Sec61

Subjects: Cell Biology

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The heterotrimeric Sec61 complex of the ER membrane represents the major entry point for precursor polypeptides into the membrane or lumen of the ER. It forms a polypeptide-conducting channel, who's gating (i.e. opening and closing) involves various interactions partners. Mutations in the genes, which are coding for the Sec61 subunits or their interaction partners, can cause diseases (termed Sec61-channelopathies).

BiP   common variable immunodeficiency   congenital disorder of glycosylation

endoplasmic reticulum   neutropenia   polycystic liver disease   Sec61-channelopathies

Sec62   Sec63   SSR/TRAP complex

1. Introduction

The heterotrimeric Sec61 complex of the ER membrane represents the major entry point for precursor polypeptides into the membrane or lumen of the ER (Figure 1 and Figure 2) [1][2][3][4][5][6][7][8][9][10][11][12][13]. Therefore, it can form an aqueous polypeptide-conducting channel, which also allows the passage of Ca^{2+} in the opposite direction [14][15][16][17][18][19][20][21][22][23]. The channel exists in two conformations, an open and a closed state that are in a dynamic equilibrium with each other (Figure 2). The closed conformation is impermeable even to Ca^{2+}. Thus, the Sec61 complex is a precursor-gated channel, which operates either coupled to translation (in co-translational transport) or after completion of translation (in post-translational transport). Sec61 gating to the open state is not solely facilitated by its substrates, the amino-terminal signal peptides (SPs) or transmembrane helices (TMHs) of precursor polypeptides [24][25][26][27][28][29], it is also supported by