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Mitochondrial Ribosomes in Cancer

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Abstract

Mitochondria play fundamental roles in the regulation of life and death of eukaryotic cells. They mediate aerobic energy conversion through the oxidative phosphorylation (OXPHOS) system, and harbor and control the intrinsic pathway of apoptosis. As a descendant of a bacterial endosymbiont, mitochondria retain a vestige of their original genome (mtDNA), and its corresponding full gene expression machinery. Proteins encoded in the mtDNA, all components of the multimeric OXPHOS enzymes, are synthesized in specialized mitochondrial ribosomes (mitoribosomes). Mitoribosomes are therefore essential in the regulation of cellular respiration. Additionally, an increasing body of literature has been reporting an alternative role for several mitochondrial ribosomal proteins as apoptosis-inducing factors. No surprisingly, the expression of genes encoding for mitoribosomal proteins, mitoribosome assembly factors and mitochondrial translation factors is modified in numerous cancers, a trait that has been linked to tumorigenesis and metastasis. In this article, we will review the current knowledge regarding the dual function of mitoribosome components in protein synthesis and apoptosis and their association with cancer susceptibility and development. We will also highlight recent developments in targeting mitochondrial ribosomes for the treatment of cancer.

Keywords

Mitochondrial ribosomes; Cancer; Apoptosis; Therapy

1. Introduction

Mitochondria play central roles in cancer cell physiology [1]. These eukaryotic organelles perform numerous bioenergetic and biosynthetic functions. Among them, mitochondria

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house pathways ranging from fatty acid oxidation to the TCA cycle, the oxidative phosphorylation (OXPHOS) system and respiration, and from the synthesis of amino acids, lipids and nucleotides to the biosynthesis of heme and iron-sulfur clusters [2]. Despite the fact that functional mitochondria are essential for the cancer cell, mitochondrial physiology is distinct in cancer and non-malignant cells [2], what initially brought to the hypothesis by Otto Warburg that a decline in mitochondrial energy metabolism might lead to the development of cancer [3]. In addition to providing fuel for life, mitochondria perform fundamental roles in the regulation of cell death pathways [4]. Considering that most tumor cells are by definition resistant to apoptosis, mitochondria may be regarded as the master regulators of both cellular life and death.

As an endosymbiotic organelle, the mitochondrion has retained a vestige of its bacterial ancestor genome, the mitochondrial DNA (mtDNA). In humans, where mitochondria contain more than 1100 proteins, the mtDNA encodes for only 13 hydrophobic subunits of the OXPHOS system, as well as for two rRNAs and a set of 22tRNAs. The vast majority of proteins are therefore encoded in the nuclear genome, synthesized by cytoplasmic ribosomes and imported into mitochondria. The expression of mtDNA-encoded genes, which depends on an organelle-specific machinery, ends with the synthesis of the 13 proteins in mitochondrial ribosomes or mitoribosomes [5]. Mitoribosomes are macrostructures of dual genetic origin, formed by 3 mitoribosomal RNA components encoded in the mtDNA and 89 specific protein components encoded in the nuclear DNA. Mitoribosomes differ from their bacterial and cytoplasmic counterparts in their composition, structure and mechanistic intricacies [6–9]. Their high degree of specialization has resulted in accelerated evolution so that significant differences exist even among mitoribosomes from different species [5–9]. However, as remnants of their eubacterial origin, mitoribosomes are as sensitive to similar antibiotics as bacteria and have many conserved proteins and RNA moieties [5, 10, 11].

The past decade has revealed new roles for the mitochondrial translation machinery and mitoribosome proteins in apoptotic signaling and the regulation of cell proliferation [12, 13]. Therefore, it is not surprising that gene expression studies have found alterations in the levels of mitoribosome proteins or assembly factors associated with the development of cancer [14, 15]. As a consequence, therapeutic approaches targeting mitochondrial protein synthesis have emerged as new interventions to combat specific types of malignancies [16–18].

Following this line of argumentation, the current review highlights the mitochondrial ribosome components and functions that have been associated with the development of cancer, and the underlying pathways. After an overview of mitoribosome composition and structure, we first describe the extraribosomal role of mitoribosome proteins in cell death regulation. Next, we address the association of mitoribosome proteins with cancer and examine their potential as biomarkers. Finally, we provide an overview of the recent evidence denoting the reliance of some cancer cells on OXPHOS, which has suggested mitochondrial translation as a target for cancer therapy.

2. Mitoribosomes: structure, biogenesis and function

2.1. Mitochondrial protein synthesis—The mitochondrial translation system evolved from that of the bacterial ancestor of mitochondria. This is evident from the fact that the proteins and RNA domains of mitochondria and bacteria that contribute to decoding and peptide bond formation, explained below, share a high degree of similarity. Therefore, mitoribosomes are sensitive to antibiotics such as chloramphenicol and tetracyclines, a property that is being exploited in the treatment of some types of cancer. Translation factors are conserved, and several mitochondrial factors can even functionally replace their homologs in bacteria [19]. However, multiple substantial differences exist, including (i) deviations in the genetic code [20–22], (ii) changes in the actual process of translation [23, 24] and (iii) the formation of mitochondrial ribosomes that differ in structure and composition, not only in comparison to their bacterial relatives but also among different species [6–9].

The mitochondrion has a simplified decoding system that allows a reduced set of mitochondrial tRNAs to recognize all the codons [25, 26]. The 22 tRNAs required in human mitochondria are encoded in the mtDNA. On the contrary, all translation factors are encoded in the nuclear genome [23, 24]. Mitochondrial mRNAs lack Shine-Dalgarno elements that could facilitate their interaction with ribosomes, and it is unclear how translation initiation is accomplished. Mitochondria have homologs of bacterial initiation factors IF2 (the functional equivalent of bacterial IF1 and IF2 [27]) and IF3 [28–32]. In mammals, IF2-mt promotes the binding of the initiator formylmethionine-tRNA (fMet-tRNA) to the AUG codon at the ribosomal peptidyl-site [33]. IF3-mt encourages the dissociation of fMet-tRNA that has bound to a small subunit in the absence of a correctly loaded mRNA [34]. Following translation initiation, it is assumed that elongation of the peptide chain occurs through mechanisms almost identical to those in bacteria [35–37] and involves homologs of the elongation factors EF-Tu, EF-G and EF-Ts [35]. However, termination of translation and recycling show stunning deviations from the bacterial pathway [38–41]. For example, mammalian mitochondria utilize only one release factor, mtRF1a [42], to decode all stop codons [43, 44].

2.2. Mammalian mitoribosomes

In all living organisms, mature ribosomes are composed of two distinct subunits, the large subunit (LSU) and the small subunit (SSU). Whereas the LSU catalyzes the peptidyl-transferase reaction, the SSU provides the platform for mRNA binding and decoding. Mammalian mitoribosomes sediment as 55S particles composed of a 28S mt-SSU and a 39S mt-LSU (Figure 1). The mt-SSU is formed by a 12S rRNA and 29 mitoribosomal proteins (MRPs). The mt-LSU is formed by a 16S rRNA, a structural tRNA ($tRNA^{Val}$ in human cells) and 50 MRPs [35, 45–49]. The two rRNA components are transcribed from mtDNA genes. The tRNA, also encoded in the mtDNA, occupies the region in the central protuberance where the cytoplasmic and bacterial ribosomes contain a 5S rRNA.

Concerning the MRPs (listed in Table 1), 16 of the 30 mt-SSU proteins and 28 of the 50 mt-LSU proteins are homologs of proteins present in *E. coli* while the rest are mitochondrion-specific proteins [7, 47, 49–51]. Moreover, most conserved proteins contain mitochondrion-

specific N- or C-terminal extensions, whereas some RNA helices present in the bacterial ribosome have been lost. As a consequence, human 55S mitoribosomes differ from bacterial (70S) and cytoplasmic ribosomes (80S) in their lower RNA:protein ratio. The recent high-resolution cryo-EM reconstruction of the mammalian mitoribosome revealed that the MRP extensions predominantly interact with mitochondrion-specific proteins whereas only a few participate in filling the space of deleted rRNA. Most mitochondrion-specific proteins are peripherally distributed over the solvent-accessible surface forming clusters at the central protuberance, the L7/L12 stalk, and contiguous to the polypeptide exit site. Similar to the protein extensions, these MRPs occupy novel positions rather than compensate for the missing rRNA [47, 49, 50, 52, 53].

Some mitochondrion-specific proteins serve to establish intersubunit bridges [7], a feature that is different from cytoplasmic ribosomes that typically contain RNA-RNA intersubunit connections. The number of intersubunit bridges is lower in mammalian mitoribosomes than in the bacterial ribosome, possibly to allow the two subunits to have flexibility in the conformation enabling them to tilt freely [52, 53]. Another major remodeling from the bacterial ribosome occurs at the aminoacyl and peptidyl-tRNA binding sites, where some proteins present in bacterial ribosomes (e.g. uL5 or bL25) have been lost to accommodate human tRNAs, which contain highly variable loops at the elbow. A unique property of mitoribosomes is the acquisition of an intrinsic GTPase activity through mt-SSU subunit mS29, a GTP-binding protein [10, 46, 48]. The GTPase activity is probably relevant to subunit association, given the localization of mS29 at the subunit interface, its involvement in coordinating two mitochondrion-specific intersubunit bridges, and the fact that the affinity for GTP is higher for mt-SSU 28S subunits than for the 55S monosome [10, 46, 48].

Mitoribosomes reside in the mitochondrial matrix and associate with the inner membrane to facilitate co-translational insertion of the nascent polypeptides into the inner membrane. In fact, the polypeptide exit tunnel is adapted to the transit of hydrophobic nascent peptides [47, 49]. The tunnel is formed by several conserved proteins that create a ring around the exit site, namely bL23m, bL29m, bL22m, bL24m and bL17m. This conserved core is surrounded by another protein layer consisting of bL33 and mL45, which promote anchoring of the mt-LSU to the inner membrane [46–49]. Another significant structural remodeling has been observed at the mRNA entrance of the mt-SSU [51–53], to accommodate mammalian mitochondrial mRNAs, which miss or have very short 5′-untranslated regions [54]. Since the structural data has disclosed the presence of mS39, a pentatricopeptide repeat (PPR) protein in the proximity of the channel entrance, it has been suggested that it could be involved in recruiting the leaderless mRNA during translation initiation [51–53].

