Chromatin Diminution

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Based in part on the previous version of this eLS article 'Chromatin Diminution' (2001) by Heinz Tobler and Fritz Müller.

Advanced article

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Chromatin diminution is defined as chromosomal fragmentation, followed by the elimination of part of the chromosome during mitosis. The process was first observed in early cleavage divisions of the parasitic nematode *Parascaris equorum* embryo by Boveri in 1887. It was later found to also occur in some other parasitic nematodes, as well as a number of unicellular and metazoan species in diverse taxonomic groups. While chromatin diminution occurs in diverse higher order taxa, within individual taxa, it occurs only in a rather small number of species. The process appears to play different biological roles in different organisms, may use different mechanisms and is likely to have arisen multiple times during evolution.

Introduction

The process of chromatin diminution was first discovered in 1887 by the cell and developmental biologist Theodor Boveri (1887) in the horse parasitic nematode *Ascaris megalocephala*, later called *Parascaris equorum* var. *univalens*, and now renamed *Parascaris univalens*. By microscopically analysing chromosomes during the early development of the embryo, he noted that during the second cleavage divisions leading to the four-cell stage, the chromosomes of the so-called S_1 cell (**Figure 1**) behaved abnormally, in that the central region of the chromosomes fragment into a large number of pieces. During the following anaphase, only these fragmented chromosomes became distributed to the two daughter nuclei. The distal chromosome ends remained in the cytoplasm, where they eventually degenerated. This chromosomal fragmentation, followed by the elimination of part of the large chromosomes, has been called chromatin diminution (L. *diminuere* meaning: to diminish or to reduce to small pieces). As a consequence of the loss of portions of the chromosomes, chromatin diminution results in two daughter nuclei that contain considerably less chromatin (cells S_{1a} and S_{1b} in **Figure 1c**) compared to the nuclei of cells which have gone through a normal mitosis (cells S_2 and P_2 in **Figure 1c**). **See also**: **Boveri, Theodor**; **Chromosomes and Chromatin**; **Chromosome Mechanics**; **Mitosis**

During the following cell divisions, chromatin diminution is repeated four more times in the S_2–S_5 cells (**Figure 2**). By carefully analysing the cell lineage, Boveri (1910) observed that all cells which undergo chromatin diminution become somatic cells, whereas nuclei retaining the original complete chromosomes give rise to germ line cells (**Figure 2**). Thus, the process of chromatin diminution is clearly linked to germ line-soma differentiation in the early embryo of *P. univalens* and leads to cytologically distinct germ line and the somatic cell lineages. **See also**: **Chromosomes during Cell Division**; **Cell Cycle**

'Chromatin diminution', 'chromosome elimination' and 'chromatin elimination' have been described and are three distinct phenomena (Tobler, 1986). 'Chromosome elimination' removes whole chromosomes from the daughter nuclei and not just parts of chromatin from chromosomes (chromatin diminution). Chromosome elimination has been reported to occur in some insects, an acarina species and a few vertebrates (Tobler, 1986; Wang and Davis, 2014). The term 'chromatin elimination' was originally used to describe the elimination of chromatin during the meiotic divisions of some lepidopteran oocytes (Tobler, 1986). According to these cytological observations, relatively large amounts of material were shed from each chromosome at anaphase of the first meiotic division in the form of a definite body, which remained in the equatorial plate, degenerated later on and ultimately disappeared. However, it later turned out that the eliminated material is probably composed of ribonucleoprotein and contains no deoxyribonucleic acid (DNA). Therefore, Tobler (1986) proposed to replace 'chromatin elimination' in this context with 'ribonucleoprotein shedding'. Thus, the term 'elimination' was proposed to be used only in conjunction with 'chromosome' or 'chromatin' and describes the loss of whole chromosomes or chromosome fragments from any stage of the cell cycle. We suggest that the general term 'programmed DNA elimination' be used to describe these two types of DNA elimination.

