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Extra-Telomeric Effects of Telomerase (hTERT) in Cell Death

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1. Introduction

1.1. Telomeres

Telomeres are heterochromatic structures found at the ends of chromosomes which are involved in the protection of chromosomes from degradation and DNA-repair mechanisms (Moyzis et al., 1988; Shay and Wright, 2004; Wyatt et al., 2010). Discovery of telomeres also solved the “end-replication problem” which was exposed after the observation that the 3'-extremity of chromosomes was not completely replicated during each cell cycle. As a consequence telomeres play a fundamental role in chromosomes and the overall genome stability (de Lange, 2005; Martinez and Blasco, 2011; O'Sullivan and Karlseder, 2010; Takai et al., 2003). In mammals telomeres are composed of tandem repeats of the oligonucleotide sequence TTAGGG and bound by a composite structure of proteins named the shelterin complex (de Lange, 2005, 2010; Diotti and Loayza, 2011; Longhese et al., 2012; Martinez and Blasco, 2010; O'Sullivan and Karlseder, 2010). In somatic cells telomeres are shortened after each division cycle and when a critical short length has been reached then the cell replication stops before these cells undergo senescence or apoptosis (Counter, 1996; Deng and Chang, 2007). This mechanism is supposed to be responsible for the “Hayflick limit” which corresponds to the number of times a cell can divide before it stops proliferating (Deng and Chang, 2007; Hayflick, 1965; Hayflick and Moorhead, 1961). The phenomenon of telomeres shortening is directly linked to the ageing process by acting as a mitotic clock and by inducing senescence and/or apoptosis once the Hayflick limit has been reached (Blasco, 2003; Djojotubroto et al., 2003; Goronzy et al., 2006; Liew et al., 2009; Martinez and Blasco, 2010; Shin et al., 2006).

1.2. Telomerase

The main mechanism involved in telomere maintenance and *de novo* synthesis of telomeric DNA is represented by the activity of the telomerase holoenzyme. Telomerase is responsible

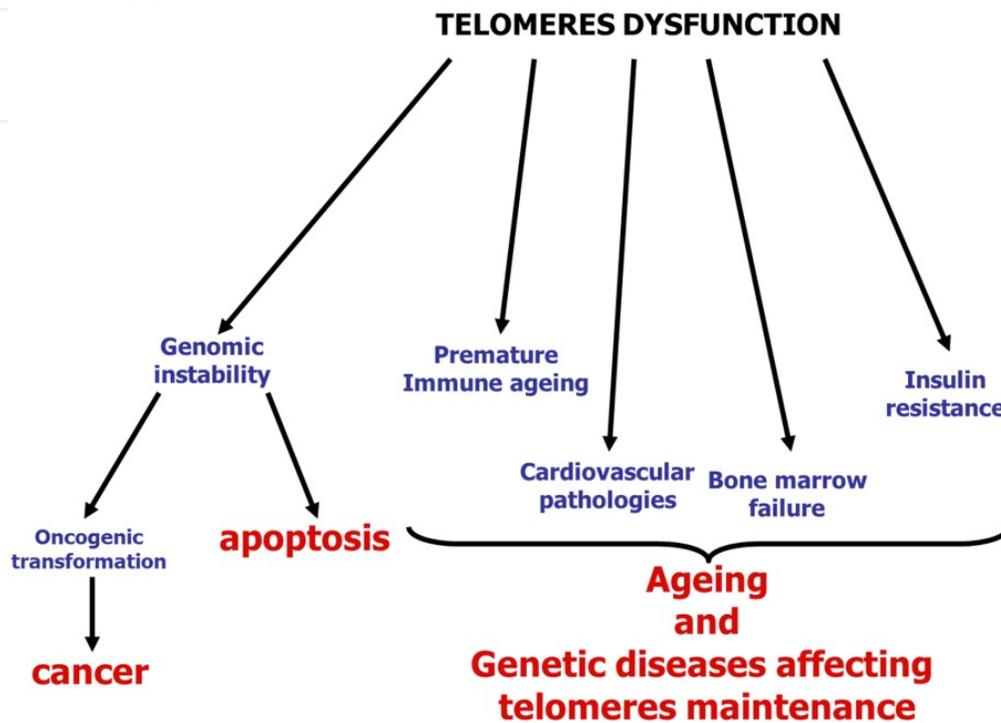
for the addition of the telomere repeats TTAGGG at the end of chromosomes (Blackburn et al., 1989; Greider and Blackburn, 1985, 1987). The catalytic core of telomerase is a ribonucleoprotein consisting of a reverse transcriptase (TERT) and a telomerase RNA template (TERC) whereas other species-specific co-factors may be required to form the whole holoenzyme (Martinez and Blasco, 2011; Wyatt et al., 2010). The catalytic subunit TERT is comprised of 3 main domains. The N-terminal extremity contains two domains called the telomerase essential N-terminal domain (TEN) and the telomerase RNA-binding domain (TRBD) which are involved in the association of TERC with TERT. The central part of the protein contains the catalytic domain for reverse transcriptase activity (RT) with seven conserved motifs which are essential for the enzymatic activity. The sequences of both N-terminal extremity and the core catalytic domain of TERT are evolutionarily conserved among species. On the other hand, the C-terminal domain displays a higher variability and therefore may be related to species-specific function (Wyatt et al., 2010).