ribosomes in co-translational transport [6][9] and/or by several Sec61 interaction partners, such as translocon-associated protein or TRAP complex [7][10][30][31] and Sec62/Sec63 complex in cooperation with BiP [23][32][33][34][35], respectively. Here, the latter are defined as allosteric effectors of the channel since they interact with the complex at sites, which are distinct from the precursor binding sites. Channel closing also appears to be facilitated by allosteric effectors, such as the ER-lumenal BiP [23] and/or the cytosolic Ca^{2+}-calmodulin (CaM) [22]. In our opinion, Sec61 channel gating can best be described in analogy to an enzyme-catalyzed reaction (Figure 3): Channel opening and closing represent two energetically un-favorable reversible reactions and the substrates and effectors are the catalysts, which lower the activation energy for the required conformational transitions by binding to the Sec61 complex [11][12].
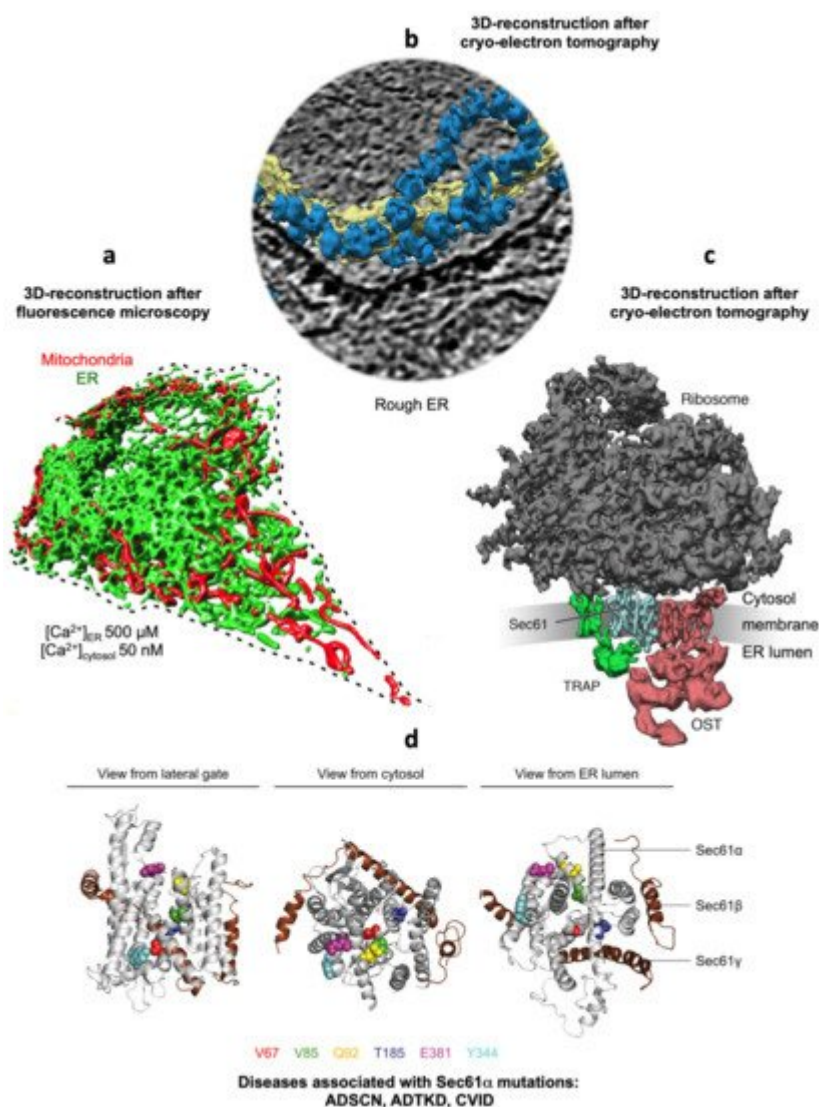
Figure 1. Collage of 3D reconstructions of a nucleated mammalian cell, a section of rough ER in such a cell and a ribosome-bound Sec61 translocon. (**a**) Represents a 3D reconstruction after live cell fluorescence imaging, following import of GFP into the ER and of RFP into the mitochondria. The plasma membrane is indicated by a dashed line. Typical concentrations of free Ca^{2+} are given for cytosol and ER of a resting cell. (**b**) depicts a 3D reconstruction of cellular rough ER after CET of a slice through the respective tomogram. ER membranes are shown in yellow; 80S ribosomes are shown in blue. (**c**) represents a 3D reconstruction of the native ribosome-translocon complex in rough microsomes. Here, the membrane density