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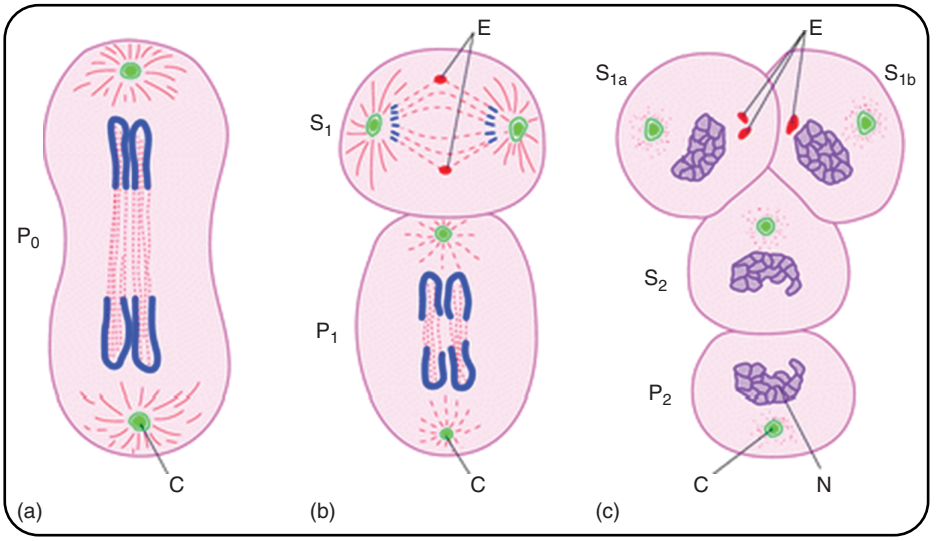

Figure 1 Chromatin diminution in *Parascaris univalens*. (a) Anaphase of the first cleavage division. (b) Anaphase of the second cleavage division. Chromatin diminution occurs in the upper S_1 cell but not in the lower P_1 cell. (c) Four-cell stage after completion of the second cleavage division. The cells S_{1a}, S_{1b} and S_2 give rise to the somatic cells, while the P_2 cell represents the germ line. P_0, zygote; C, centromere; E, eliminated chromatin; N, nucleus; P_0–P_2, germ line and S_1, S_{1a}, S_{1b}, S_2, presomatic cells. Reproduced with permission from Müller *et al.* (1996) © John Wiley & Sons Ltd.