While it appears that the primary function of telomerase is to elongate telomeres by adding telomeric DNA at the end of chromosomes, many studies in the past decade has started to uncover other potentially crucial functions of telomerase besides its direct role in telomeres maintenance (De Semir et al., 2007; Gordon and Santos, 2010; Majerska et al., 2011; Martinez and Blasco, 2011). As a matter of fact it has been observed that telomerase is able to promote tumor oncogenic transformation independently of its ability to elongate telomeres (Stewart et al., 2002) and appears to be involved in the modulation of mechanisms related to cell survival, genes regulation, cell signaling, cell proliferation and differentiation, metabolism, and DNA repair (De Semir et al., 2007; Lai et al., 2007; Majerska et al., 2011; Saretzki, 2009). Such functions have been described as extra-telomeric roles of telomerase. While these non-telomeric functions still remain generally enigmatic, their relationship with the regulation of crucial cellular mechanisms emphasize the critical importance of investigating this field in order to improve our understanding of telomerase biology. This chapter proposes to highlight and summarize the current knowledge about the non-telomeric effects of the catalytic subunit TERT and more particularly its related roles to cell death regulation, with regard to the relationships between TERT and key actors of apoptosis, i.e. mitochondria, oxidative stress and p53.

2. Telomeres dysfunctions and relationship to diseases

Telomeres alterations have been described in many diseases including aging-related disease (Hiyama and Hiyama, 2007; Martinez and Blasco, 2011; O'Sullivan and Karlseder, 2010) (Figure 1). Some inherited diseases such as Dyskeratosis Congenital and aplastic anaemia results in impaired telomerase activity leading to major bone marrow failures and premature ageing syndromes (Calado et al., 2002; Calado et al., 2009; Mason et al., 2005; Mitchell et al., 1999; Shtessel and Ahmed, 2011; Vulliamy et al., 2002). More recently it was observed that mutations in telomerase components TERT or TERC may be linked in the occurrence of the idiopathic pulmonary fibrosis resulting in dramatic destruction of lung tissues (Alder et al., 2008; Tsakiri et al., 2007). Other

studies pointed the direct correlation between telomere dysfunction and pathologies such as cardiovascular disease, carotid atherosclerosis and increased insulin resistance (Benetos et al., 2004; Epel et al., 2006; Gardner et al., 2005; Kuhlow et al., 2010). In addition it has been demonstrated that telomere dysfunction in chronically stressed patients may lead to premature immune ageing (Damjanovic et al., 2007; Goronzy et al., 2006) (Figure 1).



Telomeres shortening and/or dysfunction leads to genomic instability which induces apoptosis in order to eliminate such aberrant cells. However genomic instability can promote oncogenic transformation and lead to the appearance of a cancerous phenotype. Telomeres dysfunction seen in genomic diseases affecting telomeres maintenance have been shown to induce pathologies related to premature aging thus resulting in deficient immune system, bone marrow failure or rise in insulin resistance.

Figure 1. Relationship between telomeres dysfunction and pathologies.

While differentiated tissues display relatively low telomerase activity (Wright et al., 1996), it has been widely observed that malignant cells from a large variety of cancers present a significantly increased telomerase activity. Around 90% of tumors have been reported to be telomerase-positive tumors, thus making telomerase the most widely expressed gene across all types of cancer (Shay and Bacchetti, 1997). It appears that telomerase is a major protein that holds the key to infinite proliferative capacity which is a necessary step toward oncogenic transformation that has been described as one of the hallmarks of cancer (Hanahan and Weinberg, 2011).

The high telomerase activity levels in cancer correlate directly with malignant and metastatic potential (Oishi et al., 1998; Pirker et al., 2003). As a consequence, telomerase has become a promising target in the race to the development of new anti-cancer therapies. Therefore, it is of critical importance to understand the roles of telomerase and telomeres in

cancer development in order to design these new anti-cancer strategies. Some telomerase-based approaches have been developed in the recent years such as gene therapy, immunotherapy and small-molecule inhibitors of telomerase (Keith et al., 2007; Shay and Keith, 2008). Some of these promising candidates for telomerase-based therapies are now in different phases of clinical trials (Harley, 2008; Ouellette et al., 2011; Shay and Wright, 2011).