was removed to highlight membrane integral parts of the translocon complex. TMHs for Sec61 complex, TRAP and OST can be distinguished [10]. Helix 51 of an rRNA expansion segment and ribosomal protein eL38 represent the contact sites of TRAPγ, but are hidden by other ribosomal densities. (**d**) shows the PDB 3j7q structures for the Sec61 channel as seen from the indicated positions; disease associated point mutations are indicated. The collage is based on [11][12]. See text for details.
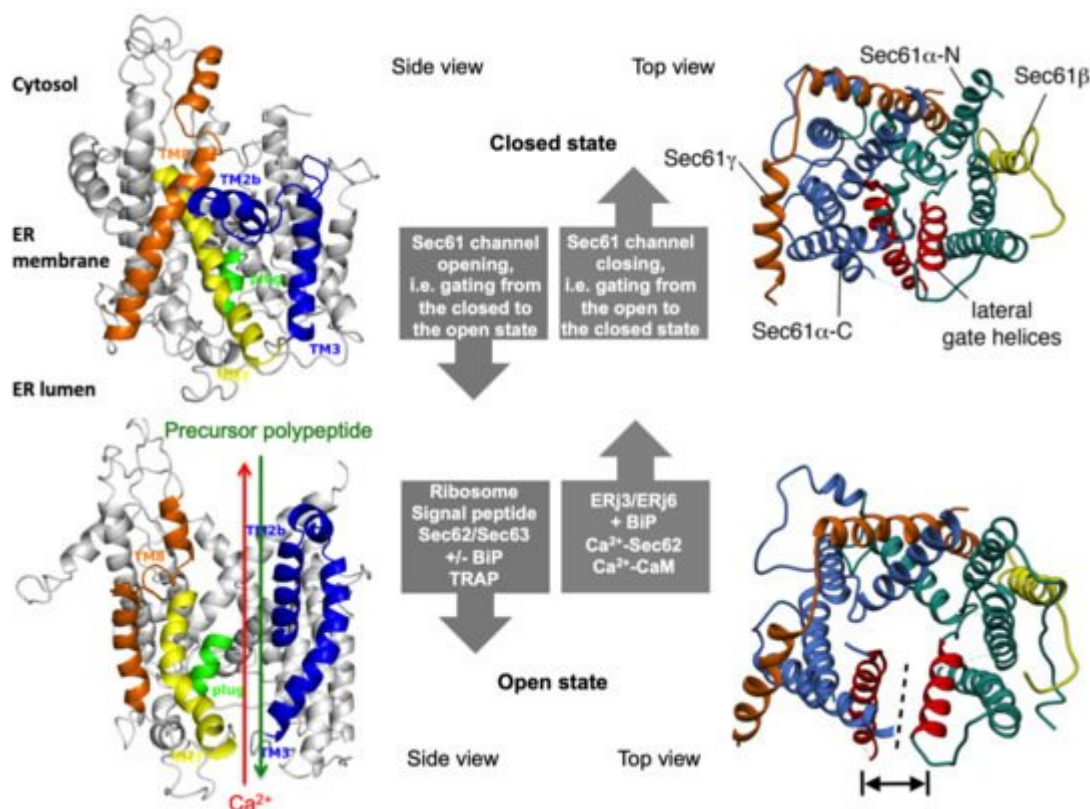
Figure 2. The concept of gating of the heterotrimeric Sec61 complex by signal peptides and allosteric effectors. The Sec61 channel is shown in its modeled closed (top) and open (bottom) conformational states, as viewed from the plane of the membrane (left) and in atomic models (PDB 3j7q, PDB 3jc2) as seen from the cytosol (right), respectively [11][12]. These two states are proposed to be in a dynamic equilibrium with each other. The fully open state of the Sec61 channel allows the initial entry of precursor polypeptides from the cytosol into the ER lumen and ER membrane, respectively, and is experimentally observed as cleavage of signal peptides by signal peptidase on the luminal side of the ER membrane. In addition, it allows the passive efflux of Ca^{2+} from the ER lumen into the cytosol and is visible in live cell Ca^{2+} imaging in cytosol and ER lumen. Ca^{2+} efflux may also be possible in the expected transition state (not shown), which may be identical to the so-called primed state that can be induced by ribosomes in co-translational- and by the Sec62/Sec63 complex in post-translational-transport. The conformational changes of the modelled Sec61 complex were