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The Golgi complex in disease and therapy

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The Golgi complex occupies a strategic position in the endomembrane system and acts not only as a key trafficking and sorting station and a vital biosynthetic center for glycoproteins and lipids, but also as an active signaling hub. As such, the Golgi complex participates in the establishment and maintenance of cell compartmentalization and in general, cell processes such as cell growth and apoptosis. The different functions of the Golgi complex are executed by composite molecular machineries that have been exhaustively dissected over the last three decades. These machineries can become dysfunctional as a result of mutations in the respective encoding genes or may be hijacked by infectious agents or misregulated in the course of multifactorial diseases such as neurodegeneration and cancer. Small molecules targeting components of these machineries have been instrumental in dissecting their functions in *in vitro* studies and some of them have been developed or are currently under development for clinical use.

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The Golgi complex (GC) is a central node at the intersection between the exocytic and endocytic routes in intracellular membrane trafficking and as such plays a key role in the sorting of newly synthesized and recycled proteins and lipids towards their final destinations [1]. It thus contributes to establishing and maintaining the identity and integrity of different cellular compartments and to the secretion of soluble factors (with structural, enzymatic or signaling roles).

In addition, the GC modifies proteins and lipids thanks to its complement of enzymes (mainly, but not exclusively, glycosyltransferases) that are distributed in an orderly manner across the different Golgi sub-compartments.

In higher eukaryotes, the GC is organized in a unique ribbon-like architecture composed of stacks of cisternae linked by tubulovesicular structures. The ribbon organization is not needed for the basic functions of the GC, however, and its physiological relevance is a matter of active investigation, as recently discussed by Gosavi and Gleeson [2].

Furthermore, accumulating evidence over the last two decades has identified the GC as a signaling hub since it has been shown to host components of signaling pathways that not only regulate local trafficking pathways but also have a significant impact on cell responses such as apoptosis and stress responses.

