Mitochondrial HSP70 Chaperone System

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Mitochondrial HSP70 (mtHSP70/GRP75/HSPA9/PBP74), also called mortalin, is an essential protein belonging to the HSP70 sub-family which has great importance for mitochondrial biogenesis and the correct functioning of the whole cellular machinery.

Keywords: mtHSP70 ; mortalin ; HEP1 ; TID-1 ; GRPE ; mitochondrial chaperones ; protein quality control

1. Introduction

The mitochondrial protein quality control (PQC) system is a network-like organization of chaperones and proteases whose major role is to preserve the functional and active states of mitochondrial proteins under diverse, and sometimes pathogenic, conditions. PQC maintains protein homeostasis or proteostasis among the mitochondrial proteins by controlling the balance between the generation of newly synthesized proteins and the removal of damaged or misfolded proteins beyond the scope of repair or refolding.

Protein damage, in the context of its structure and functionality, usually means a loss of function combined with changes to its native conformational state, both of which might occur as a result of non-physiological temperatures (heat stress) or chemical modifications (e.g., reactive oxygen species (ROS)) causing oxidative stress, which in humans may lead to a wide variety of pathologies, including cancer, neurodegenerative disorders, diabetes, cardiovascular diseases, atherosclerosis, stroke, inflammatory disorders, chronic fatigue syndrome, asthma, and age-related pathologies (review in [1]). Misfolded proteins are prone to form abnormal or irregular interactions as a result of the exposure of their normally buried hydrophobic parts; this often leads to the toxic accumulation of insoluble aggregates [2]. Interestingly, even a slight increase in temperature can trigger a heat shock response. The problem is not the temperature itself, but the protein unfolding, entanglement, and non-specific aggregation that the heat causes. In eukaryotes, the major damage appears to consist of disruption to the cytoskeleton (reorganization of actin filaments and tubulin networks), fragmentation of the membranous organelles (the Golgi complex and endoplasmic reticulum), aggregation of ribosomal proteins, and a decrease in the number of mitochondria and lysosomes [3]. Mitochondria loss leads to a dramatic drop in oxidative phosphorylation and ATP levels, causing a further imbalance in homeostasis, ultimately leading to cell death [4]. To avoid this fate, cells possess so-called heat shock proteins (HSPs), whose expression increases in response to such stresses, and which serve as the foundation of resistance to hostile conditions [3].

HSPs primarily act as molecular chaperones that monitor and regulate polypeptide folding and prevent the aggregation or precipitation of misfolded proteins. They are often overexpressed upon stress, in situations that would normally be lethal. Oxidative, cytokine and muscular stresses; nutritional deficiencies; viral infections; hyperthermia; ischemia and alterations in calcium and pH in different types of cells and tissues are all potent inducers of increased HSP levels. In humans, their deregulation often underlies the pathologies of several diseases, including such devastating neurological disorders as Alzheimer’s disease (AD), Parkinson’s disease (PD), Creutzfeldt-Jacobs disease, Huntington’s disease, prion-related diseases, and amyotrophic lateral sclerosis (ALS) [5][6].

The accumulation of misfolded proteins and proteins irreversibly modified by post-translational modifications (e.g., protein glycation, methionine oxidation, deamination of asparaginyl and glutaminyl residues) that induce conformational changes and impaired protein functions has also been observed in ageing [5]. Such alterations cannot be simply reversed by molecular chaperones, these may only accompany their substrates and by a stable association with their hydrophobic surfaces prevent their aggregation thus shifting the normal functions of HSPs from protein maintenance to fighting the growing number of damaged or non-functional enzymes [5][7]. The vulnerability of proteins to aggregation poses a great danger and the only solution in protecting the cell itself is their complete removal. However, ageing also decreases the activity of the proteasome, the main cytosolic proteolytic enzyme [8][9]. Therefore, some species developed constitutively induced chaperones (small heat shock proteins (sHSPs) and HSC70), which could fill the roles of impaired HSPs in ageing cells [10]. Under normal conditions, cytosolic HSC70 shuttles between the cytoplasm and the nucleus [11], which