previously morphed and the role of BiP plus an ERj co-chaperone, such as Sec63 and ERj1, respectively, visualized for co-translational transport at (see Data Availability). The Ca^{2+}-permeability of the open Sec61 channel as observed by live cell Ca^{2+} imaging can be seen in the video file (see Data Availability).
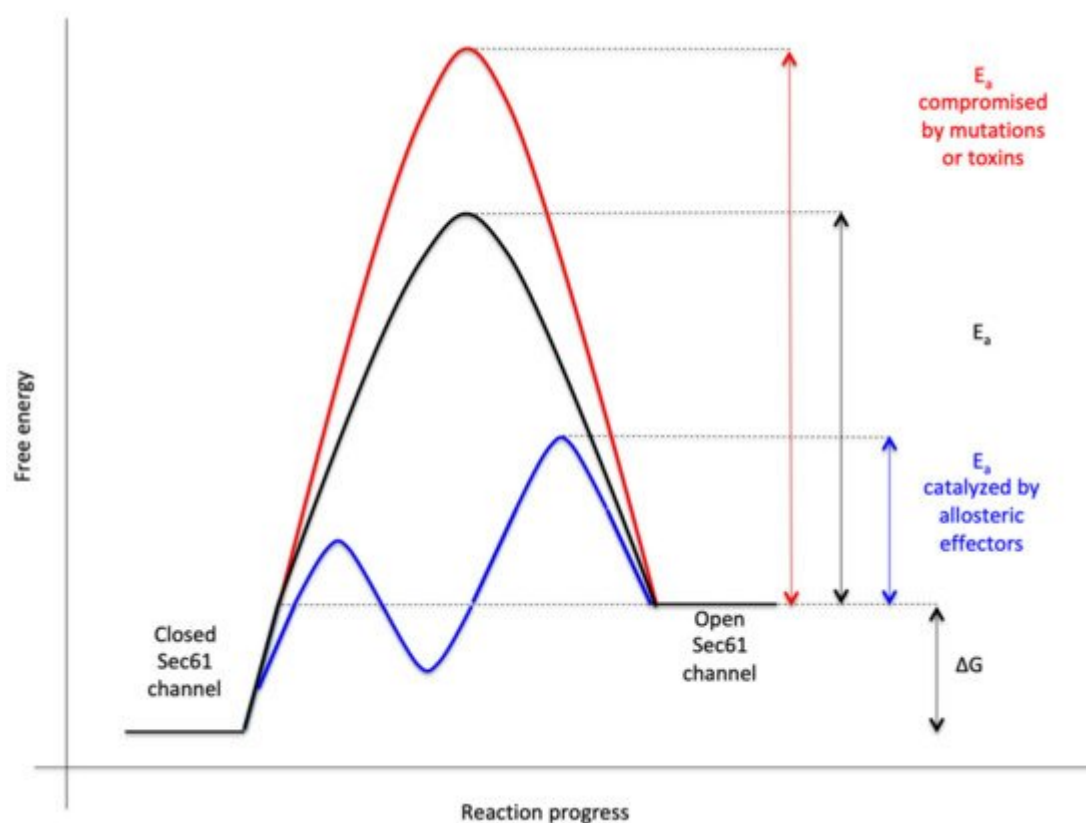
Figure 3. Energetics and kinetics of Sec61 channel gating. In our view, the TRAP− or Sec62/Sec63 +/− BiP-mediated Sec61 channel gating is best considered in analogy to an enzyme-catalysed reaction. Accordingly, TRAP, Sec62, Sec63 or BiP reduce the energetic barrier for full channel opening, which can apparently be reinforced by Sec61 channel inhibitors, such as cyclic heptadepsipeptides (such as CAM741) or certain eeyarestatins (such as ES24). At least in the case of ES24, binding of the inhibitor within the channel pore arrests the channel in a partially open state (termed "foot in the door"), which maybe identical with the primed state and is compatible with Ca^{2+}-efflux but not with full channel opening for protein translocation. TRAP and BiP contribute to full channel opening by direct interaction with ER luminal loops 5 and 7, respectively, of Sec61α (see below). *SEC61A1* mutations can increase the energy barrier for channel opening per se (V67G, V85D, and Q92R mutation) or indirectly, such as by interfering with BiP binding (Y344H mutation). Notably, all these effects are precursor specific because the amino-terminal SPs are either efficient or inefficient in driving Sec61 channel opening. Typical for an enzyme-catalysed reaction, BiP can also support efficient gating of the Sec61 channel to the closed state, i.e., the reverse reaction.