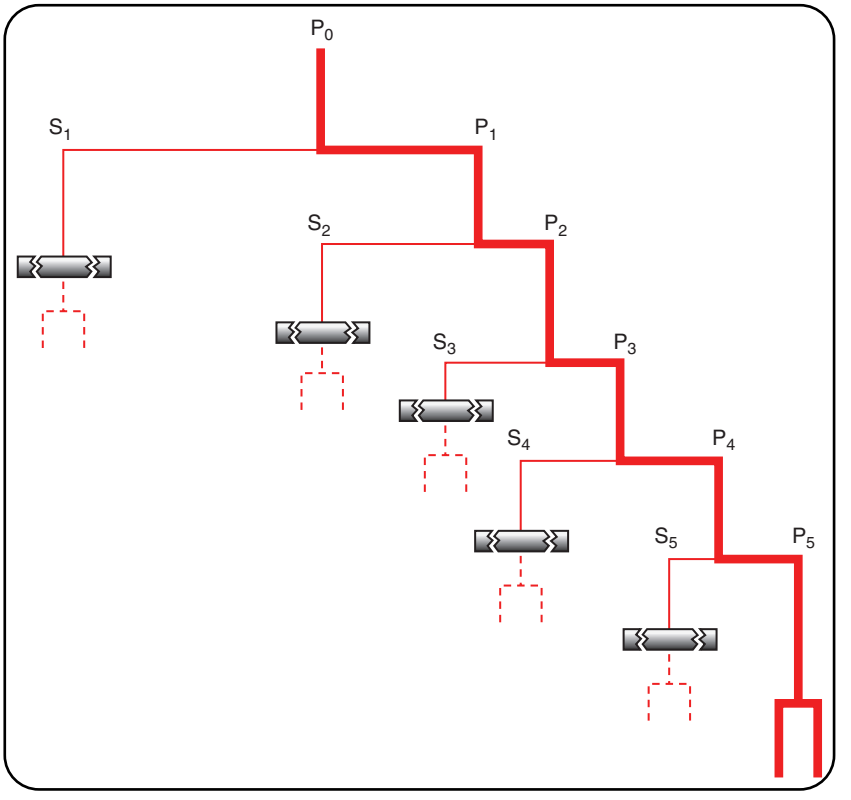

Figure 2 Cell lineage of the early embryo of *P. univalens*. Chromatin diminution is indicated by a broken bar. The germ line lineage is drawn in thick red lines. Presomatic cell lineages before elimination are represented in thin red lines and somatic cell lineages in broken red lines. Reproduced with permission from Müller *et al.* (1996) © John Wiley & Sons Ltd.

Occurrence of Programmed DNA Elimination

Elimination of whole chromosomes (chromosome elimination) and casting out of portions of chromatin from chromosomes (chromatin diminution) in certain cell types are relatively rare events in the animal kingdom and extremely infrequent in plants (Tobler, 1986; Wang and Davis, 2014). These processes have been reported to occur in taxonomically scattered groups: ciliated protozoa, nematodes, crustaceans, several orders of insects, acarina (mites), cyclostomata, chondrichthyes and even in marsupials (Müller *et al*., 1996; Tobler, 1986; Wang and Davis, 2014). From the phylogenetically widespread occurrence in the animal kingdom, one has to postulate (it seems likely) that these events arose independently a number of times during evolution. The idea of a polyphyletic origin is further supported by the fact that the elimination process differs in various aspects among different species (for references see below). Elimination of chromatin or chromosomes may take place during early cleavage stages in the presomatic nuclei, but may also occur in primordial germ cell nuclei, during spermatogenesis, or during mitotic parthenogenesis. Furthermore, the process can occur during different stages of mitosis, meiosis or at the interphase stage. Finally, single autosomes, individual sex chromosomes or an entire haploid set of chromosomes may be discarded, and the amount of eliminated material may range from a few per cent to over 90% of the genome, depending on the species (Tobler, 1986; Wang and Davis, 2014). Overall, chromatin and chromosome elimination likely serve different purposes. For the rest of this article, we concentrate on chromatin diminution in the strict sense, that is the elimination of parts of chromosomes. The best characterised examples come from unicellular ciliates where the process is involved in the formation of the macronucleus from the micronucleus (Bracht *et al*., 2013). Ciliate biology, including macronuclear formation, is covered fairly extensively elsewhere in this encyclopedia and is not discussed in this article. Here, we discuss the best studied examples of chromatin diminution in multicellular animals (**Table 1**). **See also**: **Structure, Function and Evolution of The Nematode Genome**; **Nematoda (Roundworms)**; **Agnatha (Lampreys, Hagfishes, Ostracoderms)**; **Genomic Novelty at the Vertebrate Ancestor**; **Euplotes (Dorsoventrally Flattened Ciliates)**; **Ciliophora**; **Alveolates**; **Tetrahymena**; ***Tetrahymena* Cell Culture**; **Paramecium**; ***Vorticella***

The Process of Chromatin Diminution

At the cytological level, chromatin diminution has been best analysed in two closely related nematodes, *P. univalens* and *Ascaris suum* (Müller and Tobler, 2000), in the nematode *Strongyloides papillosus* (Albertson *et al*., 1979) and in copepods (Beermann, 1977; Beermann and Meyer, 1980; Wyngaard and Gregory, 2001; Grishanin, 2014; Clower *et al*., 2016).