The understanding of the regulation of telomerase appears to be an important issue that may help to improve therapies related to pathologies mentioned above from inherited diseases to ageing-related diseases and cancers. In order to improve these telomerase-based approaches there is a crucial need to investigate closely the functions of telomerase as a mean to understand the full extent of the roles in which telomerase is involved.

3. Extra-telomeric functions of TERT and its implication in cell death

3.1. TERT, oxidative stress and mitochondria

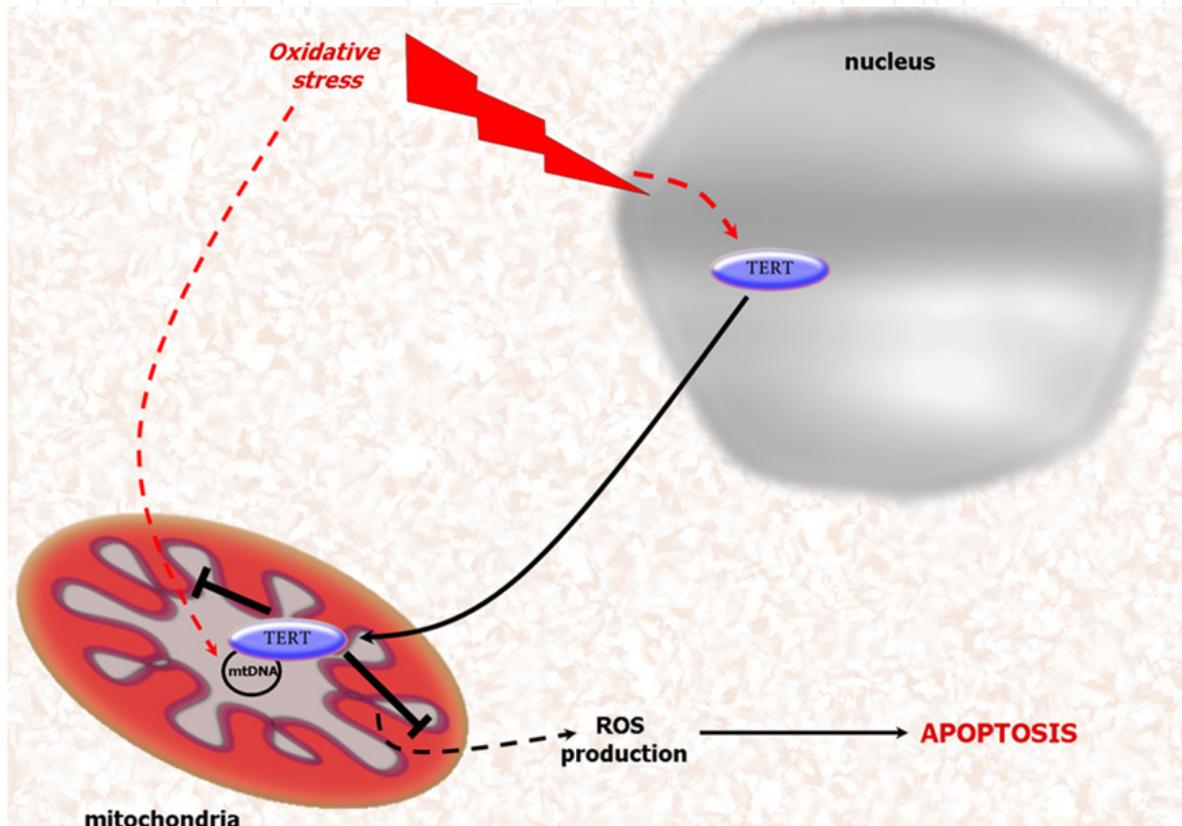
Mitochondria are key organelles of the cell as it is a major metabolic centre and mitochondrial dysfunctions are linked to many pathologic syndromes. Mitochondria hold a primary role in cell biology through its implication in energetic metabolism, production of reactive oxygen species (ROS) and also as a key regulator of apoptosis (Fogg et al., 2011; Low et al., 2011; Saretzki, 2009). The mitochondrial pathway of apoptosis, also known as the intrinsic pathway, leads to the release of apoptogenic proteins from the intermembrane space of mitochondria upon apoptotic stimuli which in turn results in the activation of caspase 9 through the formation of a protein complex called the apoptosome (Antonsson, 2004; Saelens et al., 2004; Yuan et al., 2011). This mechanism is regulated by a family of proteins called the Bcl-2 family of proteins, which are responsible for the regulation of the apoptotic mitochondrial pathway through the activation of caspases (Antonsson, 2004). On the other hand it is also of critical importance to understand that mitochondria are a major producer of ROS which activate many downstream pathways involved in the modulation of mechanisms such as cell death or cell survival, cell proliferation, senescence and ageing (Indran et al., 2011; Saretzki, 2009).