The Hsp70-type molecular chaperone immunoglobulin heavy chain binding protein or BiP [36] does not only support Sec61 channel opening for ER protein import [23][32], but also can bind to incoming precursor polypeptides and act on these as a molecular ratchet [37]. Thus, typical for an Hsp70, the ATP- and Ca^{2+}-dependent BiP modulates the conformation of a folded protein complex, the Sec61 channel, plus interacts with a more or less unfolded polypeptide chain as it emerges from the Sec61 channel, thereby contributing to a unidirectional or irreversible transport process. Also typical for an Hsp70, both BiP activities involve an ATPase cycle and their own allosteric effectors, i.e., J-domain-proteins (JDPs) [38] or Hsp40-type co-chaperones, termed ERj- or ERdj-proteins, and nucleotide exchange factors (NEFs). Following the same principles and interactions, BiP also plays a central role in folding and assembly of newly-imported polypeptides, such as heavy and light chains of immunoglobulins in the

plasma cells of the immune system [39], and supports efficient Sec61 channel closing to preserve Ca^{2+} homeostasis [23].

2. The Human Sec61 Translocon

Protein import into the ER is the first step in the biogenesis of precursors of about 10,000 different soluble and membrane proteins of nucleated human cells, which amounts to about 30% of the proteome [40][41][42]. All these proteins fulfill their functions either in the membrane or lumen of the ER (plus the connected nuclear envelope), in one of the organelles of the pathways for endo- and exocytosis (i.e., ERGIC, Golgi apparatus, endosome, lysosome), in lipid droplets or at the cell surface as plasma membrane- or secretory-proteins. ER protein import involves the two stages of membrane targeting and insertion of nascent membrane proteins into or translocation of soluble precursor polypeptides across the ER membrane. Typically, both processes depend on SPs or TMHs at the amino-termini of the precursor polypeptides [24][25][26][27][28][29]. In general, these SPs have a tripartite structure. They comprise a more or less positively charged amino-terminal or N-region, a central hydrophobic or H-region and a slightly polar carboxy-terminal or C-region (Figure 4). Other than that, they do not have sequence homologies and, as a matter of fact, show quite some variability with respect to length (15–50 amino acid residues) as well as overall properties (see below). Interestingly, various human hereditary diseases are the result of single point mutations in the SPs of certain precursor polypeptides (such as preproinsulin and preprorenin), which result in failure of these SPs to deliver their otherwise functional mature forms to the correct cellular location, thus, highlighting the fact that these amino-terminal SPs were fine-tuned to their respective receptors by evolution [43][44] [45]. In addition, insertion of SPs may occur co- or post-translationally and are facilitated by various pathways and components, which reside in the cytosol and the ER membrane or lumen, respectively (Table 1).
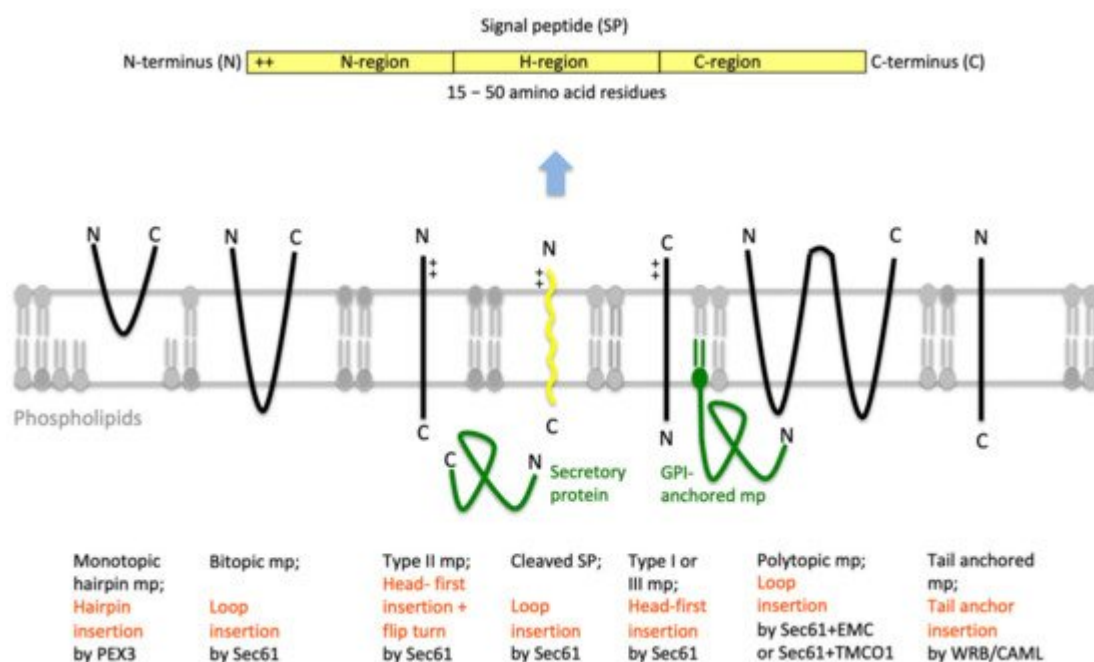
Figure 4. Features of amino-terminal signal peptides and ER membrane proteins. The cartoon depicts the signal peptides (SPs, shown in yellow) and six types of ER membrane proteins (in black), together with their membrane