The fact that *P. univalens* carries only two large chromosomes (each ~2.5 Gb in size) in the germ line cells makes a cytological analysis of the process of chromatin diminution particularly amenable. Following chromatin diminution in the presomatic cells, the somatic cell haploid chromosome number increases to 35 (Niedermaier and Moritz, 2000). The chromosomes of *P. univalens*, like those of other nematode species studied, are holocentric, that is they have diffuse centromeres (Albertson and Thomson, 1982; Goday *et al*., 1985; McKinley and Cheeseman, 2016; Pimpinelli and Goday, 1989). Electron microscopic analysis of the fine structure of the kinetochore, and spindle microtubule attachment to chromosomes before and after chromatin diminution, revealed that spindle microtubules associate only with the retained chromosomal regions in all prediminution and diminution blastomeres, whereas the eliminated, heterochromatic distal regions do not bind spindle microtubules (Goday *et al*., 1992). The heterochromatic, eliminated chromosomal regions in presomatic chromosomes are also devoid of kinetochore plates. Such a lack of kinetochore activity in the eliminated chromatin explains why, upon chromosomal fragmentation, these chromatin portions are not distributed to the spindle poles but rather remain in the equatorial plate. In the cytoplasm, these chromosome fragments eventually disintegrate. **See also**: **Centromeres**; **The Evolution of Centromeric DNA Sequences**; **Kinetochore: Structure, Function and Evolution**; **Heterochromatin and Euchromatin**

The process of chromatin diminution in the related species *A. suum*, an intestinal parasite of the pig, differs in interesting ways from that described for *P. univalens*: (1) elimination in *A. suum* does not occur before the third cleavage division; (2) chromatin diminution must be limited to the blastomeres S_2–S_4 because no S_5 cell has been observed (**Figure 2**); and (3) the germ line genome is not combined in a single chromosome (haploid is $n = 24$) (Niedermaier and Moritz, 2000). Interestingly, after chromatin diminution, there is a haploid complement of 36 chromosomes, a number very similar to the one in *P. univalens*. Despite the different genomic organisation of *P. univalens* and *A. suum*, chromatin diminution results in the loss of all detectable heterochromatin in the presomatic cells of both species (Goday and Pimpinelli, 1986). **See also**: **Germ Cell Fate Determination in *C. elegans***

In the sheep parasitic nematode *S. papillosus*, parthenogenetic parasitic females have two pairs of chromosomes of different length ($2n = 4$, two long and two medium-sized chromosomes, 2L, 2M). Through parthenogenesis, they produce parasitic females as well as free-living sexual female and male progeny (Streit, 2016). While all females have the same karyotype like their mother, in oocytes destined to become males, an internal portion of one of the two homologous long chromosomes is eliminated during the single mitotic oocyte maturation division (Albertson *et al*., 1979; Triantaphyllou and Moncol, 1977). Both chromosomal ends are retained as independent chromosomes resulting in males with $2n = 5$ chromosomes. Early during that mitotic maturation division, both homologous longer chromosomes appear fragmented in such a way that the two terminal parts, which will be retained, are separated by six chromatin beads (Albertson *et al*., 1979). Later, one of the chromosomes

Table 1 Comparison of chromatin diminution in different taxa

	Who: which cells undergo diminution	What: which sequences are eliminated	When: time point when chromatin diminution occurs	How: what is known about the mechanism	Why: proposed biological functions of chromatin diminution
Ascarids (nematode)	• All somatic precursor cells in all individuals	• Multiple terminal and internal fragments of multiple chromosomes (up to 90% of the total genomic DNA) • Repetitive sequences and germ line-specific genes • Both copies	• During embryonic cleavage divisions	• Chromosomes break at defined positions • Eliminated regions lack kinetochore activity due to lack of CENP-A • Number of chromosomes increases • Mechanism for sequence recognition and cleavage unknown	• Unburden soma from 'junk' DNA • Silence genes required only in the germ line
Strongyloides papillosus (nematode)	• Oocyte giving rise to males	• One internal portion of one chromosome (roughly half of the chromosome) • Only one copy	• During mitotic oocyte maturation division	• Eliminated regions lack kinetochore activity • Number of chromosomes increases • Mechanism for sequence recognition and cleavage unknown	• Determine male sex by functionally reconstituting the ancestral XX/XO sex determining system
Copepods	• All somatic precursor cells in all individuals	• Multiple terminal and internal fragments of multiple chromosomes (up to >90% of the total genomic DNA) • Repetitive sequences including rDNA • No protein coding genes yet identified • Both copies	• During embryonic cleavage divisions • The eliminated chromatin may persist in the cytoplasm for multiple cell divisions	• Internal eliminated regions loop out • Retained chromosomal fragments are rejoined • Number of chromosomes does not change • Mechanism for sequence recognition and cleavage unknown	• Unburden soma from 'junk' DNA • Reduction of rDNA copy number • Removal of germ line determinants
Lampreys	• All somatic precursor cells in all individuals	• Multiple fragments of multiple chromosomes (about 20% of the total genomic DNA) • Possibly also entire chromosomes • Repetitive sequences and germ line-specific genes • Both copies	• During early embryogenesis in multiple steps • The eliminated chromatin may persist in the cytoplasm for multiple cell divisions	• Number of chromosomes is reduced • Mechanism for sequence recognition and cleavage unknown	• Unburden soma from 'junk' DNA • Silence genes required only in the germ line