Interestingly in the past decade the initial relationship between increased of oxidative stress, telomeres shortening and ageing leads to the investigation of a potential connection between telomerase and mitochondria (Saretzki, 2009; Saretzki et al., 2003). Following this hypothesis it was then demonstrated that telomerase, or more specifically the catalytic subunit TERT is able to translocate from the nucleus to the mitochondria following drug treatments or increase of oxidative stress (Ahmed et al., 2008; Haendeler et al., 2009; Santos et al., 2006; Saretzki, 2009) (Figure 2). This new interesting finding was linked to the discovery of mitochondrial targeting sequence at the N-terminal extremity of TERT (Santos et al., 2004). It appears then that TERT localization is a dynamic and regulated mechanism which is induced as a response to environmental stress. It has been shown that oxidative stress can drive 80% to 90% of endogenous TERT to mitochondria and that this phenomenon does not involve *de novo* synthesis of TERT (Ahmed et al., 2008). However this function of

mitochondrial TERT (mtTERT) remains poorly understood as different investigations about this mechanism contains discrepancies between their conclusions and contradictory results. It was initially observed that mtTERT increases the mitochondrial DNA (mtDNA) damage and apoptosis following treatment by H₂O₂ (Santos et al., 2003; Santos et al., 2004; Santos et al., 2006). However many other reports have also shown that mtTERT would rather display a protective role against oxidative-stress induced mtDNA damage and apoptosis. It was observed that mtTERT under oxidative stress conditions correlates with an increase in mitochondrial potential and reduction of ROS productions thus pointing to an improvement of mitochondrial function by TERT in cells subjected to oxidative stress (Ahmed et al., 2008). An increase in mitochondrial potential was previously observed in neurons. This was correlated with an increase in calcium uptake by the mitochondria as part of mechanism protecting neurons against ischaemia (Kang et al., 2004). Other recent investigations emphasize the role of mtTERT in the protection against oxidative stress. In 2009 it was reported that TERT translocation to mitochondria follows a classical pathway of proteins imported into mitochondria. Indeed it was observed that TERT translocated to mitochondrial matrix through the translocase of outer membrane (TOM) and translocase of inner membrane (TIM) complexes (Haendeler et al., 2009). Once in the matrix, it was shown that TERT can bind to mtDNA through the coding regions of the NADH:ubiquinone oxidoreductase subunits 1 and 2. This interaction between TERT and mtDNA appears to be able to protect it against ethidium-bromide induced DNA damage (Figure 2). In addition to its binding to mtDNA it was observed that cells overexpressing TERT displays an enhanced complex I activity while it reduces the ROS production induced by ethidium-bromide treatment. It is important to note here the interesting ability of TERT to bind to the loci of subunits 1 and 2 of the NADH:ubiquinone oxidoreductase which is the complex I of mitochondrial electron transport chain. One may postulate that TERT binding to these loci may enhance the gene transcription of these subunits in order to facilitate and improve mitochondrial respiration. Such a finding deserve further investigation in order to elucidate the correlation between the mtDNA-associated TERT and the increase in complex I activity. Moreover this mechanism of protection is directly correlated with the ability of TERT to localize in the mitochondria given that a construct of TERT targeted specifically to mitochondria enhanced the protective effect seen previously with TERT wild-type. The authors also have shown that the reverse transcriptase of TERT seems to be required in order to fulfill this protective role against oxidative stress (Haendeler et al., 2009). However the requirement of the reverse transcriptase activity of TERT in this protective role still remains highly controversial as no detailed mechanism has been clearly demonstrated. Nonetheless, telomerase activity has been detected in mitochondrial extracts and the binding of TERT to mtDNA suggests that the reverse transcriptase activity may play an important role in protecting mtDNA. As a consequence, it is possible to extrapolate that mtTERT can display more than one function in mitochondria and that some of them require a catalytically active telomerase (binding to mtDNA) while others may only require TERT subunit (improvement of mitochondrial function, protection against cell death) (Saretzki, 2009).

Another recent report also confirmed the role of TERT as a modulator of ROS production (Indran et al., 2010, 2011). Indeed it was observed that TERT overexpression induces

reduction of basal levels of ROS and inhibits the ROS production induced by oxidative stress (Figure 2). This investigation also showed that the antioxidant function of TERT may be linked to an increase in the ratio of reduced glutathione to oxidized glutathione in addition to an improved recovery of the peroxiredoxin in its reduced state. As a substantiation of the previous results we mentioned earlier, the authors of this study were able to show that TERT induces an increase in complex IV activity (cytochrome c oxidase) (Indran et al., 2011). In the meantime it was also confirmed that these cells overexpressing TERT display a higher resistance to H₂O₂-induced apoptosis.