2.3. Ribosome assembly

The assembly of ribosomes requires coordinated processing and modification of rRNAs with the temporal association of ribosomal proteins. In all systems, the process is regulated by several classes of ribosome biogenetic factors, including nucleases, rRNA-modifying enzymes, DEAD-box helicases, GTPases and chaperones [55–57]. Although the mitoribosome assembly pathway is still poorly characterized, several assembly factors have been already identified. They include rRNA modification enzymes (the 16S rRNA

methyltransferases MRM1-3) and their co-factors [58–60]. Also, several poorly characterized conserved GTPases participate in the assembly of the mt-SSU (C4orf14) or the mt-LSU (MTG1 and MTG2) [61–63]. Unexpectedly, two mitochondrial transcription factor family proteins (mTERF3 and mTERF4) play roles in mt-LSU assembly, perhaps coordinating transcription and ribosome biogenesis. The precise role of mTERF3 (or mTERFD1) is not understood [64], but mTERF4 binds to the rRNA methyltransferase NSUN4 to promote its recruitment to the mt-LSU [65], possibly to facilitate monosome assembly [66]. A role in monosome formation has also been proposed for MPV17L2, a mtDNA maintenance factor [67], although its function remains intriguing. Two DEAD-box helicases, DDX28 and DHX30, participate in mt-LSU assembly [68, 69]. DDX28 interacts with the 16S rRNA and its yeast counterpart, termed Mrh4, catalyzes a late step of mt-LSU assembly required for the incorporation of proteins uL16 and bL33 to a large on-pathway intermediate [70]. FASTKD2, a member of the Fas-activated serine-threonine kinase family of proteins also binds to the 16S rRNA and participates in mt-LSU assembly [68]. Furthermore, C7orf30, a member of the DUF143 family of ribosomal silencing factors, interacts with uL14 and promotes its incorporation into the mt-LSU [71]. Finally, GRSF1 (G-rich sequence factor 1) is an RNA-binding protein that interacts with several mt-RNAs, including the 12S rRNA, and participates in mt-SSU biogenesis [72].

Mitoribosome assembly has been proposed to occur in contact with the inner membrane [70, 73] in a compartment located near the mtDNA nucleoid termed RNA granule or mitochondriolus [68, 69, 74]. The mitochondrioli contain ribosomal proteins, ribosomal RNA modifying enzymes, all the mitoribosome assembly factors listed above and a host of proteins involved in diverse aspects of mt-RNA metabolism [59, 68, 69, 72, 75]. The dynamics of these compartments in health and disease remains to be fully understood.

In eukaryotic systems, several post-transcriptional regulation events are highly linked and provide a powerful mechanism to control the fate of a cell, and therefore are of central importance in cancer research [76, 77]. Emerging data, summarized in the following sections, highlight the additional relevance of mitochondrial ribosome components and mitochondrial translation in controlling cellular proliferation in OXPHOS-dependent and independent manners, thus providing novel mechanisms for understanding tumorigenesis and novel targets for therapeutics design.

3. Mitoribosomal proteins and apoptosis

Mitochondria play crucial roles in the induction of apoptosis or programmed cell death [78]. This paradigm is central to malignant cellular transformation because altered mitochondrial function and defective apoptosis are well-known hallmarks of cancer cells. In fact, tumor initiation and progression involve the development by cancer cells of mechanisms to inhibit apoptosis at multiple stages. Recent investigations have uncovered apoptosis-regulatory roles of several protein components of the mammalian mitoribosome, which has opened the question of whether the mitoribosome, mitochondrial translation or moonlighting functions of these mitoribosome proteins could be involved in apoptotic signaling [7, 10, 12].

The caspase proteases that execute apoptosis can be activated through one of two signaling cascades responding to different signals: the extrinsic pathway, involving cell surface death-receptors (e.g. FASL, TRAIL and TNFα), and the intrinsic or mitochondrial pathway. The mitochondrial pathway can be induced by a variety of stimuli such as chemotherapeutic agents, serum/growth factor starvation, irradiation, DNA damage, free radicals and viral infections [78, 79]. These stimuli result in changes in the permeability of inner mitochondrial membrane owing to the opening of the mitochondrial permeability transition pore (MPT), which induces loss of the mitochondrial transmembrane potential, the release of pro-apoptotic proteins to the intermembrane space and disruption of mitochondrial functions. However, an essential event in mitochondria-mediated apoptosis is mitochondrial outer membrane permeabilization (MOMP), achieved through the formation of pores by pro-apoptotic members of the BCL-2 (B-cell lymphoma 2) family of proteins (e.g. Bax and Bak), in competition with anti-apoptotic members of the family (e.g. Bcl2 and Bcl-XL). The crucial event following MOMP is the release of mitochondrial pro-apoptotic proteins (cyctochrome *c,* Smac and Omi) to the cytosol, where they form the caspase-activating apoptosome (cytochrome *c*) or bind to inhibitors of apoptosis to relieve their inhibitory effects on caspase activity (e.g. Smac and Omi), resulting in the death of the cell [78, 79].

Cancer cells often escape apoptosis by shifting the balance between pro- and anti-apoptotic BCL-2 family proteins by inducing their down- and up-regulation, respectively, thereby preventing MOMP. In fact, the basis of effective cancer treatments such as chemotherapy highly depends on the levels of pro-apoptotic and anti-apoptotic BCL-2 proteins, because that balance determines the sensitivity of the tumor cells toward apoptosis [80]. Among the multiple regulators of the intrinsic pathway of apoptosis, recent studies have reported the involvement of three mitochondrial ribosomal proteins (mS29, mL41 and mL65), whose roles are discussed below.

3.1. mS29 (death-associated protein 3, DAP3)

As discussed in the previous section, mS29 is a GTP binding protein from the mt-SSU [81]. In the context of the mitoribosome (Figure 1), mS29 mediates contacts with intersubunit bridges, and its GTPase activity might fuel monosome formation [46, 48]. Additionally, a number of phosphorylation sites have been identified on mS29 that are in proximity to proteins forming the intersubunit bridges [82, 83]. Whether the phosphorylation status of mS29 might regulate mitoribosomal subunit association remains to be discovered.

mS29 was first discovered as a member of the death-associated protein (DAP) family and termed DAP3 [81, 84], before being identified as a mitoribosome protein [85]. mS29/DAP3 is known as one of the major positive mediators of apoptosis [86]. Mutations in a highly conserved P-loop motif significantly reduces DAP3-induced cell death, and overexpression of DAP3 enhances apoptosis [87]. However, the precise mechanism/s by which DAP3 induces apoptosis remain to be fully understood. mS29/DAP3 has been found outside mitochondria to initiate the extrinsic apoptotic pathway through its interactions with apoptotic factors such as Fas ligand, tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFNγ) [86, 88–90]. Nevertheless, additional studies have shown that once activated mS29/DAP3 co-localizes and strongly associates with Fas-associated death receptor (FADD)

(Figure 2) [91]. Additionally, DAP3 interacts with the factor IPS-1 (interferon-β promoter stimulator 1) to activate caspases 3, 8, and 9, resulting in a type of extracellular apoptosis known as anoikis [88, 91]. However, contrasting evidence has suggested a role for DAP3 in the mitochondrial apoptotic pathway and indicated DAP3-independent Fas-induced and TRAIL (tumor necrosis factor-related apoptosis inducing ligand)-induced apoptosis [92–94]. Moreover, mS29/DAP3 induces mitochondria-mediated apoptosis of a human laryngeal carcinoma cell line (Hep2 cells) through the activation of p38 MAPK and JNK signaling [95, 96]. The intrinsic pro-apoptotic role of DAP3 is further highlighted by the fact that overexpression of human, mouse or yeast DAP3 leads to cell death resulting in mitochondrial fragmentation, perhaps affecting mitochondrial fission [94, 97] in a manner dependent on the GTP-binding ability of DAP3 and its mitochondrial localization [94].

DAP3 is essential for life, and its knockout in embryos is lethal, resulting in abnormal, shrunken mitochondria with swollen cristae [98]. This study showed DAP3 as a bifunctional protein involved in mitochondrial protein synthesis and respiration and in the extrinsic pathway of apoptosis [98]. It is important to notice that although mS29/DAP3 localizes to the mitochondrial matrix, it is not released to the cytoplasm during induction of apoptosis [94, 97], indicating the existence of an extramitochondrial pool of mS29 to induce the extrinsic apoptotic pathway [91]. Nonetheless, the apoptotic activity of DAP3 in this compartment can be inhibited by AKT (PKB) phosphorylation [88, 91]. These observations suggest different levels of regulation of DAP3 in apoptosis by gene expression, protein localization and phosphorylation. However, the mechanism underlying the dual extraribosomal functions of DAP3 in mitochondrial physiology and cell death regulation remains unclear. In agreement with the DAP3 overexpression experiments mentioned earlier, a recent study has suggested a role of DAP3 in maintaining balanced mitochondrial dynamics (fusion and fission) by regulating the phosphorylation of Drp1 (dynamin-related GTPase involved in mitochondrial fission) [99]. Additionally, it was shown that depleting DAP3 inhibits autophagy thereby sensitizing the cells to intrinsic death stimuli [99]. Despite these efforts, it remains unclear whether the role of mS29/DAP3 in the regulation of mitochondrial translation is coupled to its role in the intrinsic apoptosis pathway.

3.2. mL41 (BCL-2 interacting mitochondrial ribosomal protein BMRP)

In the structure of the mt-LSU subunit, mL41 assumes a mostly extended conformation (Figure 1), and interacts with the 16S rRNA and several surrounding mitoribosomal proteins, including another pro-apoptotic protein, mL65 [49].

