Review

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Gene dosage imbalances: action, reaction, and models

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Single-gene deletions, duplications, and misregulation, as well as aneuploidy, can lead to stoichiometric imbalances within macromolecular complexes and cellular networks, causing their malfunction. Such alterations can be responsible for inherited or somatic genetic disorders including Mendelian diseases, aneuploid syndromes, and cancer. We review the effects of gene dosage alterations at the transcriptomic and proteomic levels, and the various responses of the cell to counteract their effects. Furthermore, we explore several biochemical models and ideas that can provide the rationale for treatments modulating the effects of gene dosage imbalances.

From single-gene misexpression to aneuploidy

The concept of gene dosage balance dates back to the early days of genetics, for example, with the work of Blakeslee using the flowering plant *Datura stramonium* [1]. The addition of a single chromosome to an organism was found to be detrimental or lethal, whereas doubling the genome to make polyploids was viable. Afterwards, similar findings characterizing the effects of an altered chromosome copy number, or aneuploidy, have been reported in many other eukaryotes [2–7]. In humans, cytogenetics allowed the discovery of several trisomies in the late 1950s and early 1960s. For instance, Down syndrome (DS) was shown to be caused by the duplication of chromosome 21 in 1959 [8]. Triple X syndrome was also described in 1959 and, in 1960, trisomies 13 and 18 were shown to underlie Patau and Edwards syndromes respectively, which involve life-threatening complications in early life [9,10]. Single-gene dosage alterations usually have small effects except for highly dosage-sensitive genes. Consistently, heterozygous mutations in developmental regulators in mice often provide only subtle phenotypic changes [11]. Therefore, it is likely that the sum (and the interactions) of the effects of the imbalances over a substantial chromosomal segment underlie, at least in part, the deleterious consequences of aneuploidy. However, in some organisms such as yeast the presence of extra copies of specific chromosomes has nearly no consequences for cell growth, whereas other aneuploidies are deleterious due to the misexpression of a single (or a few) gene(s) [2]. In humans the *DYRK1A* gene (dual-specificity tyrosine phosphorylation regulated kinase 1A), on chromosome 21, is highly dosage-sensitive and its increased copy-number in DS, disruptive *de novo* mutations, or deletions lead to intellectual disabilities and autism [12–14]. Thus, the final phenotype of specific aneuploidies is affected not only by the quantity but also by the quality of the genes involved in the relevant chromosome(s).

Many of the deleterious effects of single-gene or chromosomal deletions or duplications can be accounted for by the gene dosage balance hypothesis (GDBH). The GDBH posits that stoichiometric imbalances in macromolecular complexes or cellular networks can induce abnormal function, leading to dominant phenotypes [15,16]. Dosage balance also governs the evolutionary trajectory of duplicate genes. Indeed, most eukaryotic organisms have experienced cycles of whole-genome duplication (WGD), which do not affect the overall dosage balance. Such WGD events are often followed by a reduction of gene number to near the diploid level. On the way back to the diploid state, dosage-sensitive genes are retained for longer periods of time than other gene classes. By contrast, the former are under-represented in small-scale duplications [17]. It can be predicted that dosage-sensitive genes are more likely to encode physically or functionally interacting products whose stoichiometric imbalances would have negative fitness consequences on an evolutionary scale.

The importance of dosage balance in protein complexes and cellular networks is further epitomized by X chromosome inactivation (XCI) in mammals. XCI is a mechanism that equalizes the number of active X chromosomes in eutherian females (XX) and males (XY). However, XCI does not correct the expression imbalance between X-linked genes with those borne by the autosomes. To achieve such a balance the active X has been proposed to undergo a twofold upregulation [18]. Although there is controversy on the existence of chromosome-wide X upregulation [19], several studies have provided transcriptomic and proteomic evidence for the upregulation of genes encoding members of large protein complexes [20,21]. Others have shown that an alternative way to achieve balance is by downregulating

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autosomal genes functionally interacting with non-upregulated X-linked genes [22].

Over- or underexpression of a subunit of a complex will leave unpartnered subunits. This is self-explanatory for overexpression. In the case of gene or chromosome deletions, the deficit of the subunit(s) will leave binding partners in relative excess. For single-gene lesions, when the presence of a loss-of-function allele leads to an obvious (dominant) phenotype, this is termed haploinsufficiency. In some cases a haploinsufficient phenotype is relieved by a decrease in the concentration of an interacting partner [15,23]. For instance, Figure 1 shows the case of a trimer of the type A–B–A in which one subunit is a bridge (B: red molecules) between two identical subunits (A: blue molecules). Halving the amount of A can decrease trimer levels to as little as 25%, whereas halving both subunits leads to 50% of trimer, which in some instances can be compatible with a normal phenotype.