secures an export of nuclear proteins targeted for degradation [12]. The shuttling is transiently inhibited upon stress, when HSC70 becomes sequestered within the nucleus [13], thus protecting the stressed cells against possible damage and ensuring their survival when conditions improve [14]. When cells are exposed to excessive stress, a common response is to undergo cell death by either necrosis or apoptosis. HSPs are responsible for inhibiting both apoptotic and necrotic pathways and thus, they are also involved in cancer progression. The action of HSPs may cause uncontrolled cell growth, reduced tumor suppression, enhanced cell survival and may fuel tumor cell invasion, metastasis, and angiogenesis [15]. In various human cancers, HSPs were found to be expressed at high levels, providing an environment for tumor development and leading to poor patient prognosis and a resistance to therapy. Therefore, HSPs could also serve as biomarkers of cancer formation in several tissues and show the degree of progression and aggression of several types of tumors [16].

2. The 70-kDa Heat Shock Proteins (HSP70s)

Of all molecular chaperones, the HSP70 sub-family occupies a central position in every cellular proteostatic activity, from protein folding to disaggregation and degradation [17][18]. Its representatives are found in archaebacteria, prokaryotes, and eukaryotes, including plants and mammals [19], and possess one of the highest levels of conservation of all organismal proteins, with around 40–60% identity between the prokaryotic and eukaryotic homologues [20][21].

HSP70s reside in the cytoplasm of prokaryotes and in all major eukaryotic cellular sub-compartments [22][23][24]. At least one HSP70-encoding gene is expressed in all prokaryotes and eukaryotes. For example, E. coli harbors three Hsp70 isoforms: in addition to DnaK, the most thoroughly studied one, which mainly controls the folding of newly synthesized cytosolic proteins, two other HSP70 proteins have been identified, HscA and HscC [25][26]. HscA works together with its co-chaperone HscB in a chaperone/co-chaperone pair similar to that of DnaK/DnaJ [27][28]. It is required for the maturation of iron-sulfur clusters (ISC) [85,86] and is induced by cold stress [29]. HscC is heat induced, possesses ATPase activity, and is likely a chaperone [30], but does not act against denatured proteins [31]. S. cerevisiae expresses in total 11 HSP70 paralogues: 4 semi-redundant cytosolic/nuclear forms (SSA1, SSA2, SSA3, SSA4), 3 ribosome-associated chaperones (SSB1, SSB2, SSZ1), 3 mitochondrial chaperones (SSC1, SSQ1, SSC3) and 1 form specific for the endoplasmic reticulum (KAR2) [19][25][32][33]. Humans express 13 HSP70 homologues in different cellular compartments, including the cytosol and nucleus (HSPA1A/B, HSPA1L, HSPA2, HSPA6, HSPA7, HSPA8, HSPA12A/B, HSPA13, HSPA14), the ER (HSPA5) and the mitochondria (HSPA9) [25]. Human HSP70s differ not only in cellular localization but also in activity and expression [33][34]. Despite the large number of human isoforms, HSPA8 (also called HSC70) is the major, non-inducible cytosolic HSP70. It is constitutively expressed and provides the essential housekeeping functions in cellular protein quality control. Recent findings have also emphasized its involvement in regulating lysosome activity in specialized autophagy pathway called chaperone-mediated autophagy (CMA) (review in [35]). The second most abundant cytosolic homologue is the stress-inducible form of HSP70, HSPA1A (also named HSP72), whose expression increases in response to the accumulation of damaged or misfolded proteins [19][33][36].

In general, HSP70s consist of an N-terminal nucleotide-binding domain (NBD) and a C-terminal substrate-binding domain (SBD) connected by a flexible and highly conserved hydrophobic linker, which is crucial for allosteric inter-domain communication (review in [25]). The NBD domain is formed of four subdomains (Ia, IIa, Ib and IIb), organized into two lobes separated by a deep cleft, where the ATPase catalytic site resides (**Figure 1** a). In E. coli , the Ia NBD subdomain functions as a key mediator of inter-domain allostery, representing a signal transduction between the binding sites for ATP and substrate [37]. The SBD domain is capable of binding extended polypeptides rich in aliphatic residues and is composed of two parts, a β-sandwich subdomain (SBDβ) with the binding site and an α-helical subdomain (SBDα) acting as its flexible lid [25][36][38][39][40]. Both domains, NBD and SBD, are linked by a flexible linker that transfers the structural re-arrangements caused by the ATP hydrolysis from NBD to the SBD, which enables folding of the client protein [25].