Beyond its role in mitochondrial protein synthesis, mL41 has been found to suppress the growth of cancer cells in nude mice, possibly by induction of p53-induced mitochondrion-dependent apoptosis [100]. In short, when p53 translocates to the mitochondria in response to cell death signals, mL41 would stabilize p53 and enhance its local abundance - thereby contributing to p53-induced apoptosis in response to inhibition of cellular proliferation. In addition, in the absence of p53, mL41 stabilizes the $p27^{Kip1}$ protein and $p21^{WAF1/CIP1}$, a cyclin-dependent kinase inhibitor, and arrests the cell cycle at the G_1 phase [100, 101], suggesting that mL41 is a negative regulator of cell cycle and plays a strong tumor-

suppressive role associated with p53, $p27^{Kip1}$ and $p21^{WAF1/CIP1}$ [100]. However, the mechanism/by which mL41 increases the stability of p53, p27 and p21 remains unknown.

mL41 has also been named BMRP (BCL-2 interacting mitochondrial ribosomal protein) [102], based on the observation that when overexpressed in human cells, mL41 induces cell death which is counteracted by BCL-2. mL41/BMRP-induced cell death was also repressed by p35, a caspase inhibitor, further suggesting its involvement in the regulation of apoptosis via its interaction with anti-apoptotic members of the BCL-2 family of proteins. Most probably, this interaction/s do not occur with mL41 embedded within the mt-LSU structure [47, 49]. In fact, the BCL-2 binding sites have been found near the N-terminus of mL41 [103, 104]. They correspond to motifs that are either absent in the mature protein owing to the cleavage of the mitochondrial targeting sequence after its import into mitochondria, or might be buried within the 16S rRNA - thereby making it inaccessible for interaction with BCL-2. Therefore, the interaction of mL41 with BCL-2 and its apoptotic activity are likely to occur in the cytosol before its import into mitochondrial and incorporation in mitoribosomes [10, 104]. Further studies are needed to unravel the mechanisms by which the mL41 precursor induces apoptosis, and those that control mL41 processing in non-malignant and cancer cells.

3.3. mL65 (programmed cell death protein 9, PDCD9)

Initially known as MRPS30 and considered to be a mt-SSU protein, structural studies found mS30 to be present as a single copy in the mt-LSU and was renamed mL65. In the mt-LSU, mL65 has close contacts with its homologous protein mL37 [47, 49, 105] and also Cα-Cα crosslinks with pro-apoptotic mL41 [49], as mentioned earlier.

mL65 has homology to the chicken pro-apoptotic protein p52 which, when overexpressed in mouse fibroblasts, induces apoptosis, upregulation of transcription factor c-Jun and activation of c-Jun N-terminal kinase 1 (JNK1), through a pathway distinct from the extrinsic death receptor-induced apoptosis [13]. The human counterpart of p52 was termed PDCD9 (programmed cell death 9), and the corresponding gene mapped to chromosome 5q11 [106]. However, little is known about the molecular mechanisms underlying the pro-apoptotic roles of mL65. Future studies should focus on disclosing whether mL65 acts independently or in conjunction with the other pro-apoptotic mitoribosomal proteins, particularly its interactor mL41.

4. Mitoribosome components as biomarkers and their association with cancer

Advances in tumor and cancer cell genomics and proteomics are providing remarkable insights into the genetic and metabolic basis of most cancers. The identification of novel mutations, epigenetic dysregulation, and aberrant gene expression or protein abundance patterns has yielded deep insights into specific cancer pathogeneses [15, 107, 108]. Genetic, genomic and proteomic variations may serve as markers for diagnostics and in some cases, when a causal relationship is established, as therapeutic targets as well. These studies have uncovered the value of mitoribosome components, mitoribosome assembly factors and

mitochondrial translation function as biomarkers that could reflect the molecular functional profile of specific tumors [15, 109, 110]. This is not that surprising, considering the involvement of mitoribosome proteins in the induction of apoptotic pathways, described earlier.

In this section, we will describe the combination of results obtained from candidate gene studies (on mS29, mL41 and mL65), genome-wide association studies (GWAS) and analysis of the cancer proteome (http://www.proteinatlas.org/humanproteome/cancer), which are shedding light onto the contribution of mitoribosome composition and function to the transformation of normal cells to tumorigenic. For example, a GWAS study on human breast cancer cells yielded significantly increased transcripts from more than 90 genes that are associated with mitochondrial biogenesis and/or mitochondrial translation, nearly 40 of them being MRPs [110]. Also, immunohistochemical analysis revealed that antibodies directed against 15 markers of mitochondrial biogenesis and/or mitochondrial translation selectively labeled epithelial breast cancer cells and that the signal was extremely lowered or excluded from adjacent tumor stromal cells. These were a regulator of mitochondrial function through cAMP signaling (AKAP1), mitochondrial lipid biosynthesis markers (GOLPH3 and GOLPH3L), a transporter that regulates the uptake of high-energy mitochondrial fuels (MCT1), mitoribosome proteins (mL40, uS7m, uS15m, and mS22), nuclear transcription factors that regulate mitochondrial biogenesis (NRF1, NRF2, PGC1-α), mtDNA metabolism (POLRMT, TFAM) and components of the mitochondrial import machinery (TIMM9 and TOMM70A). These results suggested that human breast cancers contain two distinct metabolic compartments, namely mitochondria-rich epithelial cancer cells and their surrounding glycolytic tumor stroma cells, which would establish a metabolic symbiosis.

Protein profiling using immunohistochemistry has allowed the Human Protein Atlas Project for the assessment of the distribution and relative abundance of proteins in tumor tissues. We have presented in Table 1 an evaluation of the differential expression of mitoribosome proteins and assembly factors between each of ten forms of cancer and their corresponding normal tissue counterparts. As an overview, our analysis shows that certain proteins have enhanced abundance in most tumors, including uL10m, mL38, mL52, uS2m, bS18m, mS27, NSUN4 and TFB1m, although the latter is specifically attenuated in breast cancer. On the contrary, another group of proteins has decreased abundance in most tumors, including bL17m, bL33m, bS6m (although elevated in liver cancer) and C7Orf30 (although elevated in thyroid cancer). From a tumor perspective, some display a general decrease in the levels of all proteins, such as colon carcinomas and particularly renal tumors, suggesting that mitochondrial OXPHOS might have limited relevance in these cancer cells. On the contrary, liver tumors display a general increase in mitoribosome-related proteins, as it occurs in melanomas, although in this case, a few proteins (uL18m, uL24m, bL27m, mL42, bS6m, mS31) have decreased abundance. Finally, limited changes were observed between lung tumors and normal lung tissue because only the levels of a few proteins (uL11m, bL19m, bL33m and uS11m) were found decreased. As a conclusion, our analysis shows differential mitoribosome protein abundance among different forms of cancer, but also highlights some potential tumor biomarkers. Below, we will discuss the published evidence on the potential of individual mitoribosomal proteins as cancer diagnostic markers based on GWAS and proteomics studies.

4.1. uL11m

In the mitoribosome structure, uL11m is located in the L7/L12 stalk and is involved in the binding and recruitment of translation factors to support mitochondrial translation [50]. uL11m was considered a potential cancer biomarker when tissues from patients suffering from head and neck squamous cell carcinoma (HSNCC) presented altered expression of OXPHOS complexes and defective mitochondrial translation over the progression of HSNCC, associated with a decrease in *MRPL11* expression [14]. This observation was in agreement with microarray analyses of HNSCC primary tumor tissues and cell lines and HN cancer cell lines showing that transcription of mitoribosomal genes *MRPL11* and *MRPL21* were aberrantly expressed in squamous cell carcinoma tissues [111]. In addition, expression of *MRPL11* was different between the node positive and negative tumors. The prognostic genes were clustered into two groups based on their metastatic phenotypes, and *MRPL11* and *MRPS23* were grouped based their association with rapid proliferation, oxidative phosphorylation, invasiveness, and tumor size [112]. In yeast, the cytoplasmic ribosomal homolog RP11 binds and suppresses the E3 ubiquitin-protein ligase function of HDM2 and leads to the stabilization and activation of the p53 tumor suppressor protein [113, 114] under conditions of growth inhibition, DNA damage and oncogenic insults [115]. It is currently unclear whether there is any functional interaction between cytoplasmic and mitoribosomal L11 in the context of cancer.

4.2. bL20m

The expression level of *MRPL20* could have a potential role in androgen resistance since it was observed significantly downregulated in androgen-independent prostate cancers [116]. Prostate cancer accounts for approximately one-third of all cancer diagnosed in men in the United States, and the survival and growth of prostate cancer cells are initially dependent on the presence of androgens. In the first stages, prostate cancer treatment based on androgen ablation works for almost all patients. However, when prostate cancers become resistant to hormone blockade, they turn into highly aggressive and metastatic cancers, which are clinically defined as androgen-independent (AIPC). Best et al. [116] analyzed the differentially expressed genes in tumor biopsies between 10 androgen-independent tumors and 10 primary and untreated prostate tumors. The 239 genes whose expression levels were statistically different were divided into two distinct groups; genes associated with ribosomes and protein synthesis and genes related to cell adhesion and the extracellular matrix. The first group included *MRPL20*, with a 0.65-fold decreased expression in AIPC.

4.3. uL16m and uL21m

In partial agreement with our analysis presented in Table 1, the expression of several MRP genes was found to be a potential prognostic marker in colorectal tumorigenesis and tumor growth [117]. Analysis of gene expression profiles in sporadic colorectal cancer biopsies identified 7 new differentially expressed genes that included *MRPL21* and *MRPL16*, which were particularly upregulated in synchronous adenoma. Tumor location was the dominant factor influencing differential gene expression caused by canonical molecular changes [117], suggesting that location-specific analysis could identify location-associated pathways

(OXPHOS, in the location where *MRPL21* and *MRPL16* expression were augmented) and enhance the accuracy of tumor class prediction.

4.4. bL12m and bL28m

Mitochondrial functions in metabolism and apoptosis are strongly associated with the altered metabolic profile of pancreatic cancer cells through differential expression of genes such as *MRPL28* [118]. Knockdown of *MRPL28* in pancreatic tumor cells results in decreased mitochondrial activity and increased glycolysis, accompanied by reduced cellular proliferation. In an interesting experiment, these *MRPL28*-silenced cells were injected into a nude mouse, which developed tumors with approximately 2-3-fold increased growth compared to non-silenced cells. However, this effect was not specific for *MRPL28*, because injection of nude mice with pancreatic cancer cells silenced for *MRPL12* or *COX4* (cytochrome *c* oxidase subunit 4) reproduced these phenotypes [118], suggesting that alteration in mitochondrial metabolic profiles, mainly OXPHOS, is central to the progression of pancreatic tumors.