protein type and mechanism of membrane insertion (both indicated below the cartoon). Cleavable SPs (in yellow) can facilitate ER import of secretory proteins (in green), glycosylphosphatidylinositol (GPI)-anchored membrane proteins (in green) and various types of membrane proteins, except for hairpin-, type II- and tail anchored-membrane proteins. Positively charged amino acid residues (+) play an important role in membrane protein and SP orientation, i.e. typically, follow the positive inside rule. Bitopic and polytopic proteins can also involve SPs and have the opposite instead of the shown orientation. Alternatively, amino-terminal transmembrane helices (TMHs), which serve as SPs, facilitate membrane insertion. The shown bitopic protein is also named double-spanning membrane protein, the example polytopic protein is also named tetra-spanning membrane protein, if the shown type I membrane protein did not involve a cleavable SP it is also defined as signal anchor protein. In the case of membrane proteins with amino-terminal TMHs, membrane insertion typically involves the same components and mechanisms, which deliver secretory proteins (in green) and glycosylphosphatidylinositol (GPI)-anchored membrane proteins (in green) to the ER lumen. In certain cases, however, auxiliary membrane protein insertases, such as EMC or TMCO1 complex play a role. The latter two membrane protein complexes can also operate as stand-alone membrane protein insertases, an activity they have in common with the PEX- and the TRC-systems. Following their ER import, GPI-anchored membrane proteins become membrane anchored via their carboxy-termini by GPI-attachment. C, carboxy-terminus; N, amino-terminus.

3. Gating of the Sec61 Channel by BiP

The Hsp70-type molecular chaperone immunoglobulin heavy chain binding protein or BiP, which was discovered by I. Haas, also goes through a cycle of open and closed conformation [36][46][47][48][49][50][51][52][53][54][55][56][57]. However, in this case the description refers to the state of the substrate-binding domain (SBD). It also involves allosteric effectors in its conformational changes and, in contrast to Sec61, the hydrolysis of ATP. It does not only support Sec61 channel opening for ER protein import [23][32][58][59][60], but also can bind to and act on the incoming precursor polypeptide as a molecular ratchet [37]. Thus, typical for an Hsp70, the ATP- and Ca^{2+}-dependent BiP modulates the conformation of a folded protein complex, the Sec61 channel, plus interacts with a more or less unfolded polypeptide chain as it emerges from the Sec61 channel, thereby vectorizing the transport process. These two kinds of substrates (folded and unfolded substrates) have previously also been observed for various other Hsp70s, such as sigma factor 32 in the bacterial cytosol and clathrin triscelions in the cytosol of human cells. Also typical for an Hsp70, both BiP activities involve an ATPase cycle, where the chaperone goes through states of substrate trapping in its ADP-bound state and substrate release in its ATP-bound state (Figure 5b). Furthermore, these activities involve JDPs, termed ERj- or ERdj-proteins, which stimulate the hydrolysis of BiP-bound ATP [38] [61], and NEFs [62][63][64][65][66][67][68], which stimulate the exchange of ADP for ATP, thereby affecting BiP conformations allosterically [54][55]. Following the same principles and interactions, BiP also plays a central role in folding and assembly of newly-imported polypeptides, such as heavy and light chains of immunoglobulins in plasma cells of the immune system [39][46][47], and supports efficient Sec61 channel closing to preserve Ca^{2+} homeostasis [23][69]. In addition, BiP is a key player in various Ca^{2+}-dependent and -independent signal transduction pathways, which report on ER energy homeostasis and proteostasis, respectively, and can first increase ATP/ADP exchange between ER and cytosol, next increase the folding- and ERAD-capacity via UPR and,

at last, switch to apoptosis under conditions of ever increasing protein mis-folding or ER stress [70][71][72][73][74][75][76] [77][78][79][80].