The components of macromolecular complexes have been predicted to be synthesized in amounts reflecting their stoichiometric proportions in the relevant complexes [24]. Li *et al.* 2014 systematically analyzed 64 complexes from *E. coli*, and showed that more than half of the components are indeed synthesized at levels perfectly correlated with their stoichiometry within the complexes. In bacteria, proportional protein synthesis from a polycistronic message relies on translational tuning. As expected, the budding yeast *S. cerevisiae* also showed tightly controlled synthesis for stable complexes [25]. Consistently, previous work in eukaryotes had shown that the mRNAs encoding subunits of such complexes tended to have similar levels ([26,27] and references therein). This is in agreement with the idea of post-transcriptional operons in eukaryotes according to which a set of monocistronic mRNAs encoding functionally related proteins are regulated by a group of RNA-binding proteins and small non-coding RNAs such that protein expression is coordinated [28].

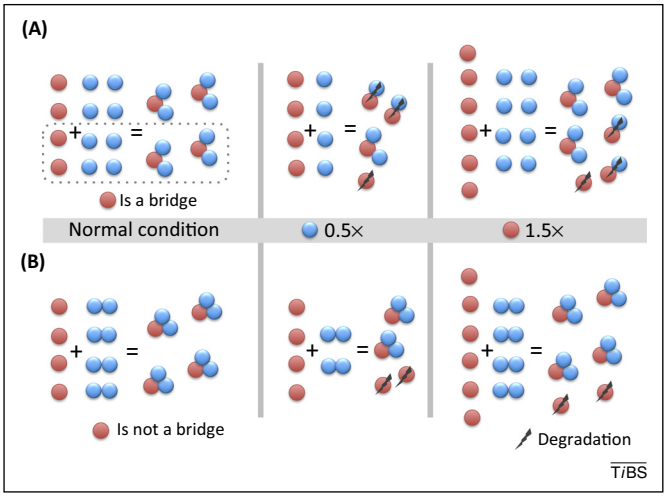

Figure 1. The link between the structure of a complex and its dosage sensitivity. **(A)** In the case of a trimer A–B–A, in which the red subunit, B, is a bridge and the blue subunits, A, are 'separable' subunits, halving of the blue subunits leads to trimer levels between 25 and 50% of normal levels depending on the specific kinetics of the assembly process (middle). Monomers and subcomplexes in excess can be degraded. Interestingly, halving both subunits leads to 50% of trimer (as highlighted by the rectangle in the left panel), which might still be compatible with a normal phenotype. This explains why some cases of haploinsufficiency can be relieved by a decrease in the amount of an interacting partner. Overexpression of the blue subunits can be inconsequential from the perspective of the trimer output whereas overexpression of the red subunit (right) can lead to a titration effect (formation of dimeric subcomplexes), which reduces trimer output. **(B)** When the blue subunits can preassemble into (homo)dimers (left), halving their amount (middle) translates into a proportional decrease of trimer, and the increase of the red subunits (right) does not alter the amount of trimer. These examples show how the pathway of assembly of the complex, and not only its composition, modulate dosage sensitivity.

Evolutionary theories suggest that protein expression can be tuned to maximize fitness. This was experimentally addressed by a study in *E. coli*, which measured the growth burden due to production of *lac* operon proteins (cost) and the growth advantage (benefit) they conferred when lactose was present. Within a few hundred generations, cells evolved optimal expression levels [29]. This shows that protein expression can be rapidly tuned by evolution, a paradigm that applies to macromolecular complexes.

Current genome- and proteome-wide techniques have allowed the analysis of global changes in gene expression as a result of aneuploidy in systems ranging from yeast [30] to human cell lines [5] carrying supernumerary chromosomes. In general, DNA copy number correlates with mRNA and to some extent with protein levels [5,30,31]. However, this is not always so. For instance, we and others have shown that many of the genes with three copies in DS do not show the expected 1.5-fold excess of expression and are compensated at the mRNA level [32] (see [33] for a meta-analysis). Moreover, individuals with trisomy 21 may display clinical features of different intensity, suggesting that DS is affected by many factors including the extent of the trisomic chromosomal segment, mosaicism [34–36], and a varying degree of buffering of the chromosomal imbalance from one individual to another. In this review we explore the effects of gene under- or overexpression and the ways in which the cell can deal with dosage imbalances, with a particular emphasis being placed on the components of macromolecular complexes.

Protein interfaces, protein disorder, and gene dosage imbalance

By the 1970s, it was already recognized that the 3D structure of an isolated monomer can differ from its structure when it is complexed with binding partners [37]. It is now accepted that the assembly of a complex may involve unstable intermediates (i.e., a 'conformational transition state') that are stabilized during the oligomerization process [38]. For instance, α- and β-tubulins are only found as heterodimers, which suggests that each subunit provides folding information for the other [39]. It is also possible that, in other cases, a subunit that is able to reach its final conformation autonomously can serve as a folding template for its partner(s). A dosage defect of such a subunit would then obviously affect the folding process of its partner(s). Thus, complex components that are in absolute or relative excess of other components may be either in a non-final conformation, misfolded, or expose interfaces or hydrophobic segments that should normally be hidden within the complex, which may contribute to abnormal protein–protein associations [40].

A study of the aggregation propensities across protein complex interfaces and surfaces has improved our understanding of the principles behind the attractive forces

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