4.5. bL36m

The association of bL36m with cancer is indirect and poorly characterized. It is based on the physical interaction of this protein with the mitochondrial inner membrane protein LETM1 (leucine zipper/EF-hand-containing transmembrane-1). It has been suggested that LETM1 acts as an anchor protein for complex formation with the mitoribosome via bL36m to regulate mitochondrial biogenesis [119]. LETM1 was first identified in association with Wolf-Hirschhorn syndrome, being deleted in most patients with the syndrome [119]. LETM1 overexpression can induce necrotic cell death in HeLa cells, and LETM1 levels have been suggested to correlate with multiple human malignancies and tumor progression. However, the pathological relevance of different expression levels in LETM1 may be tumor cell-dependent. LETM1 expression was found elevated in breast cancers [120]. Yet, in a mouse model of human non-small cell lung cancer, adenovirus-mediated LETM1 overexpression in lung cancer cells induced mitochondrial degeneration, ATP depletion and cell cycle inhibition while facilitating apoptosis, ultimately resulting in the suppression of lung cancer cell growth *in vitro* and *in vivo* [121]. Furthermore, the involvement of bL36m remains intriguing, particularly considering the data presented in Table 1, showing that bL36m protein levels are elevated in liver tumors and melanomas, whereas they are decreased in breast, colon and pancreatic tumors and unaltered in lung cancers.

4.6. mL37

The possible involvement of mL37 in cell transformation and tumor cell proliferation is supported by two observations. Treatment of human lymphocytes with concanavalin A, a mitogenic activator of cytokines, which stimulates cell proliferation and can induce apoptosis, resulted in specific overexpression of *MRPL37* [105]. *MRPL37* mRNA levels were also highly elevated in different lymphoma human tissues and cell lines. Notably, mL37 shares 45% homology with the proapoptotic mitoribosomal protein mL65/PDCD9. The relevance of the homologous region in these to their potential properties in apoptosis and tumorigenesis deserves further investigation.

4.7. mL38

Gene expression profiling of mouse precursor T-cell lymphoblastic lymphoma/leukemia (pre-T LBL) identified *MRPL38* gene expression as an oncogenic pathway indicator and a prognostic marker [122]. *MRPL38* was one of the two genes found to be overexpressed more than four-fold in thymic tumors from clinically-sick transgenic mice generated by overexpression of SCL, LMO1 or NHD13, three known pre-T LBL genes [122]. The relevance of mL38 to cancer prognosis was also highlighted in another study aiming to explore the alterations of mitochondrial protein abundance in ovarian cancer, by comparing the mitochondrial proteomics profile of a pair of human ovarian carcinoma cell lines (SKOV3/SKOV3.ip1) with different metastatic potentials [123]. SKOV3.ip1 cells, with higher migration potential, were derived from ascitic tumor cells of nude mice bearing a tumor of SKOV3 ovarian cancer cells. mL38 was one of the four proteins found to be more abundant in SKOV3.ip1 cells, and therefore positively correlated with the aggressiveness of the tumor. Consistently with these investigations, mL38 abundance has been found highly increased in most tumor types (Table 1).

4.8. mL41

Consistent with its role in promoting p53-induced apoptosis, *MRPL41* expression was found lowered or absent in most tumor tissues and cell lines [100]. This is particularly true in colon cancers and lymphomas (Table 1).

4.9. mL49

Oncocytic neoplasms or oncocytomas are tumors composed of cells characterized by an aberrant proliferation of mitochondria that is responsible for their ultrastructural alterations [124]. A microarray analysis carried out on thyroid oncocytomas revealed 126 genes that were found overexpressed in thyroid, parathyroid and renal oncocytic tumors compared with normal tissue samples. The gene cluster included *MRPL49* and 13 genes coding for subunits of the OXPHOS complexes [125]. In the same line, a genome-wide transcriptional profiling analysis in human breast cancer cells also reported increased levels of the *MRPL49* transcript [110]. These data are in agreement with the mitoribosomal protein expression profiles presented in Table 1, where mL49 abundance was found low in colon, renal and pancreatic tumors, and elevated in melanoma, thyroid and breast tumors.

4.10. mL64

Fist known as CR6-interacting factor 1 (CRIF1), this protein has been found in mitochondria and the nucleus. Consistent with a role as a tumor suppressor, CRIF1 interacts with and inhibits CDK2 thereby inducing cell cycle arrest in leukemia cells [126]. CRIF1-induced cell cycle arrest can also be mediated though its interaction with other nuclear proteins, including GADD45 family of proteins [127]. Similar to the tumor suppressor role of nuclear CRIF1, its depletion promotes leukemic T cell survival in the absence of growth factors [128]. CRIF1 also binds to the lymphocyte-specific protein tyrosine kinase (Lck), whose overexpression and hyperactivation have been associated with leukemia development. In a model, Lck would bind to CRIF1 and inhibit its function as a tumor suppressor [128]. Thus, the available data suggest that CRIF1 may play a role in negative regulation of cell cycle

progression and cell growth. Expression of *CRIF1* is hardly detectable in adrenal adenoma and papillary thyroid cancer and markedly lower than in adjacent normal tissue [127]. It remains to be determined how CDK2, Lck, GADD45 and other nuclear proteins compete in binding to CRIF1 and regulate its tumor suppressor activity. The role of CRIF1 in mitochondrial protein synthesis as mL64 may also be relevant to blood tumors that are highly dependent on OXPHOS, since, as explained in the next section, inhibition of mitochondrial translation has been identified as a potent therapeutic strategy for acute myeloid leukemia in human patients [129].

4.11. mL65

mL65/MRPS30 was first discovered as programmed cell death protein 9 or PDCD9. A study supports *MRPS30* gene expression as a potential diagnostic marker to detect estrogen-responsive (ER) breast tumors. When searching for loci linked to gene expression in breast adenocarcinoma tissues by using a gene expression Quantitative Trait Locus (eQTL) approach, a single nucleotide polymorphism (SNP) on chromosome 5p12 (rs7716600), previously found to be specifically linked to ER-positive breast tumor susceptibility in several GWAS, was significantly associated with elevated expression of the nearby gene *MRPS30* in ER-positive tumors [130]. The rs7716600 risk genotype was associated with decreased *MRPS30* promoter methylation exclusively in ER-positive breast tumors. Based on their studies, the authors suggested that the 5p12 risk allele affects mS30 gene expression in ER tumor cells after tumor initiation by a mechanism affecting chromatin availability [130].

4.12. mS40 (formerly MRPS18B or S18-2)

When overexpressed, mS40/S18-2 binds to retinoblastoma protein (RB) and prevents the formation of the E2F1-R transcriptional complex [131]. The resulting elevated free E2F1 proteins in the nucleus subsequently promote S-phase entry and cell proliferation [131]. Also, overexpression of *S18-2* in primary rat skin fibroblast induced malignant transformation and resulted in their immortalization. In human tumors, mS40 levels are not uniformly increased. They remain unchanged in most cancers, and are elevated only in liver tissues and lowered in renal and thyroid tumors (Table 1).

4.13. mS29/DAP3

Besides being the single ribosomal subunit with GTPase activity, mS29/DAP3 has been proposed to induce both the extrinsic and the intrinsic apoptotic pathways. As such, it is not surprising that mS29/DAP3 has been connected to numerous cancers. DAP3 expression was found to be from low to nonexistent in B-cell lymphoma cells, non-small cell lung cancers, as well as in head and neck, breast, colon and gastric cancers, possibly owing to hypermethylation of the *DAP3* gene promoter [132, 133]. The role of DAP3 in cancer might be tissue-dependent. In some cases, *DAP3* expression has been positively correlated with improved cancer prognosis, suggesting that DAP3 could combat cancer progression through its proapoptotic function [132, 133]. In these cases, DAP3 could serve as a potential biomarker to monitor the effectiveness of chemotherapy or other therapeutic treatments. However, in other cancers, such as thymoma and glioblastoma multiforme (GBM), *DAP3* expression was found to be upregulated [134, 135]. Particularly interesting was the finding

that *DAP3* is overexpressed in the thyroid tumor cell line XTC-UC1, and that the expression of the *DAP3* gene directly depends on the mtDNA level in these cells [136]. This observation has suggested that the variations of mtDNA levels, which are strongly involved in mtDNA-related disorders and various cancers, may dysregulate the balance between cellular life and death mediated by apoptotic processes.

4.14. Mitoribosome assembly factors

A recent large-scale analysis of gene expression profiles across nine distinct human tumors has indicated that RNA-binding protein-encoding genes, including ribosome assembly factors, are consistently differentially expressed in cancer tissues compared with other gene classes [137]. Among the mitochondrial proteins included, two mitoribosome assembly factors. The mt-SSU assembly factor GRSF1 presented a significant decrease in expression level while the mt-LSU assembly factor DDX28 showed a robustly elevated expression in cancer versus non-malignant counterpart tissues, particularly in colon and thyroid cancers [137], suggesting the existence of multiple mitoribosome assembly gene dysregulation patterns governing tumorigenesis. Indeed, DDX28 has been identified as a risk factor for colorectal cancer [15]. This study examined 18 of the 19 GWAS-identified colorectal cancer risk variants, most of which reside outside the coding regions of genes, for association with the expression of neighboring genes in 40 patients with colon cancer using paired adjacent normal and colon tumor samples [15]. The analysis indicated decreased expression of *DDX28* in adjacent normal colon tissues of individuals carrying a particular variant associated with reduced risk of colorectal cancer, which has suggested that this gene may lower the risk of colorectal cancers by functioning to inhibit early events in colorectal carcinogenesis [15].