Environmental stress such as oxidative stress has been described to induce the translocation of TERT from the nucleus to the mitochondria. Once in mitochondria, TERT has been shown to interact with mtDNA and protects it against oxidative-stress-induced DNA damage. Mitochondrial TERT is also able to modulate ROS production thus promoting cell survival by inhibiting ROS-induced apoptosis.

Figure 2. Translocation of TERT into mitochondria and its potential involvement in the protection against oxidative stress.

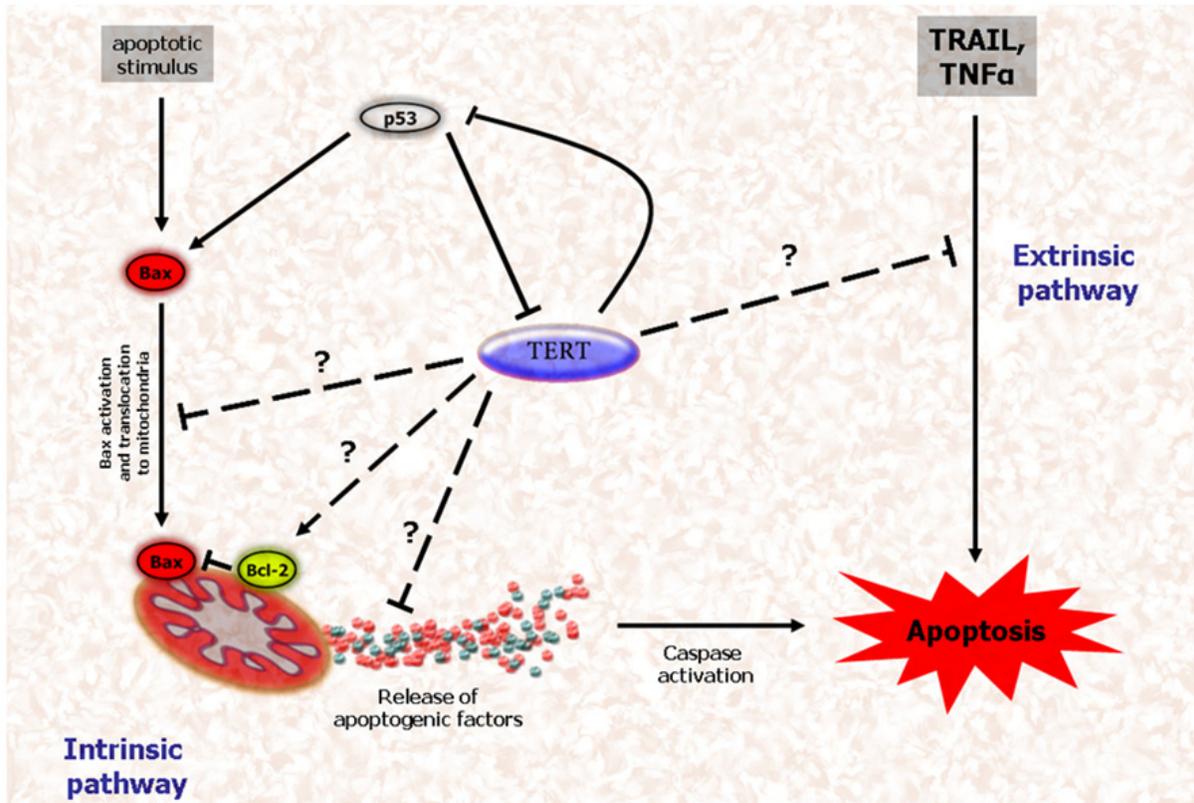
Taken together all these studies highlight an important crosstalk between the mitochondrial localization of TERT and the modulation of ROS production. While some results are contradictory, most data suggest an involvement of TERT as part of a mechanism alleviating ROS production by mitochondria thus protecting cells against oxidative stress induced damages and cell death. The discrepancies between these different studies may be explained by the different models used in the investigations and the varied experimental settings. In addition the level of oxidative stress may also be responsible for these differences as it may represent the different responses of the cells toward mild or acute oxidative stress. As a

result, TERT seems to be part of a mechanism modulating ROS production and cell response to oxidative stress. Considering the important role of ROS in cell death, cell survival and in ageing, these investigations have outlined a major new function for TERT as an upstream actor regulating ROS production and mitochondrial function which may be of critical importance to determine the fate of a cell.