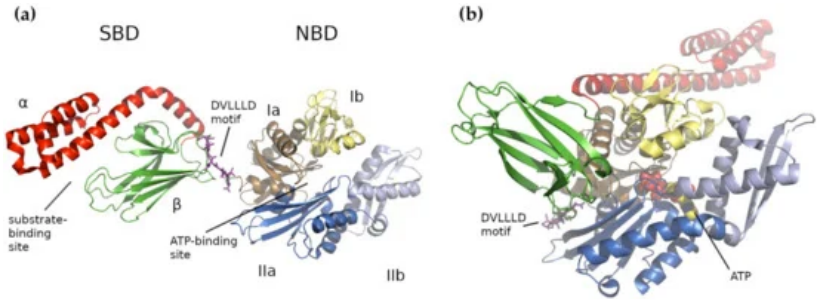

Figure 1. Structure of *E. coli* HSP70 DnaK. No complete structure of the human Hsp70 mortalin exists, so *E. coli* DnaK is used to illustrate the major structural features. (**a**) The Apo/ADP bound form with a compact substrate binding domain—closed state. The nucleotide-binding domain (NBD) is colored according to its four lobes: Ia is tan, Ib is pale yellow, IIa is

marine blue and IIb is light blue. The α- and β-domains of the substrate-binding domain (SBD) are colored red and green, respectively. The substrate-binding and ATP-binding regions are indicated. The conserved DVLLLD linker is shown in magenta sticks. (**b**) The ATP-bound compact form showing an extended substrate-binding domain—open state. The bound ATP is shown as spheres and the DVLLLD motif is again indicated. Coloring is as in (a) and the orientation is roughly based on the location of the NBD in (**a**). (**a**) shows PDB structure 2KHO [41] and (**b**) is 4B9Q [42].

For HSP70, two conformational states have been described, denoted as open and closed [43][44], or domain-docked and domain-undocked, respectively [45] (**Figure 1**a,b). In the closed state, ADP is bound in the nucleotide pocket of the HSP70 NBD and the SBD forms a closed cavity, binding client substrates with high affinity. The hydrolysis of ATP promotes NBD conformational changes, which are transduced through the linker domain to the SBD. The structural rearrangements trigger the clamping down/closure of the SBDα onto an unfolded protein, preventing its dissociation and allowing its folding. The replacement of ADP with ATP gives rise to further conformational changes leading to the open state, when the flexible linker becomes ordered, and the α-helical lid of the SBD is held open by an interaction with the ATPase region of the NBD [44][45].

The HSP70s function primarily as monomers, but they are tightly regulated by two types of co-chaperones [2][46]. Both are classified according to their bacterial homologues as (i) DnaJ-like or J-domain proteins (JDP) and (ii) GrpE-like nucleotide exchange factors, which appear in the endosymbiotic organelles. HSP70s were shown to require a bidirectional mechanism of nucleotide-dependent allosteric regulation, where ATP binding induces the release of the bound peptide, and substrate binding stimulates ATP hydrolysis [47][48][49] (**Figure 2**). HSP70 itself exhibits rather weak intrinsic ATPase activity, which increases in the presence of a protein substrate. However, the efficiency of the ATPase cycle is incomparably higher in the presence of its co-chaperones. The synergistic effect of a substrate binding with JDPs can stimulate the low basal ATP hydrolysis by more than 1000-fold [50], leading to a tighter binding of the substrate proteins to the HSP70 peptide-binding pocket. Additionally, the nucleotide-exchange factor promotes the release of imported precursors, and thus controls the overall cycle rate [47][46][51].