5. Targeting mitoribosome biogenesis and function for therapeutic interventions

5.1. Inhibitors of apoptosis

One of the hallmarks of tumorigenesis and tumor progression is the evasion of apoptosis by cancer cells. Dysregulated apoptosis can often translate into drug resistance of cancer because most of the conventional cancer treatments such as chemotherapy and radiation largely depend on their ability to induce apoptosis in cancer cells. Hence, over the past decade, a promising cancer therapeutic strategy has been targeting anti-apoptotic proteins that will restore the apoptotic pathway. Because none of the three mitoribosomal proteins shown to possess a role in apoptosis induction (mS29, mL41 and mL65) has been so far directly targeted for therapeutics, we refer the reader interested in the targeting of apoptosis pathways for cancer treatment to several extensive reviews published elsewhere [138–140].

5.2. Inhibitors of mitochondrial protein synthesis

Another hallmark of cancer is the extensive metabolic reprogramming that accompanies tumor progression and allows cancer cells to generate a large amount of ATP and biosynthetic precursors required for their growth. A well-described aspect of this metabolic remodeling is the Warburg effect or aerobic glycolysis. However, despite the increase in

glycolytic flux, the mitochondrial function remains essential for cancer cell survival and proliferation, and it is emerging as a key target for therapeutic interventions [141]. Recent evidence has supported the “reverse Warburg effect” model, where some types of cancer cells utilize the energy-rich metabolites (e.g. lactate) provided by neighboring glycolytic and glutaminolytic stromal cells [142] or by cancer cells in more poorly oxygenated regions of the tumor [143] to drive ATP generation via OXPHOS [142]. Consistently, upregulation of mitochondrial translation has been reported in a subset of human tumors likely to meet the energy requirements of cancer cells [10]. Therefore, inhibition of mitochondrial translation can be viewed as a promising target for cancer therapy [144].

5.2.1. Targeting mitochondrial translation factors—Potentially, all components of the mitochondrial translational machinery, including tRNAs, rRNAs, mitoribosomal proteins and assembly factors, aminoacyl synthetases, tRNA modifying enzymes, as well as initiation, elongation and termination factors could be promising targets. As a case in point, shRNA-mediated transient silencing of mitochondrial translation elongation factor EF-Tu in acute myeloid leukemia cells reduced their growth rate and viability [129]. The suppression effect was associated with decreased mitochondrial membrane potential and oxygen consumption without changes in ROS generation, typical phenotypes of protein synthesis inhibition. The same study failed to observe a similar anti-leukemia effect by silencing of the mitochondrial initiation factor 3 (IF-3). However, the most plausible reason of the failure is that silencing in this case was not deep enough to affect mitochondrial translation given that the treatment did not disturb mitochondrial membrane potential or oxygen consumption capacity [129].

5.2.2. Targeting the mitoribosome—Another strategy has taken advantage of the susceptibility of mitochondrial ribosomes to antibiotics usually targeting bacterial protein synthesis [145]. The several classes of antibiotics that have been used in anti-cancer therapies include erythromycins, chloramphenicol, tetracyclines, glycylcyclines, actinonin, and aflatoxin B_1 (Table 2).

A recent study showed that antibiotics targeted to inhibit mitochondrial translation can be used to eradicate cancer stem cells across multiple cell types [16]. Lamb and coworkers tested several FDA-approved antibiotics to inhibit mitochondrial translation. They included erythromycins and chloramphenicol that selectively bind to the mitoribosomal large subunit and block the peptide exit channel or peptide bond formation, respectively. The study also included tetracyclines and their analogs glycylcyclines (tigecycline) that bind to the small subunits to block the codon-anticodon interaction. Twelve different cancer cell lines, representing 8 different tumor types (invasive/non-invasive breast, ovarian, prostate, pancreatic, lung, melanoma, and glioblastoma cancers), were treated with these antibiotics and screened for mammo-sphere and tumor-sphere formations.

Erythromycin and chloramphenicol: Treatment with 50 μM azithromycin, a potent erythromycin derivative, inhibited mammo-sphere formation in two different MCF7 and T47D breast cancer cell lines [16]. In addition, 250 μM treatment inhibited tumor-sphere formation in eight cancer cell lines, representing six different cancer types [16]. Consistently, treatment of human neuroblastoma cell line SH-SY5Y with erythromycin in a

range from 62.5 μM to 500 μM inhibited cell proliferation in a concentration- and time-dependent manner [146]. In their report, Lamb et al. reported that chloramphenicol, which inhibited mammo-sphere generation of MCF7 cells at ~200 μM, was the weakest antibiotic tested in the study [16].

Tetracyclines: Regarding doxycycline, a tetracycline derivative with improved efficacy and stability, it has been reported to inhibit tumor growth through two potential mechanisms. It inhibits mitochondrial translation, and also inhibits matrix metalloproteinases, which appear to be essential for proliferation and dissemination of a variety of tumors [147]. Treatment with low doses of doxycycline induced cytostatic effects of variable extents in all eight mesothelioma cell lines tested but did not affect normal lung fibroblasts [148]. In addition, chronic doxycycline treatment inhibited induced T-cell type rat leukemia induced complete tumor eradication in a concentration-dependent manner [148]. Furthermore, treatment of epithelial-origin malignant cells, renal and prostate carcinomas with low tetracycline concentrations induced the inhibition of mitochondrial protein synthesis and arrest of proliferation [149, 150]. Similarly, tetracycline treatment strongly retarded the development of carcinogen-induced tumors and the development of a hypernephroma from human origin transplanted in the cheek pouch of the Syrian hamster [149, 150]. Moreover, treatment with 2 μM and 10 μM doxycycline prevented mammo-sphere formation in two breast cancer cell lines, MCF7 and T47D, and tumor-sphere formation in ten cancer cell lines, representing six different cancer types [16]. These data support the idea that tetracycline has a strong potential as a cytostatic agent in the mitochondrial translation system-targeting chemotherapy [151] and have encouraged some clinical trials. Clinical trials have proved the anti-lymphoma activity of doxycycline. Ocular adnexal lymphoma of the MALT type (OAL) is one of the most common forms of extragastric marginal zone B-cell lymphoma, openly associated with *Chlamydia psittaci* (*Cp*) infection. Ferreri and his group reported on a phase II trial testing the activity of first-line doxycycline therapy in a homogeneous cohort of patients with newly diagnosed stage-I OAMZL [152, 153]. Thirty-four patients who had measurable or parametrable disease were treated with 100 mg doxycycline administered orally twice daily for 3 weeks, and the response was assessed 3 and 12 months after treatment. Lymphoma regression was complete in 6 patients and partial in 16; stable in 11, and one had progressive disease. Moreover, 20 patients remained relapse-free at a median follow-up of 37 months, supporting the conclusion that lymphoma regression depends on *Cp* eradication upon doxycycline treatment.

Glycylcyclines: Among the glycylcyclines, which are tetracycline analogs, tigecycline is the only FDA-approved antibiotic. Tigecycline has been shown to have anti-leukemia properties in murine models [129]. Also, treatment of MCF7 and T47D breast cancer cell lines with 10 μM to 50 μM tigecycline suppressed mammo-sphere formation, and a single concentration of 50 μM significantly prevented tumor-sphere generation in eight different cancer cell lines [16]. Furthermore, treatment of 20 primary acute myeloid leukemia (AML) cell lines with tigecycline for 48 hrs selectively killed leukemia stem and progenitor cells with efficacy similar to EF-Tu silencing [129]. Preclinical efficacy and safety of tigecycline have been tested in patients with relapsed and refractory AML, but none of the patients had a clinical response in a phase I study of escalating tigecycline doses [154].

Actinonin: Actinonin is a naturally occurring antibacterial agent against gram-positive and gram-negative microorganisms [155], able to induce a progressive growth arrest in 16 different cancer cell lines [17]. Actinonin treatment induces a time-dependent loss of mitoribosomal proteins with different degrees of severity [156, 157]. This might be the effect of the peptidyl deformylase activity of Actinonin. Mitochondrial translation requires a formylated methionine-tRNA for the initiation of protein synthesis, and this formyl group is removed by the peptide deformylase as a part of N-terminal methionine excision (NME). Human mitochondrial peptide deformylase (*Hs*PDF) is able to remove formyl groups from N-terminal methionines of several newly synthesized mitochondrial proteins to unmask the amino group of the first methionine, which is a prerequisite for the subsequent action of methionine aminopeptidase. *Hs*PDF is overexpressed in many different cancer cell lines and primary myeloid leukemias [158]. Actinonin inhibition of HsPDF in cancer cells induced repression of mitochondrial translation [159], caused apoptotic death of Burkitt's lymphoma [158], and rendered the side effects of the anti-tumor agent celastrol by controlling the heat shock response [160]. Treatment with actinonin stalled HsPDF on the mitoribosomal large subunit, near the exit channel, and triggered mitochondrial ribosome and RNA decay pathways [156]. This could explain why the inhibition of mitochondrial protein synthesis also affects cancer cells that depend on cytoplasmic glycolytic metabolism [156, 161]. Interestingly, the oncogene c-myc indirectly regulates the expression of HsPDF, and actinonin inhibition of HsPDF occurred exclusively in myc-positive cells.

Aflatoxin B_1: Aflatoxins are poisonous and cancer-causing chemicals that are produced by the fungi *Aspergillus*. An early study had shown that treatment of hepatocytes with aflatoxin B_1 (AFB_1) progressively inhibited mitochondrial translation and transcription in the early stages of hepatocarcinogenesis, even 24 hr after carcinogen treatment [162]. However, the deleterious side effects induced by treatment with AFB_1, which directly binds to the mtDNA altering transcription and mitochondrial polypeptide patterns [163, 164], should prevent its use in human patients.

6. Conclusion and Perspectives

The last decade has witnessed multiple advances in the understanding of the mitochondrial role in cancer physiology. Contrary to an old dogma, recent evidence has indicated that some types of cancer cells are highly dependent on mitochondrial oxidative phosphorylation. Because several mitoribosome proteins perform extra-ribosomal pro-apoptotic activities and many are differentially expressed in tumor tissues, they have the potential of becoming tumor-specific biomarkers. Further work is required to precisely decipher the mechanism underlying apoptosis induction by mS29, mL41 and mL65 proteins. In those tumor cells that are OXPHOS-dependent, inhibition of the mitochondrial translation machinery is emerging as a promising therapeutic approach, with the use of tetracycline derivatives leading the path to cancer treatment.