3.2. Relationships between TERT and apoptotic pathways

Many studies pointed to the anti-apoptotic role of TERT independent of its enzymatic activity. Early studies in postmitotic neurons highlighted the ability of TERT to inhibit apoptosis induced by stimuli such as amyloid-beta peptide, NMDA (*N*-methyl-D-aspartate) receptor-mediated excitotoxicity or through removal of brain-derived neurotrophic factor (BDNF) (Fu et al., 2002; Kang et al., 2004; Zhu et al., 2000). Additional studies demonstrated the ability of TERT to antagonize apoptosis induced by topoisomerase inhibitors in PC12 cell line or by oxidative stress in lymphocytes CD4+ model (Lu et al., 2001; Luiten et al., 2003). Such results illustrating the protective role of TERT against ROS were confirmed later in other models (Ahmed et al., 2008; Haendeler et al., 2009; Indran et al., 2011). Although most of these early investigations did not explore the involvement of the reverse transcriptase activity of TERT in this anti-apoptotic mechanism, these results had already outlined a potential function of TERT unrelated to its enzymatic activity and ability to lengthen telomeres (Sung et al., 2005). This was further elucidated following the discovery of TERT's pro-tumorigenic function which is independent of its ability to maintain telomeres (Stewart et al., 2002).

The anti-apoptotic effect of TERT has been related to an inhibition of the mitochondrial pathway of apoptosis as it was described to inhibit the major hallmarks of the intrinsic pathway i.e., the translocation of Bax to mitochondria, the decrease in mitochondrial potential and the release of cytochrome c (Indran et al., 2011) (Figure 3). This effect was observed using a dominant negative form of TERT which resulted in an enhancement of apoptosis induced by sodium butyrate (Xi et al., 2006). Other studies highlighted the role of TERT as an antagonist of the intrinsic pathway of apoptosis. Indeed it was observed that TERT overexpression inhibits Bcl-2 dependent apoptosis (Del Bufalo et al., 2005). In this study, TERT function directly supported the anti-apoptotic role of Bcl-2, which showed that the requirement of its reverse transcriptase activity is unnecessary (Figure 3). It would be of interest to study this potential aspect on improving the survival function of Bcl-2 involved in the anti-apoptotic role of TERT, as it was described earlier that Bcl-2 itself appears to be able to regulate telomerase activity (Mandal and Kumar, 1997). As we discussed previously about the function of TERT in modulating ROS production, it is also important to note that Bcl-2 has been described as an important modulator of ROS production by mitochondria (Chen and Pervaiz, 2007, 2010; Low et al., 2011; Velaithan et al., 2011). Using these findings we can extrapolate that TERT may interact directly or indirectly with Bcl-2 and promote its anti-apoptotic function and modulate or block its pro-oxidant role as well.



TERT has been described as an inhibitor of the mitochondrial pathway of apoptosis by blocking key events of this pathway such as Bax translocation to mitochondria and release of apoptogenic factors such as cytochrome c; however the mechanism by which TERT inhibits these events remains poorly understood. TERT has been also described as an inhibitor of the extrinsic pathway of apoptosis by blocking cell death induced by TRAIL and TNF α .

Figure 3. Relationship between TERT and the intrinsic and extrinsic pathways of apoptosis.

Other investigations have also demonstrated the ability of TERT to block the intrinsic pathway of apoptosis. The knock-down of TERT has been shown to increase the sensitivity of cancer cell lines (HeLa and HCT116) to treatments such as cisplatin, etoposide, mitomycin C and ROS mainly by facilitating the conformational activation of Bax which is the major effector of the mitochondrial pathway of apoptosis (Massard et al., 2006). This sensitization observed following TERT silencing was rescued by overexpression of Bcl-2 which constituted a hallmark of TERT contribution to the mitochondrial pathway. More recently it was also depicted in a human pancreatic cancer cell model that the silencing of TERT led to growth inhibition which associated with a decrease of Bcl-2 and cyclooxygenase 2 levels thus further deepening the connection between mitochondria, Bcl-2 and TERT (Zhong et al., 2010).

In addition other studies also confirmed the anti-apoptotic role of TERT in apoptosis induced by other stimuli such as 15-deoxy- $\Delta^{12,14}$ -prostaglandin J2 (15d-PGJ2) which kills cells through induction of ROS production (Kanunfre et al., 2004; Shin et al., 2009). Interestingly it was observed that 15d-PGJ2 treatment induces TERT downregulation which seems to be an important feature of 15d-PGJ2-mediated cell death and may outline the anti-apoptotic function of TERT (Moriai et al., 2009).