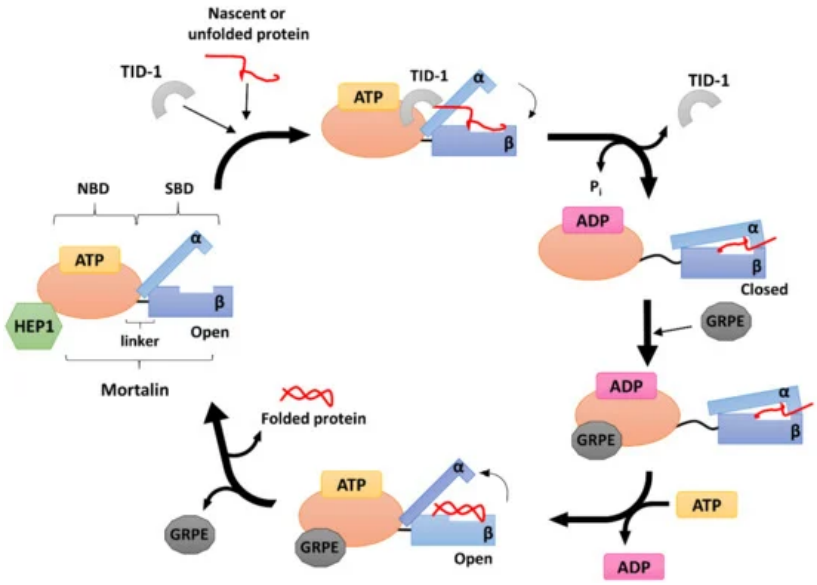

Figure 2. A likely model of the human mitochondrial HSP70 (mortalin) reaction cycle. Mortalin is composed of a nucleotide binding domain (NBD) and a substrate binding domain (SBD), which is divided into β and α sub-domains. The function of mortalin is tightly regulated by three co-chaperones, HEP1, TID-1 and either isoform of GRPEL1/2. HEP1 protects mortalin against self-aggregation and controls its ATPase activity. In the ATP-bound state, mortalin is in an open conformation and the flexible linker (located between the NBD and SBD) binds closer to the NBD. TID-1, which binds directly to mortalin, stimulates its ATPase activity, and prevents substrate protein aggregation. Substrate binding to the mortalin SBD binding cavity induces ATP hydrolysis and mortalin shifts into a closed conformation. GRPEL1/2 subsequently assists in the exchange of ADP for ATP. After ATP binding, mortalin returns into the open conformation and a folded substrate is released.

3. Human Mitochondrial HSP70 (mtHSP70)

Mitochondrial HSP70 (mtHSP70/GRP75/HSPA9/PBP74), also called mortalin, is an essential protein belonging to the HSP70 sub-family which has great importance for mitochondrial biogenesis and the correct functioning of the whole cellular machinery [52].

Mortalin was first identified in cell fusion studies of normal and immortal mouse fibroblasts as a marker of the mortal or lethal phenotype [53]. Mortalin was classified as a HSP70 stress chaperone based on its high degree of homology to other HSP70 members, including *E. coli* DnaK (51%), *S. cerevisiae* SSC1 (65%), and the rat cytosolic HSP70, HSC70 (46%) [53]. In humans, mortalin is a 74 kDa (679 amino acid), constitutively expressed protein and is one of the most abundant proteins in the mitochondrial matrix, accounting for approximately 1% of its total protein content [54]. Although mortalin is predominantly found in the mitochondrial matrix, when overexpressed it can also be found in extramitochondrial sites, including the cytosol and the perinuclear region.

Mortalin has the canonical HSP70 family structure, with a ~42 kDa NBD and a ~25 kDa PBD connected by a short hydrophobic linker (D^{434}VLLLDVTP$^{442)}$, used for allosteric regulation by its co-chaperones [55][56][57]. Since mortalin is predominantly a mitochondrial protein, it also has a 46 residue mitochondrial pre-sequence at its N-terminus [58][59][60], but its C-terminus has the sequence K^{671}EDQKEEKQ^{679}, which differs from the EEVD motif found in other human HSP70 homologues [61].