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Abbreviations

AIPC	Androgen-independent prostate cancer
AKAP1	cAMP signaling
AML	acute myeloid leukemia
BAK	Bcl-2 homologous antagonist killer
BAX	Bcl-2-associated X protein
BCL-2	B-cell lymphoma 2
BMRP	BCL-2 interacting mitochondrial ribosomal protein
C7Orf30	chromosome 7 open reading frame 30
CIFR1	CR6-interacting factor 1
DAP3	Death Associated Protein 3
DDX28	DEAD-Box Helicase 28
DHX30	DEAH-Box Helicase 30
DEAD box	helicase family of proteins characterized by the presence of an Asp-Glu-Ala-Asp (DEAD) motif
DRP1	Dynamin-related protein 1
EF-G	elongation factor G
EF-Ts	elongation factor thermos-stable
EF-Tu	elongation factor thermo-unstable
FADD	Fas-Associated protein with Death Domain
FASL	FAS ligand
FASTKD2	Fas-activated serine/threonine kinase domain-containing protein 2
fMet-tRNA	formylmethionine-tRNA
GOLPH3/3L	Golgi phosphoprotein 3/3L
GRSF1	G-Rich RNA Sequence Binding Factor 1
GTP	guanosine triphosphate
GWAS	genome-wide association studies
HDM2	human double minute 2
HSNCC	head and neck squamous cell carcinoma

***Hs*PDF**	human mitochondrial peptide deformylase
IF-3	initiation factor 3
IF2-mt	mitochondrial translation initiation factor 2
IFN-γ	Interferon-gamma
IPS-1	interferon-γ promoter stimulator 1
JNK	c-Jun N-terminal kinases
Lck	lymphocyte-specific protein tyrosine kinase
SNP	single nucleotide polymorphism
LETM1	leucine zipper/EF hand-containing transmembrane-1
LSU	large subunit
MAPK	mitogen-activated protein kinases
MCT1	monocarboxylate transporter 1
MPV17L2	MPV17 Mitochondrial Inner Membrane Protein Like 2
Mrh4	4th Mitochondrial DEAD-Box RNA Helicase
MRM1-3	mitochondrial rRNA methyltransferases
mRNA	messenger RNA
MRPs	mitoribosomal proteins
mtDNA	mitochondrial DNA
MTERF	mitochondrial transcription termination factor
MTG1-MTG2	mitochondrial ribosome associated GTPase1 and 2
mtRF1a	mitochondrial translation release factor
NRF1	nuclear respiratory factor 1
NRF2	nuclear respiratory factor 2
NSUN4	NOP2/Sun RNA Methyltransferase Family Member 4
OAMZL	ocular adnexal marginal zone lymphoma
OXPHOS	oxidative phosphorylation
PDCD9	programmed cell death protein 9
PGC1-α	PPARγ coactivator-1
PKB	protein kinase B

POLRMT	mitochondrial RNA polymerase
PPR	pentatricopeptide repeat protein
ROS	reactive oxygen species
rRNA	ribosomal RNA
SMAC	Second mitochondria-derived activator of caspase
SSU	small subunit
TCA	tricarboxylic acid cycle
TFAM	transcription factor A, mitochondrial
TFB1m	mitochondrial transcription factor B1
TIMM9	mitochondrial import inner membrane translocase subunit Tim9
TNFα	tumor necrosis factor alpha
MOMP	mitochondrial outer membrane permeabilization
TOMM70A	translocase of outer mitochondrial membrane 70A
TRAIL	tumor necrosis factor-related apoptosis-inducing ligand
tRNA	transfer RNA

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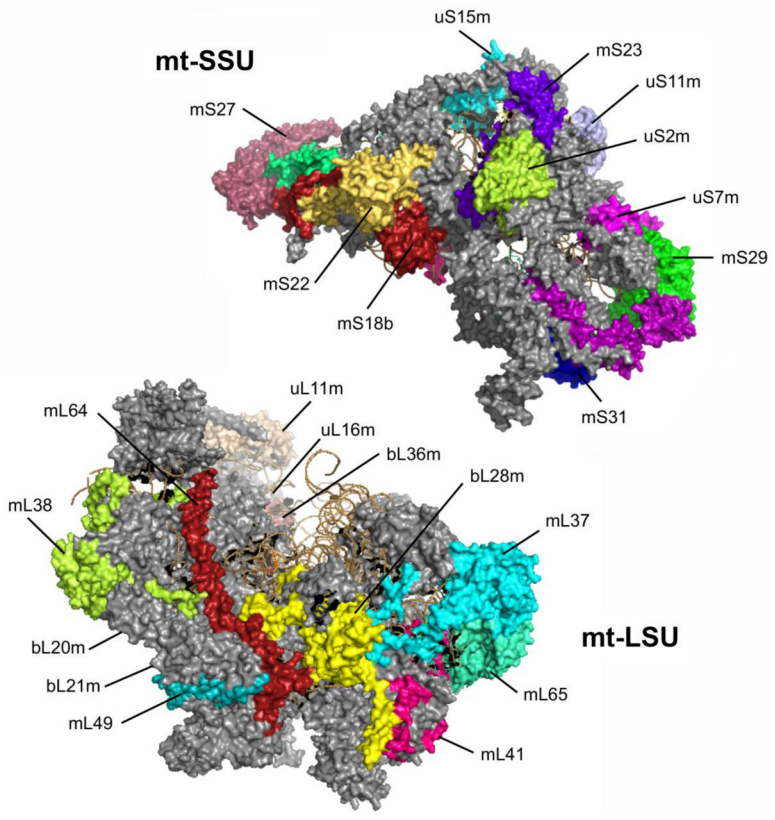


Figure 1. Structure of mitochondrial ribosomes

Cryo-EM structures of human 28S mt-SSU and 37S mt-LSU (PDB 3J9M). Individual proteins relevant to apoptosis and cancer, which are mentioned in the text, are depicted in different colors and labeled.

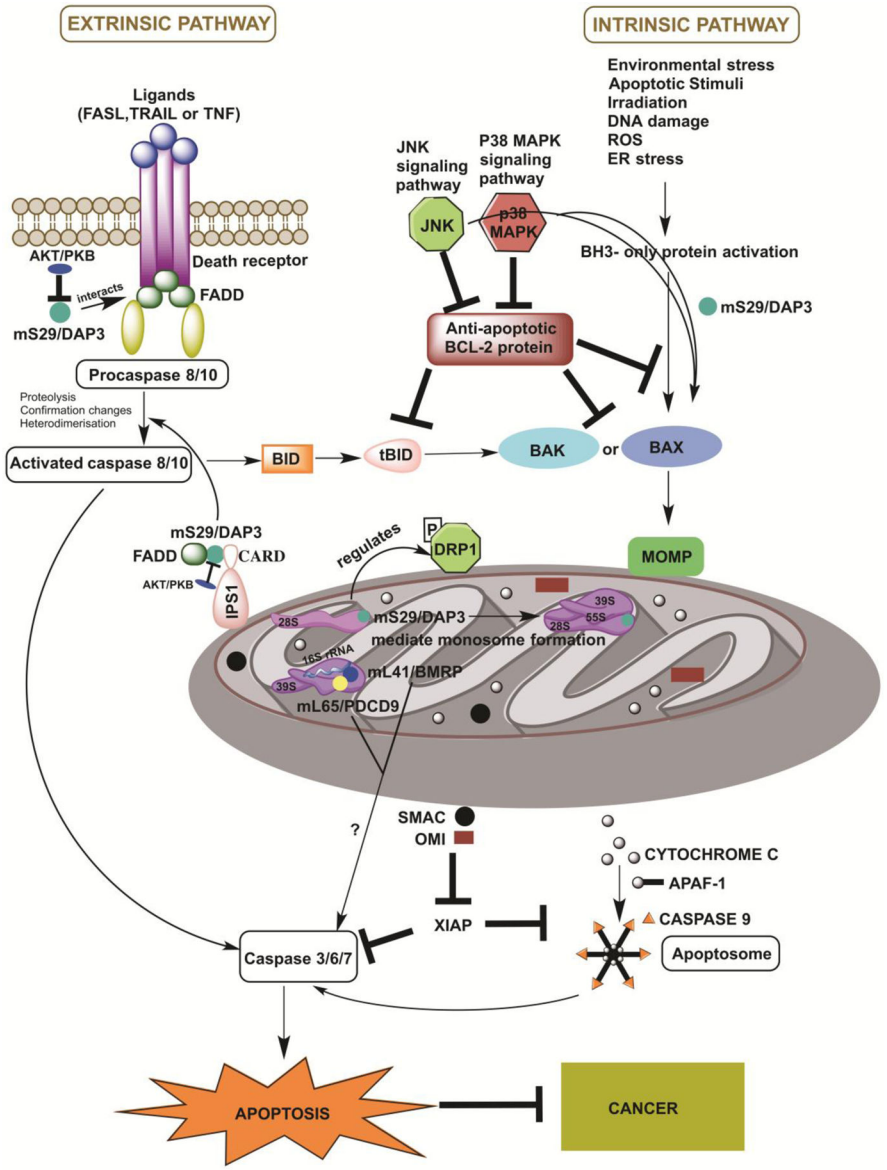


Figure 2. Involvement of mitoribosome subunit mS29/DAP3 in activating the extrinsic and intrinsic pathways of apoptosis

The schematic portraits the components and major events of the extrinsic and mitochondrial apoptotic pathways. The extrinsic pathway or the death receptor pathway is activated by the binding of death receptors to their ligands such as FASL (FAS ligand), TNFa, (tumor necrosis factor) or TRAIL (TNF-related apoptosis-inducing ligand). This promotes the recruitment of adaptor proteins such as FAS-associated death domain protein (FADD) that bind to death effector domain containing caspase −8 or −10. Formation of this complex results in dimerization and activation of caspase −8 that can induce two different pathways to apoptosis; the first one is the direct cleavage and activation of executioner caspases −3, −6 or −7. The other one is the cleavage and activation of the BH3-interacting domain death agonist (BID), the truncated product of which is tBID. tBID leads to the interaction of BCL-2-associated X protein (BAX) and BCL-2 antagonist or killer (BAK) and induction

mitochondrial outer membrane permeability (MOMP), thereby generating a crosstalk between the extrinsic and intrinsic apoptotic pathways.