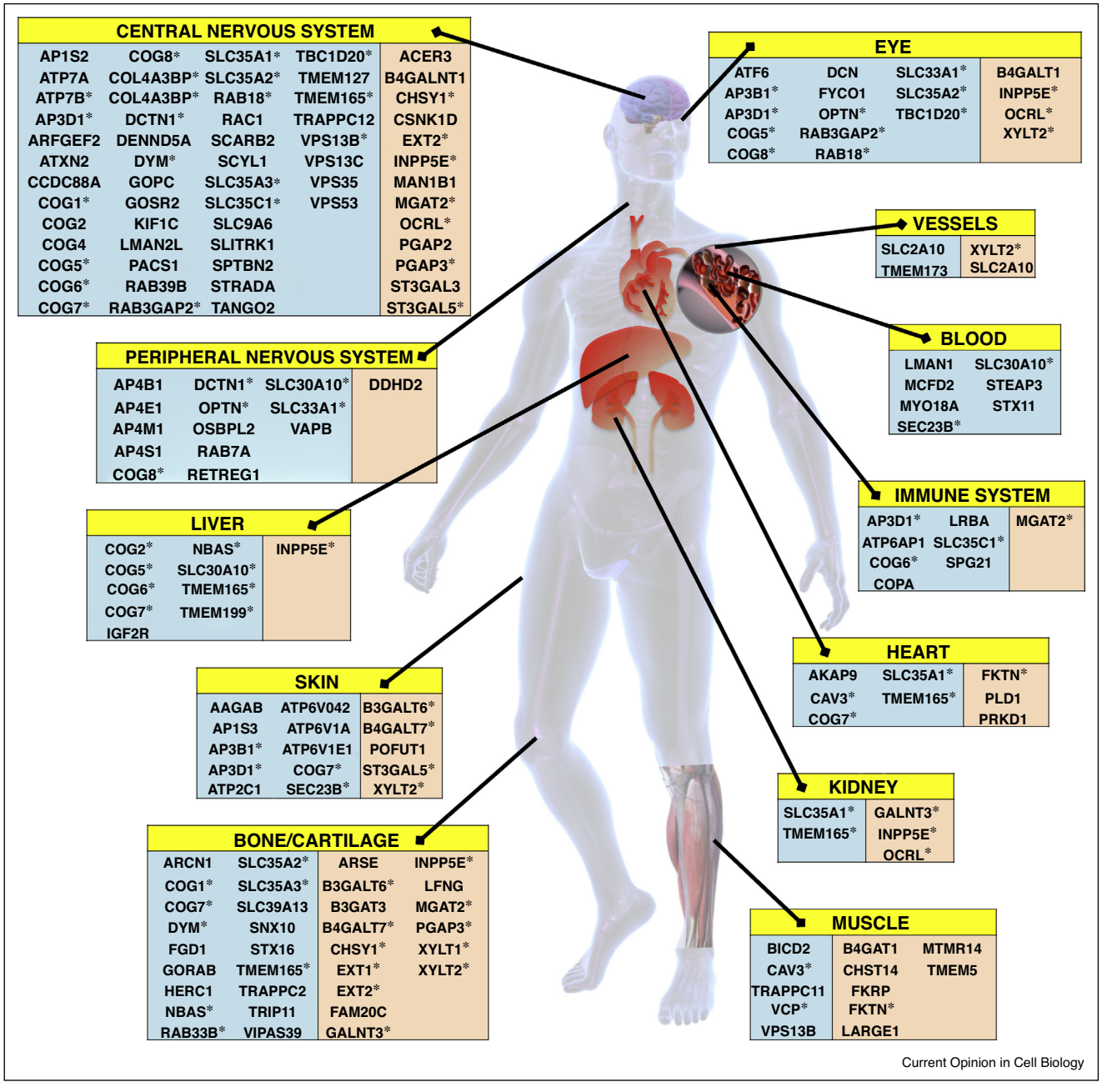
All of the above functions are guaranteed by an array of molecular machineries which are mostly ubiquitously expressed and are invariably subjected to homeostatic tuning by local and general controllers, with the small GTPases and phosphoinositides playing a prominent role.

Monogenic and complex disorders affecting the GC

Given the key and multiple functions of the GC, it comes as no surprise that mutation and the consequent loss of Golgi-based molecular machineries has serious consequences on human health. What is surprising, however, is that these consequences are usually restricted to selected tissues and organs despite the ubiquitous expression of the affected components [3]. This discrepancy highlights our incomplete knowledge of the physiology of the numerous Golgi-based molecular machineries and their components while at the same time, solicits studies using physiologically-relevant settings rather than the immortalized non-specialized cell lines that have been used to date. Figure 1 and Tables 1 and 2 provide an updated summary of monogenic disorders, classified on the basis of the main organ/tissue affected (Figure 1), caused by mutations in genes encoding components of Golgi-based molecular machineries that operate in membrane trafficking (Table 1) or of the enzymes (Table 2) that reside at or associate with the GC.

In addition to being the primary target in disorders caused by genetic defects of Golgi components, the GC can act as

Figure 1



Disease genes encoding Golgi proteins. Genes coding for Golgi complex components whose mutation causes Mendelian disorders are grouped according to the tissues affected in the disorder. Cyan boxes: components of molecular membrane trafficking machinery; light-orange boxes: enzymes. * indicates genes mutated in diseases with multi-organ involvement.

an intermediate station along pathogenic cascades in the course of infectious or multifactorial diseases.

In regards of infectious diseases, the GC is the main membrane source for the assembly of several ssRNA viruses that use Golgi membranes directly and/or hijack master controllers of Golgi membrane biogenesis to build up their replicative niche. Exemplary in this regard is the hijacking of the ARF activator GBF1 and/or the ARF effector PI4KIIIβ through which the membrane of the replicative organelle acquires a Golgi-like identity in terms of GTPase and phosphoinositide composition while the GC of the host cell undergoes fragmentation [4].