Taken together, these results highlight an important role of TERT as an antagonist of the intrinsic pathway of apoptosis. This protective role does not seem to be linked to TERT ability to elongate telomeres. Although the death mechanisms induced by telomere attrition are mostly linked to the DNA repair machinery, we have described above many studies showing TERT inhibits apoptosis induced by a wide range of stimuli which are not necessarily related to the induction of DNA damage signalling. Moreover most of the effects on apoptosis sensitization occur in a short time following silencing of TERT expression (Massard et al., 2006) which does not match the timing required for a mechanism involving telomere shortening.

While most of the studies related to the involvement of TERT in apoptosis regulation pointed toward a main role of TERT as a modulator of the intrinsic pathway, several investigations also highlighted a potential role in the extrinsic pathway or receptor pathway of apoptosis. Indeed it was observed that TERT inhibits cell death induced by TNF- α and TRAIL but does not protect against etoposide and cisplatin (Dudognon et al., 2004) (Figure 3). Of note, this work also showed that the blockade of the extrinsic pathway was independent of TERT ability to maintain telomere length. It was later confirmed in another publication describing that knock down of TERT sensitizes cells to TRAIL-induced cell death (Zhang et al., 2010). More recently, it was demonstrated that TERT inhibits TNF α induced cell death by blocking the ROS-induced signalling pathways which in turn activated the downstream TNF α signalling (Mattiussi et al., 2012). Nevertheless these results remain controversial and are in contradiction to other published work. Massard and colleagues showed that TERT silencing does not affect cell sensitivity to CD95/Fas-mediated cell death (Massard et al., 2006). These discrepancies may be explained by the differences in the models used in the studies. Indeed while CD95/Fas ligand, TNF- α and TRAIL are inducers of the receptor pathway of apoptosis, the signalling pathways involved downstream are not exactly the same which may contribute to the differences between these experimental results. In addition, it may also suggest that there is a crosstalk between extrinsic and intrinsic pathways of apoptosis (Li et al., 1998) in which the mitochondrial pathway can act as an amplification loop to execute the response to stimulate the receptor pathway of apoptosis. In some cells this amplification system is essential for the total completion of the response to the receptor pathway of initiating apoptosis. As a consequence, this crosstalk between extrinsic and intrinsic pathways may help explain that in some models, TERT inhibits extrinsic pathways of apoptosis whereas in other models, it cannot fulfil its anti-apoptotic role and thus need not require the mitochondrial pathway amplification system. Another possible explanation may involve the differences in the p53 status of the cells used in these studies which often lead to different responses toward apoptotic stimuli. Taken together these results emphasize the role displayed by TERT in apoptosis regulation and more specifically in the modulation of the mitochondrial pathway of apoptosis which is in line with its ability to translocate and localize to this organelle and its capacity to modulate and protect mitochondrial functions.

3.3. Relationship between TERT and p53-dependent apoptosis

Considering the major role of the tumor suppressor p53 in the response to DNA damage and the ability of TERT to induce cell cycle arrest, apoptosis and senescence when telomeres

reach a critical short length, it is important to question the relationship between TERT and the regulation of p53-mediated apoptosis (Beliveau and Yaswen, 2007; Martinez and Blasco, 2011; Vogelstein et al., 2000). Previously, it was shown that p53 is able to downregulate TERT (Kanaya et al., 2000; Xu et al., 2000). While the potential connection between the anti-apoptotic role of TERT and p53-dependent apoptosis still remains poorly understood, some results published within the past ten years may constitute as a starting point to explore this question.