recovers and undergoes a normal mitotic sister chromatid separation. The six central beads of the other chromosome appear not to attach to the division spindle and are not incorporated into the daughter nuclei. Which one of the two homologous chromosomes undergoes diminution appears random as brothers can differ in which of the chromosomes they retain (Nemetschke *et al*., 2010).

In copepods, chromatin diminution occurs in somatic cells during the early embryonic cleavage divisions (Beermann, 1977; Grishanin, 2014). At which cleavage division it occurs varies between species (see Table 1 in Grishanin, 2014). Internal heterochromatic regions are removed from the chromosomes. Notably, unlike what occurs in nematodes, the retained fragments of the chromosomes are rejoined such that only the size but not the number of chromosomes differs between the germ line and somatic cells (Beermann, 1977; Grishanin, 2014). The eliminated chromatin has been observed to loop out, reminiscent of the excision of bacteriophage DNA (Beermann and Meyer, 1980). Similar to the cases in nematodes, the chromosome fragments destined for elimination fail to attach to the division spindle and remain at the metaphase plate upon segregation of the somatic chromosomes to the spindle poles (Wyngaard and Gregory, 2001). Very recently, Clower *et al*. (2016) published a detailed description of the cytological process in *Mesocyclops edax*. These authors found that the eliminated material persists in the cytoplasm for extended periods of time, opening the possibility that it still serves a function after its exclusion from the nuclear chromosomes.

In sea lampreys, chromatin diminution occurs in somatic cells and is complete around the blastula to gastrula transition at 2–3 days of development (Smith *et al*., 2009; Timoshevskiy *et al*., 2016). The process results in a reduction in the number of chromosomes (Smith *et al*., 2010). However, the identification of break points (Smith *et al*., 2012) and cytological studies (Covelo-Soto *et al*., 2014; Timoshevskiy *et al*., 2016) suggest that entire chromosomes and internal regions are eliminated. However, cytological elimination analysis is rather difficult. The lamprey has a large number of relatively small chromosomes that undergo extensive rearrangements and the reduction of the chromosome number from $n = 99$ in the germ line to $n = 86$ in the soma may also involve chromosome fusion (Smith *et al*., 2010; Covelo-Soto *et al*., 2014). In a very recent study, Timoshevskiy *et al*. (2016) found that the process occurs over multiple consecutive cell divisions. From about the 7th cell division, lagging chromatin can be observed during mitosis. Comparable to *M. edax* (Clower *et al*., 2016), the eliminated chromatin persists in the cytoplasm until about 2 days postfertilisation in structures the authors describe as micronuclei. These micronuclei are first rich in H3K9me3 (histone 3 lysine 9 tri-methylation), which later is replaced with 5meC (5-methyl cytosine) chromatin modification. The presence of these repressive chromatin marks might indicate that chromatin diminution is mechanistically related to other gene silencing mechanisms. Finally, the micronuclei become positive in TUNEL (terminal-desoxynucleotidyl-transferase-mediated dUTP nick-end labeling) indicating DNA breaks and then shortly thereafter they disappear.