In mitochondria, mortalin performs two specific roles: as a chaperone and stress-survival factor, it assists in protein quality control by (re)folding or degrading non-functional proteins [62][63][64], and as an essential component of the presequence translocase-associated motor (PAM), it binds precursor proteins to promote their unidirectional [65][62][66][67] translocation across the two mitochondrial membranes and into the mitochondrial matrix [67]. An excellent review by Pfanner et al. [68] provides a more detailed characterization of the biogenesis of mitochondrial proteins. In addition to mortalin, the PAM complex contains TOM20 and TOM22, the receptors on the surface of the mitochondrial outer membrane which recognize the cytosolic precursors carrying the mitochondrial localization signal (these form positively-charged amphipathic α-helices) [69][70]. These cytosolic pre-proteins are subsequently transported through the major outer membrane protein translocation channel, TOM40, and are then engaged by the presequence translocase of the inner membrane, TIM23 [71][72][73]. In the PAM complex, mortalin is the central ATP-driven chaperone and, together with its co-chaperones, ensures the translocation of the pre-protein into the mitochondrial matrix [68]. In humans, mortalin was shown to directly interact with the TIM23 complex, as well as cardiolipin-containing lipid bilayers, enabling its insertion into the inner mitochondrial membrane [74]. Although mortalin is approximately ten times more abundant than TIM23 [68], only a small amount of it acts in the TIM23-associated PAM in driving pre-protein import; the majority is involved in mitochondrial protein folding [73]. The overall maintenance of mitochondrial homeostasis is ensured by the cooperation of mortalin with the HSP60–HSP10 chaperonin complex; together, these play a central role in the correct folding of matrix-localized proteins, preventing protein misfolding and promoting the refolding and proper assembly of unfolded polypeptides that are generated under stress conditions inside the mitochondria [75].

In addition, mortalin also plays an important role in iron-sulfur cluster (ISC) biogenesis within the matrix and the proper insertion of Fe-S apoproteins [76][77][78]. It also closely cooperates with other mitochondrial homeostasis maintenance factors, including the tumor necrosis factor receptor-associated protein type 1 (TRAP-1) [79][80] and the mitochondrial voltage-dependent anion channel (VDAC) [81]. It regulates mitochondrial properties, including ATP levels, membrane potential and permeability [82][83], and it associates with the mitochondrial contact site and cristae organizing system (MICOS) complex [84]. Moreover, together with HSP60 and the mitochondrial ATP-dependent protease LON, mortalin forms part of the peripheral region of human mitochondrial nucleoids [85]. Outside the mitochondria, mortalin is also involved in other cellular activities, such as regulation of p53 activity, calcium and ROS signaling, intracellular trafficking, control of centrosome duplication, differentiation, and many others [86][87][88][89][90][91].

4. Human mtHSP70 Co-Chaperones

4.1 HEP1

The mortalin escort protein HEP1 (also called Zim17/TIM15/DNLZ) is a small (15 kDa) DNL-type zinc finger protein that functions as a mtHSP70 partner on the matrix side of the inner mitochondrial membrane (**Figure 2**). Structurally, HEP1 forms asymmetric monomers, but it can also oligomerize depending on its actual concentration with Trp115 playing an important role in the process. Trp115 as the part of the zinc-binding domain (ZDB), lies on the surface of the monomer. The zinc finger motif seems particularly important for HEP1 itself, as well as for its interaction with mtHSP70. It has been shown that HEP1 is highly unstable in the presence of the EDTA chelator, indicating that the zinc ions are crucial for stabilizing its structure [92]. Moreover, when deletions or mutations in this motif occurs, HEP1 loses the ability to bind mortalin [93].

Studies in yeast demonstrated that HEP1 is essential for the mitochondrial import machinery. Deletion of its gene impaired the TIM23-dependent import of mitochondrial pre-proteins, which are necessary for yeast growth at elevated temperatures. When complexed with mtHSP70, HEP1 has a dual character: it protects mtHSP70 from self-aggregation,

as mentioned above, and also participates in controlling its ATPase activity [43][94]. Zhai et al. [95] showed that His107, conserved in all mitochondrial and chloroplast HSP70-escort proteins, is especially required for ATPase stimulation. In humans, HEP1 binds the mortalin NBD directly [94], while in yeast, an interdomain linker is needed [43]. As noted above, the interdomain linker is a short loop of hydrophobic amino acids that connect the mtHSP70 NBD to its SBD, providing for their mutual communication [96]. Interestingly, the presence of human HEP1 increases the mtHSP70 ATPase activity by up to 49-fold [97], similar to the effect reported for the J-domain co-chaperones [98][44], and it also enhances the rate of nucleotide exchange, similar to the GRPE-type co-chaperones [47].

4.2 GRPE

In complex with mtHSP70, GRPE acts as a nucleotide exchange factor (NEF) (**Figure 2**), mediating the opening of the HSP70 nucleotide binding cleft to facilitate the dissociation of ADP, which, in turn, allows the binding of another ATP molecule and promoting the release of the protein substrate [99][100].

