge the support of NBFC to IS, funded National Recovery and Resilience Plan (NRRP), Mission 4 Component 2 Investment 1.4 – Call for tender No. 3138 of 16 December 2021, rectified by Decree n.3175 of 18 December 2021 of Italian Ministry of University and Research funded by the European Union –NextGenerationEU; Award Number: Project code CN_00000033, Concession Decree No.1034 of 17 June 2022 adopted by the Italian Ministry of University and Research, Project title "National Biodiversity Future Center-NBFC" Sapienza CN5-Spoke 7. AIRC IG-24614 to IS. Istituto Pasteur Fondazione Cenci Bolognetti Anna Tramontano call 2020 to IS. MIUR-Sapienza RP1201729E377B2D, RP11916B-7F20A9E3, RP12218167BDB0A9 to IS. MIUR-Sapienza RM12117A5D970AB9 and GA122181AFEB4283 to IS as co-PI. MIUR-Sapienza RG12218166E3EE68 and AH12218100A1640A to RDI. 20229LHY5L-PRIN2022 to RDI. POR FESR Lazio 2014-2020-code A0375E0189-2020-36640 to RDI. MIUR-Sapienza AR22117A575BCFA5 to MLT. Italian ministry of health 2022 Programma di ricerca e formazione to IS. Singapore ministry of health HLCA22Feb-0029 to IS as co-PI. IS is affiliated to the following institutions: School of Biological Sciences Nanyang Technological University Singapore Singapore, NISB Institute of Structural Biology Nanyang Technological University Singapore Singapore, CNR Institute of Molecular Biology and Pathology, Rome, Italy, Istituto Pasteur Fondazione Cenci Bolognetti Rome Italy. And by Ministerio de Ciencia e Innovación (MICINN) of Spain PID2022-140719NB-I00 to MPG-G as IP2.

Author contributions
E.D.P., R.B., M.L.T., M.P.G-G wrote and prepared figures, I.S and R.D.I supervised, conceptualized and wrote the manuscript.

Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

Received: 9 September 2024 Accepted: 3 November 2024
Published online: 20 November 2024

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