The intrinsic or mitochondrial pathway is initiated by different apoptotic stimuli or environmental stresses such as DNA damage, ROS, endoplasmic reticulum (ER) stress, irradiation, which activate B-cell lymphoma 2 (BCL-2) homology 3 (BH3)-only proteins leading to translocation of BAX and BAK to mitochondria and induction of MOMP. Anti-apoptotic BCL-2 proteins prevent MOMP by binding to BH3-only proteins, tBID and activated BAX or BAK. MOMP induces the release of cytochrome *c* from the mitochondrial intermembrane space (IMS) to the cytosol that promotes caspase activation and apoptosis. Cytochrome *c* binds to the apoptotic protease-activating factor 1 (APAF1) and promotes the formation of the apoptosome that subsequently recruits and activates the initiator caspase, caspase 9. Caspase 9 further cleaves and activates executioner caspases −3, −6 or −7 leading to apoptotic cell death. Other proapoptotic proteins that are released following MOMP are second mitochondria-derived activator of caspase (SMAC; also known as DIABLO) and OMI (also known as HTRA2) that interacts with the X-linked inhibitor of apoptosis protein (XIAP) to prevent its inhibitory function on caspase −9 and −3.

mS29 (death-associated protein 3, DAP3) is depicted in the figure as an example of one of the three mitoribosomal subunits involved in apoptosis. mS29/DAP3 is predicted to regulate mitochondrial translation and apoptosis in various ways. mS29/DAP3 mediate contact with intersubunit bridges thereby assisting in monosomes formation and mito translation. mS29/DAP3 is also involved in mitochondrial dynamics by regulating the phosphorylation of DRP1 (dynamin-related GTPase involved in mitochondrial fission). In addition, mS29/DAP3 can initiate the extrinsic apoptotic pathway through its interactions with ligands of death receptors such as FASL, TRAIL and TNFα. mS29/DAP3 also co-localizes with FADD and participates in the formation of Death-Inducing Signaling Complex (DISC), which exists in the cell in an inactive form by the action of protein kinase B (AKT/PKB). DAP3 also interacts with FADD through the involvement of interferon-β promoter stimulator 1 (IPS1), which is a caspase activation and recruitment domain (CARD) bearing protein, present in the mitochondrial outer membrane. This complex further recruits procaspase-8, thereby triggering further downstream cleavage and activation of caspase resulting in cell death. mS29/DAP3 induces mitochondria-mediated apoptosis through the activation of p38 MAPK and the JNK signaling pathway.

Two other pro-apoptotic mitoribosome LSU proteins, mL41/BMRP that interacts with 16S rRNA and associates with mL65/PDCD9, have been also being depicted in the schematic. However, their pro-apoptotic mechanism/s of action remain to be unveiled.

Table 1

Mitoribosome proteins, assembly factors and their expression in cancer

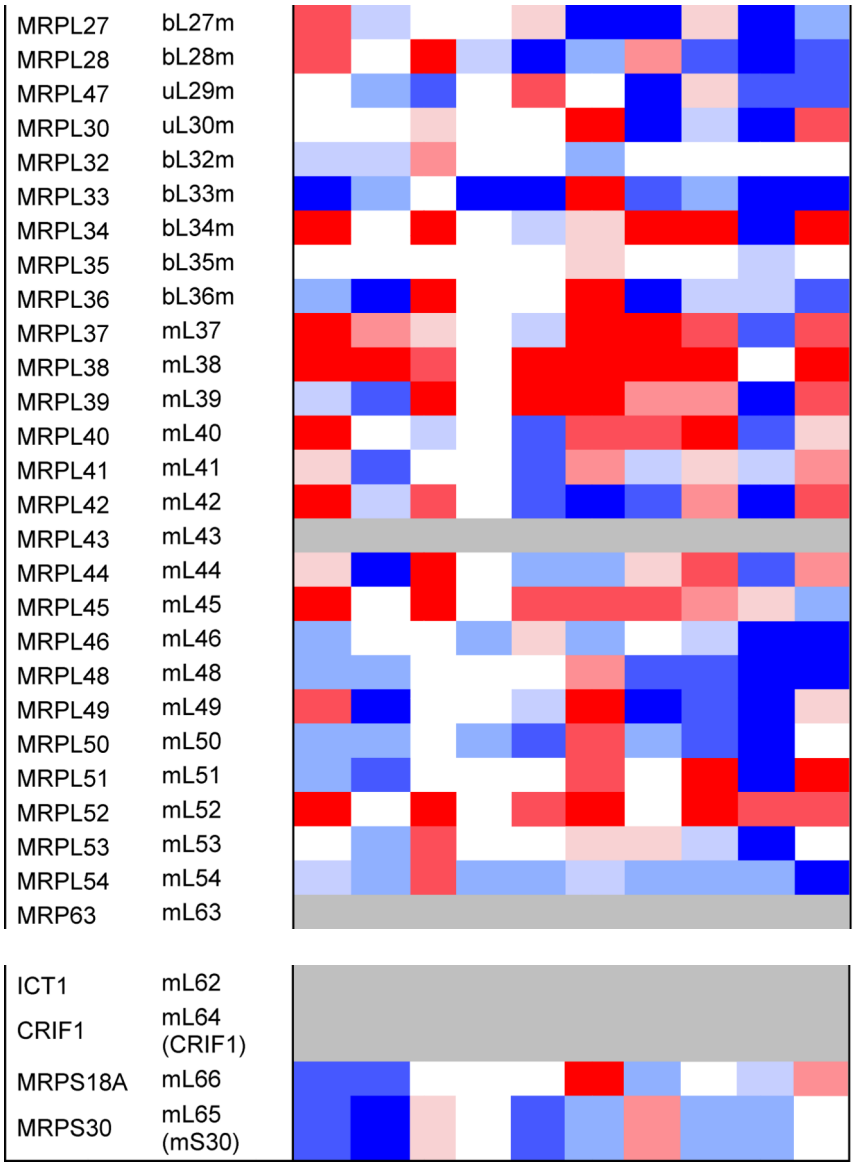
Proteins under and over-represented in the indicated cancers tissues relative to corresponding normal tissue, collected from the "Protein Atlas" database (http://www.proteinatlas.org). The percentages and color code reflects the proportion of analyzed cancer tissues with lowered or elevated protein levels. The old nomenclature for mitochondrial ribosome proteins has been substituted by an unifying nomenclature [165, 166] where proteins with a prefix "u" (for universal) are present in all kingdoms of life, proteins with a prefix "b" are bacterial in origin and do not have a eukaryotic (or archaeal) homolog, and proteins with a prefix "m" are mitochondrion-specific.