Other studies investigating the ability of TERT to inhibit the mitochondrial pathway of apoptosis as well as the role of p53, concluded that p53 was not involved in this mechanism (Del Bufalo et al., 2005; Massard et al., 2006). Nevertheless, it has also been demonstrated that TERT overexpression blocked the p53-dependent apoptosis induced by 5-fluorouracil, mitomycin C or activation of a temperature sensitive p53 (Rahman et al., 2005). Besides, the authors were able to show that a catalytically inactive TERT displayed an anti-apoptotic effect thus confirming a real extra-telomeric function of TERT as an antagonist of p53-mediated apoptosis. Such an inhibition of the p53-dependent apoptosis was described recently by the ability of TERT to induce basic fibroblast growth factor (bFGF) which in turn lead to a decrease in activation of p53 under DNA damage conditions (Jin et al., 2010). The induction of bFGF by TERT was independent of its reverse transcriptase activity as the catalytically inactive TERT mutant was also able to display the same response and block the DNA damage response. The results of this last study may be complementary to an earlier study highlighting a mutual regulation between p53 and TERT. Indeed it has been published previously that TERT knock down induces an increase in p53 and p21 levels (Lai et al., 2007). These results seem to outline a potential role of TERT in the regulation of its own factors which may then constitute a feedback loop in which TERT level may determine the regulation (Figure 3). As a consequence of this feedback loop, TERT appears to be able to control the level of p53 and antagonizes the p53-dependent apoptosis. Furthermore it has been observed that oxidative stress induced by hypoxia (HIF1- α upregulation) in myocardial tissues of young rats lead to an increase in p53 level. This is associated with a dramatic decrease of TERT level which then correlates with an increase in apoptotic cells in the tissue (Cataldi et al., 2009). It is also important to note that this mechanism was mostly described in myocardial tissues of young rats whereas it was less pronounced in the tissues of older rats likely due to the lower level of TERT expression. Taken together these results emphasize the important role of the HIF1- α /p53 axis in ageing as a consequence from the oxidative stress, cell death and repression of TERT expression. This mechanism while initially a tumor suppressing system may then in turn become highly tumorigenic in case of p53 mutation leading to an increase in genomic instability. Another surprising report showed that p53 and TERT were important in the mechanism known as herpes simplex virus dependent apoptosis (HDAP) specifically in the response to the viral oncoprotein E6 from human papillomavirus HPV16 and HPV18 (Nguyen et al., 2007). However the study reported that the HDAP mediated by E6 is linked to a repression of p53 while concomitantly increasing the level of TERT. This study is one of the few to report a pro-apoptotic role of the catalytic subunit TERT compared to many others highlighting its anti-apoptotic

function. In addition the repression of p53 is commonly known to be associated with a higher resistance to apoptosis induced by DNA damage (Vogelstein et al., 2000). Nevertheless this mechanism of response to viral infection by HPV may outline a wider function of TERT in apoptosis regulation, which was previously reported as a “switch-like” role between life and death depending on the stress inflicted to the cells. These results emphasize a plausible link between p53-dependent apoptosis and TERT that warrants further investigation. The ability of p53 to induce apoptosis through induction of pro-apoptotic proteins such as Bax, Noxa, Fas and increase of ROS production has been well described (Vogelstein et al., 2000). On the other hand, the TERT ability to modulate p53 level as part of a mechanism of mutual regulation has been also documented previously (Jin et al., 2010; Lai et al., 2007). As a consequence, these results point toward a potential relationship between these two proteins which indicates the capacity of TERT to modulate p53-dependent apoptosis in response to a wide range of stimuli thus reflecting the ability of TERT to antagonize the p53-dependent apoptosis (Rahman et al., 2005).

4. Concluding remarks

The investigations about the extra-telomeric functions of the catalytic subunit of telomerase, TERT in the modulation of cell death has been documented in the past 10 years and has offered new insights concerning the role of telomerase in cell biology and signaling. These new findings on the supplementary role of TERT suggest that the catalytic subunit of telomerase may modulate the mitochondrial function and apoptotic cell death. This implies that TERT displays role(s) beyond the ability to lengthen telomeres and it is of importance to improve our current knowledge about these potential extra-telomeric functions of TERT. The modulation of ROS production, mitochondrial respiration and apoptosis are indeed crucial mechanisms involved in many different diseases and play a key role in tumor progression (Antonsson, 2004; Fogg et al., 2011; Hanahan and Weinberg, 2011; Low et al., 2011; Sung et al., 2005; Vogelstein et al., 2000). However most of these extra-telomeric roles of TERT remain controversial thus highlighting the need to further study this field. While the results appear to be contradictory when some emphasize the ability of TERT to prevent apoptosis while others showed the ability of TERT to enhance apoptosis (Saretzki, 2009), we must take into account the differences between the models used in these studies as well as the experimental settings. Furthermore among the studies showing the anti-apoptotic effect of TERT, the localization of TERT was not verified while it seems likely possible that nuclear TERT and mitochondrial TERT may play different roles. Indeed the mitochondrial localization of TERT has been clearly demonstrated and it was observed by Santos and colleagues that mtTERT is responsible for the sensitization to apoptosis while nuclear TERT was associated with an increase in cell survival (Santos et al., 2006). While it still needs further detailed investigations, this result could indicate that the main switch between enhancement and inhibition of cell death might be the ratio between mitochondrial and nuclear TERT. In addition, a recent work of Santos *et al.* reported that TERT can bind mitochondrial RNAs which in turn may reconstitute a reverse transcriptase activity specific to this organelle and are required for a proper mitochondrial function (Sharma et al., 2012).

As it appears that TERT clearly plays a fundamental role in mitochondria, ROS production and mitochondrial metabolism, further details concerning the mechanisms are still required to understand fully this phenomenon. Moreover, in order to determine the full extent of TERT's extra-telomeric function involved in apoptosis regulation, anti-apoptotic functions of TERT need to be methodically investigated.

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