The molecular mechanisms underlying the process of chromatin diminution in multicellular organisms have almost exclusively been analysed in *A. suum*. Chromosome fragmentation in the presomatic cells takes place at specific chromosomal regions termed chromosomal breakage regions (CBRs), and is followed by the *de novo* addition of 2–4 kb of telomeric TTAGGC sequences (Müller *et al*., 1991). Interestingly, the telomeric repeats are added not only to the broken ends of the retained chromosomal portions in the presomatic cells, where they are probably required for the maintenance of the chromosomal integrity but also to the eliminated portions of the chromosomes. Thus, telomere addition during chromatin diminution occurs on any broken chromosome end in a nonspecific manner. Telomere addition at CBR does not occur at a specific nucleotide position but is heterogeneous over 100 bp up to a few kilobases (Bachmann-Waldmann *et al*., 2004; Wang *et al*., 2012). Although individual CBRs are conserved between *A. suum* and *P. univalens*, there is no obvious sequence similarity between different CBRs within a species. This and the absence of pre-existing $(TTAGGC)_n$ motifs suggests that *de novo* telomere formation during chromatin diminution is most likely mediated by the activity of a telomerase (Magnenat *et al*., 1999) rather than a recombinational event. This hypothesis is supported by the presence of 1–4 bp of sequences identical to the telomeric repeats at the junction region of all telomere addition sites, which may have provided limited homology for telomerase priming. **See also**: **Telomeres**; **Telomerase: Structure and Function**; **Telomere**

It is not yet known how the different CBRs are recognised and how the chromosomes are broken during chromatin diminution. However, recent work by (Kang *et al*. 2016) demonstrates that there is a loss of the centromere-specific Histone H3 isoform CENP-A on the chromatin to be eliminated before diminution. While these findings explain the lack of division spindle attachment of the eliminated chromatin, the mechanisms that identify the regions where DNA breaks will occur and where centromeres/kinetochores will be lost to enable diminution remain unknown. Chromatin diminution must be controlled by morphogenetic determinants, which become committed to specific blastomeres during early cleavage processes. Such factors have not yet been identified in *A. suum*. However, experiments with *P. univalens* strongly suggest that the fertilised oocytes contain localised cytoplasmic factors, close to or at the vegetal pole, which are segregated to the primordial germ cells and function to prevent chromatin diminution in the germ line (Boveri, 1910; Esteban *et al*., 1995; Moritz, 1967). Chemical treatments that induce or prevent chromatin diminution in eggs indicate that these cytoplasmic factors are already present in the zygote. The correct segregation of these inhibitory factors to the pregerminal P_0–P_4 cells (**Figures 1** and **2**) seems to be microfilament mediated (Esteban *et al*., 1995). Interestingly, chromatin diminution can be chemically induced in pregerminal P_0–P_4 cells but not in P_5 and its descendants. This differential response strongly suggests that, in contrast to the P_0–P_4 blastomeres, the behaviour of the chromosomes in the P_5 cell is strictly determined and cannot be reversed. **See also**: **Germ Cell Fate Determination in *C. elegans***

Amount and Composition of the Eliminated DNA

Among the examples discussed earlier, there are fundamental conceptual differences with respect to the eliminated material between *S. papillosus* and the other species. In *S. papillosus*, only one of the two homologous chromosome copies is eliminated and in only one sex and in all tissues. This results in a dose difference but not in the complete loss of the genes. The eliminated part of the chromosome in *S. papillosus* is homologous to the X chromosome of closely related species and contains a large number of genes and few repetitive sequences (Hunt *et al*., 2016; Kulkarni *et al*., 2013; Nemetschke *et al*., 2010). Conceptually, it is noteworthy that the elimination of one copy leads essentially to the same result as differential chromatin amplification, which can occur in *Drosophila* spp. polytene chromosomes and nurse cells (Andreyeva *et al*., 2008; Redi *et al*., 2001). In these examples, the genome undergoes endoduplication, not destruction, but heterochromatic regions are underreplicated compared with euchromatic regions resulting in different copy numbers (Andreyeva *et al*., 2008; Redi *et al*., 2001). Interestingly, differential chromatin amplification appears also at work in *S. papillosus* and other species of *Strongyloides*. Both sexes in these species contain in their gonads a population of giant nuclei with autosomal genes present at higher copy numbers than X chromosomal/male-diminished genes (Kulkarni *et al*., 2016).