4. Sec61-Channelopathies

As outlined above, the Sec61 channel of the human ER membrane and its allosteric effectors (TRAP, Sec62, Sec63, and BiP) plus BiP´s co-chaperones and NEFs play central roles in extra- and intra-cellular proteostasis as well as in intracellular Ca^{2+}-homeostasis. Therefore, the term Sec61-channelopathies was coined for diseases, which are the result of toxin-driven or hereditary defects in one of the three Sec61 subunits themselves or in one of the many allosteric effectors of the Sec61 channel (Figure 6) [81]. In general, genetically-determined defects can affect a single or both alleles coding for a certain component and are termed heterozygous or homozygous; heterozygous mutations can result in haploinsufficiency, where the product of the wild type allele cannot compensate the loss of function of the mutated one, or in a dominant negative effect of the product of the mutated allele. Bacterial and fungal toxins can have similar effects as mutations [82]. On the other hand, some components of the interaction network of our interest here appear to have overlapping functions and, therefore, may be partially able to substitute for each other. In addition, some of the components were found to be overproduced in various types of tumor diseases, suggesting that overproduction and gain-of-function of a component can cause or support a disease state, too. Next, we summarize the current knowledge about these diseases, knowing the basic medical principle that "he who has fleas can also have lice" or, at the molecular level, that a certain disease may be the result of simultaneous lack of one function of the component and dominant negative effect of one of its additional functions.
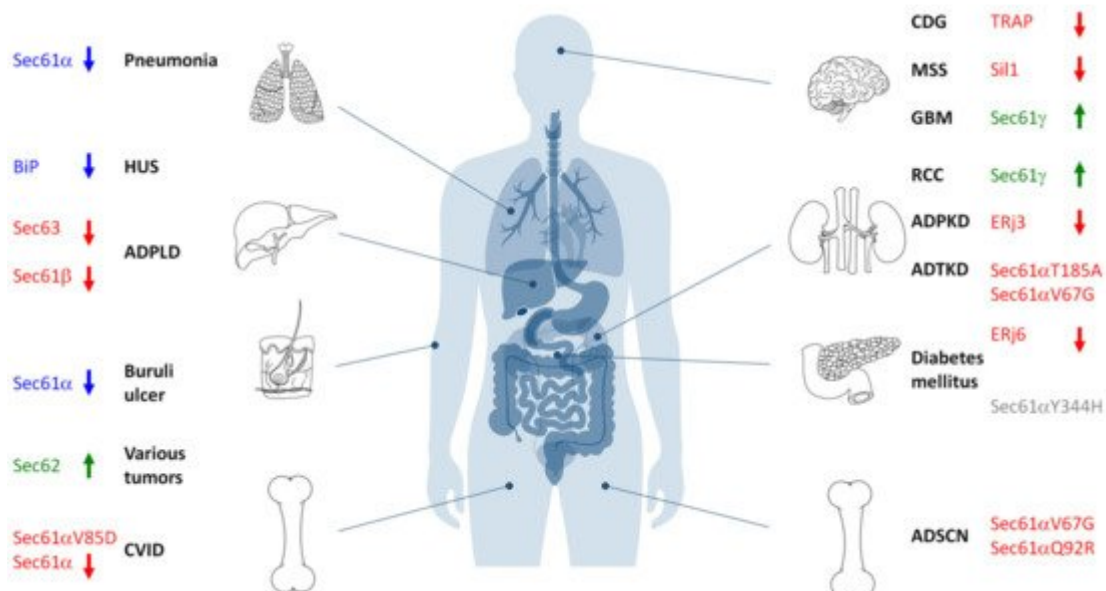
Figure 6. Hereditary and acquired diseases that are linked to the Sec61 complex and its allosteric effectors. The figure highlights various disease phenotypes, which are discussed in the text. Proteins affected in human hereditary diseases are indicated in red, protein targets of toxin-determined human diseases in blue, over-produced proteins in human tumor diseases in green (see below) and a genetically-determined variant causing

murine Diabetes mellitus in grey. The arrows point upwards for increased activity of the indicated component and downwards for decreased activity. ADPKD, autosomal dominant polycystic kidney disease; ADPLD, autosomal dominant polycystic liver disease; ADSCN, autosomal dominant severe congenital neutropenia; ADTKD, autosomal dominant tubulo-interstitial kidney disease; CDG, congenital disorder of glycosylation; CVID, common variable immunodeficiency; GBM, glioblastoma multiforme; HUS, hemolytic uremic syndrome; MSS, Marinesco–Sjögren syndrome; RCC, renal cell carcinoma.

It is noteworthy in the context of Sec61-channelopathies that endosome-resident Sec61 complexes were shown to be involved in antigen transport from endosomes into the cytosol for cross-presentation to CD8^{+} T cells [83]. In the so-called endosome to cytosol pathway of cross-presentation, antigens are exported from endosomes into the cytosol by endosome-resident Sec61 channels and degraded by the proteasome, in possible analogy to Sec61-dependent ERAD. Therefore, this moonlighting function of the Sec61 channel has always to be considered in Sec61-related diseases, as may equally be true for possible specialized functions of Sec61 channels in ERAD.

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