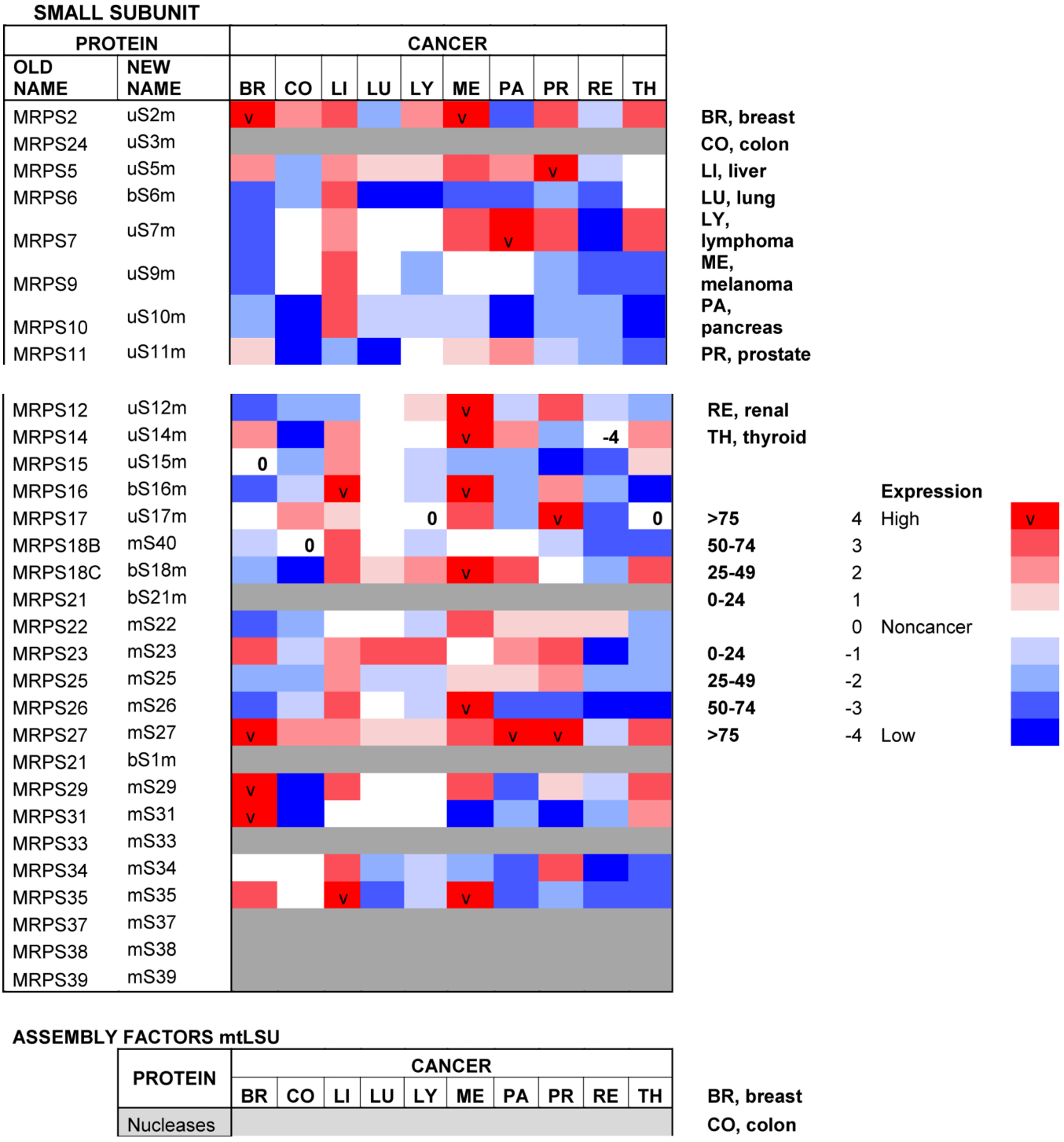
LARGE SUBUNIT

PROTEIN		CANCER TYPE									
OLD NAME	NEW NAME	BR	CO	LI	LU	LY	ME	PA	PR	RE	TH
MRPL1	uL1m										
MRPL2	uL2m										
MRPL3	uL3m										
MRPL4	uL4m										
MRPL9	bL9m										v
MRPL10	uL10m	v	v		v		v	v			v
MRPL11	uL11m						v				
MRPL7/L12	bL12m			v			v				
MRPL13	uL13m										
MRPL14	uL14m							v	v		
MRPL15	uL15m						v				
MRPL16	uL16m				v		v				
MRPL17	bL17m										
MRPL18	uL18m								v		
MRPL19	bL19m										
MRPL20	bL20m							v	v		
MRPL21	bL21m			v				v			
MRPL22	uL22m			v							v
MRPL23	uL23m										
MRPL24	uL24m										

BR, breast
CO, colon
LI, liver
LU, lung
LY, lymphoma
ME, melanoma
PA, pancreas
PR, prostate
RE, renal
TH, thyroid

		Expression
>75	4	High
50-74	3	
25-49	2	
0-24	1	
	0	Noncancer
0-24	-1	
25-49	-2	
50-74	-3	
>75	-4	Low





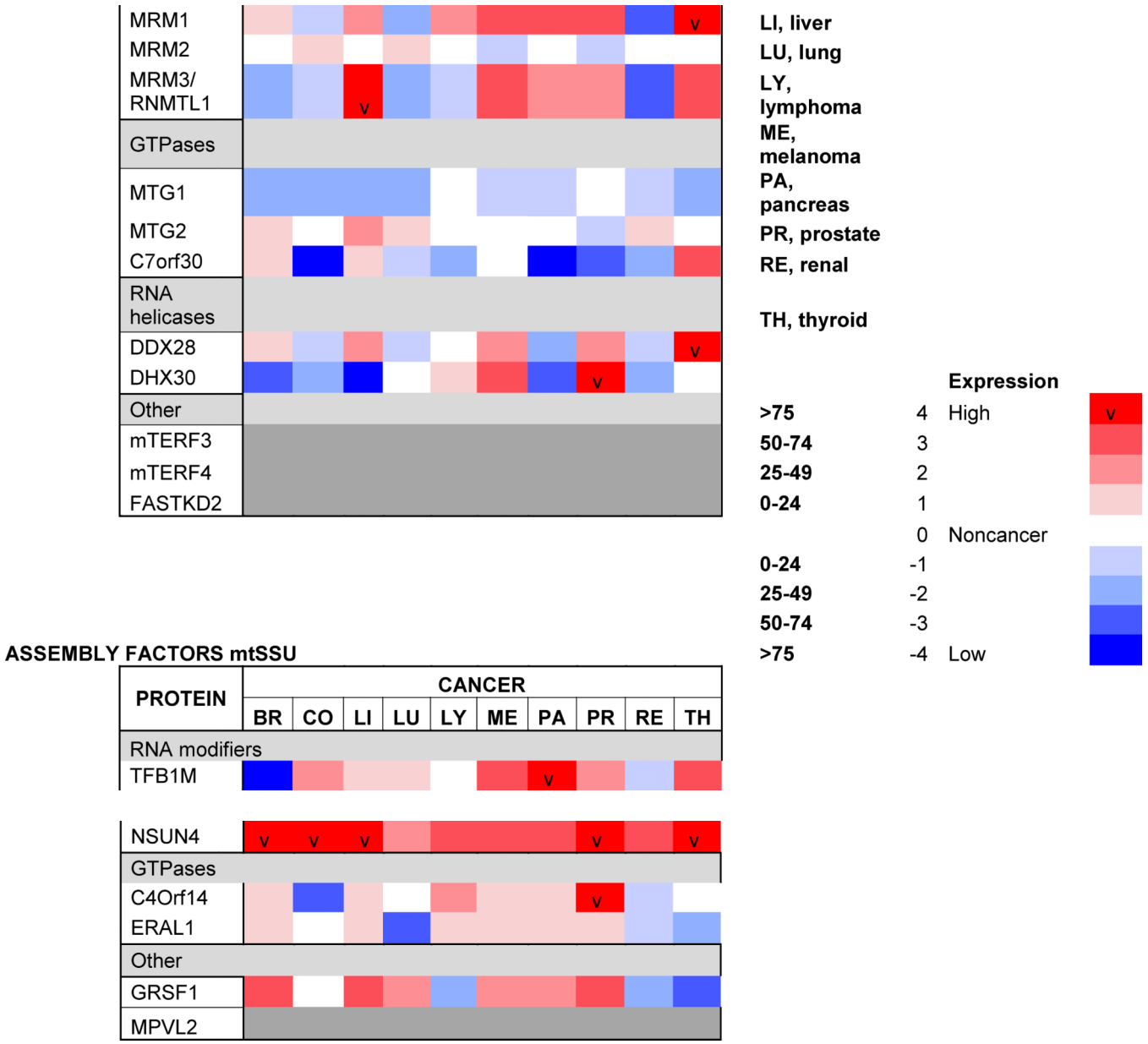
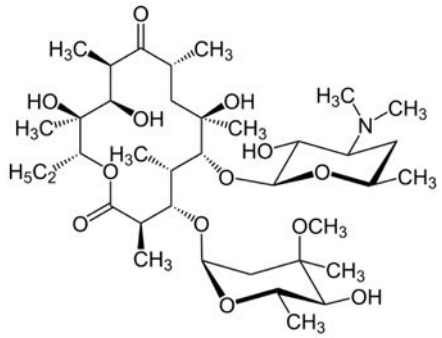
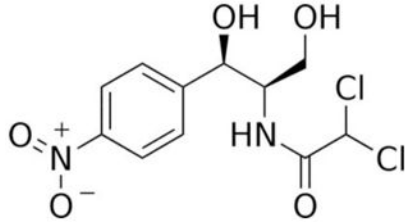
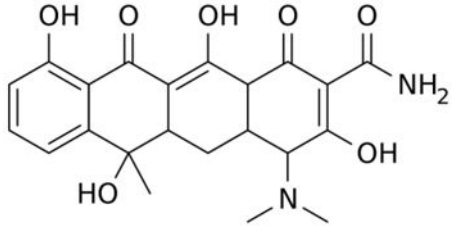
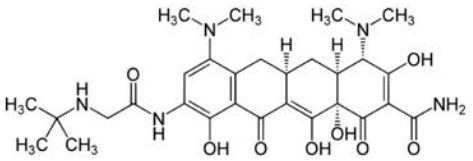
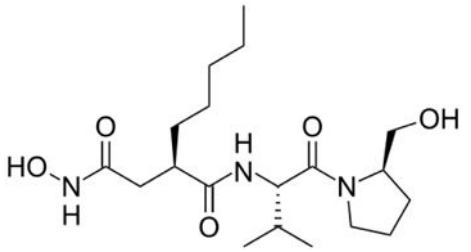
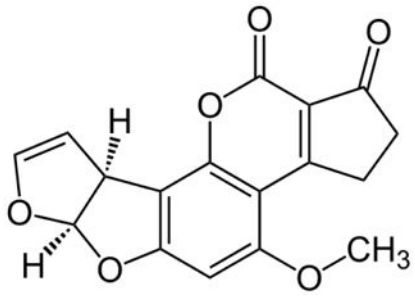


Table 2

Mitochondrial protein synthesis inhibitory antibiotics tested for cancer treatment

The chemical structures were obtained from Wikipedia (https://en.wikipedia.org).

ANTIBIOTIC	MECHANISM OF ACTION	CHEMICAL STRUCTURE	TREATED CELL TYPES	REFS
Erythromycins	Binds to the LSU-rRNA complex in bacteria and mitochondria, and interferes with aminoacyl translocation, preventing the transfer of the tRNA bound at the A site of the rRNA complex to the P site of the rRNA complex.		Breast cancer Neuroblastoma	[1–4]
Chloramphenicol	Binds to the LSU-rRNA complex in bacteria and mitochondria, specifically binds to A2451 and A2452 residues in the 23S rRNA, and interferes with peptidyl transferase, preventing protein chain elongation.		Breast cancer	[3]
Tetracyclines (Doxycycline)	Binds to the SSU-rRNA complex in bacteria and mitochondria, and prevents the interaction of aminoacyl-tRNA with the A site of the ribosome. The binding is reversible in nature.		Mesothelioma Leukemia Renal & prostate carcinomas Nephroma Lymphoma * Leukemia	[5–7]

ANTIBIOTIC	MECHANISM OF ACTION	CHEMICAL STRUCTURE	TREATED CELL TYPES	REFS
Glycylcyclines (Tigecycline)	Mechanism of action like tetracyclines.		Breast cancer	[8–10]
Actinonin	A hydroxamate-containing compound and strong inhibitor of metalloenzymes, especially matrix metalloproteases (MMPs). The hydroxamate group of actinonin acts as the chelating group to bind the metal ion of the enzyme.		Leukemia Lymphoma	[11–13]
Aflatoxin B_1	A strong genotoxic hepatocarcinogen that induces DNA adducts, leading to genetic changes in the target cells, which then cause DNA strand breakage, DNA base damage and oxidative, presumptively results in cancer.		Hepatocarcinoma	[14–16]

*Denotes a Clinical trial of doxycycline monotherapy to ocular adnexal lymphoma patients.

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