In the other species with chromatin diminution, the elimination creates a difference between tissues, namely the soma and the germ line and, as far as is known, both homologous copies are eliminated resulting in a qualitatively distinct genetic content in pre- and postdiminution cells. The amount of chromatin removed can be very large. In *P. univalens*, about 90% of the total nuclear germ line DNA becomes eliminated from the presumptive somatic cells during chromatin diminution (Wang *et al*., Davis laboratory, unpublished), whereas in *A. suum*, 13% is eliminated (Wang *et al*., 2012). The eliminated chromatin varies in different copepods ranging from 45% to more than 90% of the germ line chromatin (Grishanin, 2014), whereas 20% of the germ line DNA is eliminated from somatic tissues in the sea lamprey *P. marinus* (Smith *et al*., 2012). In all these species, the vast majority of eliminated chromatin is composed of repetitive sequence that includes transposable elements (Degtyarev *et al*., 2004; Smith *et al*., 2012; Sun *et al*., 2014; Wang *et al*., 2012). While a small number of protein coding genes were known to be eliminated in *A. suum* (Etter *et al*., 1991, 1994; Huang *et al*., 1996; Spicher *et al*., 1994), recent analyses indicate that hundreds of genes are eliminated from the germ lines in Ascarids and lampreys (Smith *et al*., 2012; Wang *et al*., 2012; Bryant *et al*., 2016). The finding that a rather large number of functional genes undergo diminution demonstrates that the eliminated chromatin does not just contain useless or 'junk' DNA but may play key roles in the germ line. This finding represents the first molecular support for Boveri's original hypothesis (1910) on the significance of chromatin diminution in *A. suum*, namely, that the germ line-limited chromatin is essential for the germinal quality of a blastomere, whereas its elimination is necessary to ensure the somatic fate of a blastomere. Typically, genes are silenced at the transcriptional level. However, some organisms might have adopted chromatin diminution as an alternative means of gene regulation. Such a radical 'gene throw-away approach' could be used to eliminate those genes which code for germ line-specific functions, such as meiotic chromosome pairing, recombinational events and gamete formation. However, it should be noted that not all germ line specifically expressed genes are eliminated. Contrary to the ascarid nematodes and in the lamprey, elimination of single copy and expressed protein encoding genes has not yet been documented in copepods (Degtyarev *et al*., 2004; Grishanin, 2014; Sun *et al*., 2014). However, ribosomal RNA (ribonucleic acid) gene copy numbers are reduced in the copepod *Cyclops kolensis* during chromatin diminution (Zagoskin *et al*., 2010). In the copepod *M. edax*, chromatin diminution eliminates nonsimple repetitive elements of clear or presumed transposable element origin including some repetitive sequences with short open reading frames (Sun *et al*., 2014). In spite of the absence of clear evidence for the elimination of protein coding genes, multiple authors have argued that also in copepods the eliminated genetic material is not just composed of 'junk DNA' but chromatin diminution also in this taxon serves a regulatory developmental purpose (Degtyarev *et al*., 2004; Grishanin, 2014; Sun *et al*., 2014; Zagoskin *et al*., 2010). **See also**: **Transposons in Eukaryotes (Part A): Structures, Mechanisms and Applications**; **Sex Chromosomes**

Summary and Conclusions

Chromatin diminution, the programmed elimination of portions of chromosomes during mitotic divisions, occurs in various largely unrelated metazoan taxa. Chromatin diminution appears to serve various functions. In the nematode *S. papillosus*, it functionally reconstitutes an ancestral XX/XO sex-determining mechanism. In other organisms, for example ascarid nematodes, copepods and lampreys, it functions in soma differentiation from the germ line. In these species, chromatin diminution appears (1) to unburden somatic tissue from excessive, probably partially 'selfish' repetitive DNA, and (2) to eliminate and thereby silence germ line expressed genes in the soma. Although some initial progress has been made, our understanding of the mechanisms that recognise the sequences to be eliminated and the overall process of DNA elimination is still very limited. Given that chromatin diminution has almost certainly arisen independently in different taxa, the mechanisms for elimination may differ in different taxa. More than 120 years after its discovery by Boveri, many questions and mysteries remain about this fascinating process which contradicts the dogma that all cells in metazoa possess identical genetic material (**Table 1**).

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