In E. coli , GrpE acts as a NEF for the bacterial Hsp70 homologue DnaK [47]. In S. cerevisiae , MGE1 acts as a NEF for the yeast mtHSP70 SSC1 [101]. Mammals have two mitochondrial GRPE homologues, GRPEL1 (a 23 kDa protein) and GRPEL2 (25 kDa) [102] together with an additional exchange factor, BAG1, for cytosolic HSP70 [103]. The actual reason for such duplicity in mitochondria is still unknown, though several experiments have shown that GRPEL1 is essential for cell viability while GRPEL2 is not [104][105][106]. Konovalova et al. [106] found that GRPEL1 serves as the major exchange factor for mtHSP70 (mortalin), which is necessary for maintaining the proper translocation of proteins to the mitochondrial matrix through the PAM complex, while GRPEL2 acts as a “helper” protein. Konovalova et al. [106] also found that human GRPEL2 is a redox-sensitive protein, which can form dimers (through disulfide linkages) under oxidative stress. This suggests that even though GRPEL2 is not essential in cultured cells, it has may have adapted to fine-tune protein import and folding in response to altered redox conditions.

4.3 TID-1

TID-1 (tumorous imaginal disc protein 1), also known as DnaJ homolog subfamily A member 3 (DnaJA3), is a small mitochondrial protein belonging to the HSP40 sub-family. TID-1 is a human homologue of the bacterial protein DnaJ and the tumor suppressor protein TID-56 present in Drosophila [107][108]. Its translation occurs in the cytosol, and mRNA splicing produces two isoforms: a 43 kDa long isoform called TID-1L, and a shorter 40 kDa isoform called TID-1S. These isoforms differ in the length of their C-terminal ends (33 residues for TID-1L and 6 for TID-1S) [109][110]. NMR studies have shown that TID-1 contains a highly conserved J-domain at its N-terminus, typical for all DnaJ proteins, which is extremely important for its binding to mtHSP70 [111][112][48]. TID-1L resides mainly in the cytosol, where it interacts with cytosolic HSP70 and participates in the induction of apoptosis and various cellular signaling pathways. TID-1S, on the other hand, localizes primarily to the mitochondrial matrix, where it is responsible for mtDNA stability and maintains the mitochondrial membrane potential, thus acting against apoptosis [113][114][115][116]. TID-1 is one of the major co-chaperones of mtHSP70 and is mainly involved in stimulating its ATPase activity (**Figure 2**). Indeed, when other HSP70 co-chaperones are missing, a TID-1–mtHSP70 complex can still bind unfolded substrates and prevent their aggregation [117].

TID-1 is involved in numerous cellular processes, including cell growth, proliferation, differentiation, ageing, and survival [118][119][120][121]. In mammals, it is also involved in movement and plays an important role in the development of embryos and skeletal muscles [122][123][124]. Loss of TID-1 in heart results in cardiomyopathies and a decrease in mtDNA levels because it aids in the proper folding of DNA polymerase γ [125]. The protein is also involved in regulating mitochondrial homeostasis. Deregulation of TID-1 impairs its interaction with the mitochondrial dynamin-1-like protein DNM1L, causing fragmentation of the mitochondrial network [119] and negatively influences the CR6-interacting factor 1 (CRIF1) involved in the proper localization of the OXPHOS subunits into the inner mitochondrial membrane [126]. Similarly, an imbalance between TID-1 and mtHSP70 may be responsible for the mitochondrial fragmentation seen in patients diagnosed with optic atrophy 1 [127]. A recent study by Patra et al. [128] linked ataxia and developmental delay in one patient to a homozygous mutation in the TID1 gene (Arg151Thr), which produced a TID-1 variant that was less efficiently imported into the mitochondria and had severely impaired co-chaperone functions.

5. Conclusions

The mitochondrial HSP70 chaperone system consisting of mortalin and its co-chaperones HEP1, TID-1, and GRPE, forms one of the key components of PQC in mitochondria. As an essential protein that participates in proliferation, functional maintenance, and cellular stress response, mortalin has been implicated in many human pathologies, including neurodegenerative disorders, autosomal recessive diseases, and carcinogenesis. Indeed, recent studies indicate that

mortalin could serve as a prognostic and predictive marker of cancer invasiveness as its up-regulation has been detected in a variety of malignancies, such as brain tumors, hepatocellular carcinoma, colon carcinoma, breast cancer, and leukemia.

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