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❀ **The evolutionary conserved PcG proteins maintain stable transcriptional epigenetic repression, established earlier by transiently acting regulator proteins. The exact mechanism of PcG-mediated repression is not identified yet, and here we outline existing models of the repression mechanism. We also shortly summarize the current knowledge about PcG proteins and their role in various processes and present an insight into the evolution of PRC1 and PRC2 complexes.**

❀ **Key words:** PcG proteins, evolution, transcriptional repression, epigenetic

TOWARDS UNDERSTANDING THE MECHANISMS OF EPIGENETIC REGULATION: PART 1. AN EVOLUTIONAL INSIGHT INTO PcG-MEDIATED GENE REPRESSION

Cell fate in multicellular organisms is defined at early development stages by a specific expression profile of genes. Homeotic (Hox) genes provide one of the best-studied examples of such differential expression. Since the function of these genes is to determine where particular body parts will develop, mechanisms that regulate the correct time and place of their expression are of paramount importance. This regulation is a two-step process: first, the transcriptional state needs to be established; second, it has to be maintained and transmitted through cell generations as specialized cells proliferate.

Establishment of the expression patterns of Hox genes in early embryogenesis is made by different regulatory cascades (Ingham, Martinez Arias, 1992). For example, spatially restricted expression of *Drosophila* gene *Abdominal-B* is set by several gap genes, such as *hunchback* and *Krüppel* (Casares, Sanchez-Herrero, 1995). During subsequent stages of development, established active or repressed states of Hox genes are maintained by two antagonistic groups of proteins: trithorax group (TrxG) proteins, which are essential for maintaining active states, and PcG proteins, which are required to maintain repressed states (Pirrotta, 1998; Francis, Kingston, 2001; Ringrose, Paro, 2004; Breiling et al., 2007). Relationships between proteins from these two groups are complex and very interesting (Francis, Kingston, 2001; Ringrose, Paro, 2004; Ringrose, Paro, 2007); however, we will concentrate on PcG proteins and their functioning.

PcG proteins are currently one of the hot topics in cell biology, owing to the fact that they are highly conservative (homologues of numerous PcG proteins were found in many species from different taxa (Levine et al., 2002; Ringrose, Paro, 2004; Whitcomb et al., 2007; Yang et al., 2007)) and are implicated in various key processes, such as body patterning, epigenetic cellular memory, vernalization in plants, X-inactivation in mammals, stem cells self-renewal and pluripotency (Jacobs, van Lohuizen, 2002; Isono et al., 2005; Sun, 2005; Lee et al., 2006; Wang et al., 2006; Schwartz, Pirrotta, 2007). But still, despite great many studies performed in this field, the mechanism of PcG-mediated repression is not yet understood. Here we attempt to summarize the current state of knowledge on this subject and examine existing hypotheses.

DROSOPHILA PcG PROTEINS

At the moment there are about 15 PcG proteins found in *Drosophila*, and most of them form multiprotein complexes. Currently there are three separate complexes identified (the complexes are listed in the order of their recruitment):

(1) The **PhoRC** (**P**ho **r**epressive **c**omplex) was purified from *Drosophila* embryos and characterized rather recently (Klymenko et al., 2006). PhoRC contains Pleiohomeotic (Pho) and dSfmbt, a novel PcG protein that is crucial for Hox gene silencing. Of all characterized PcG proteins of *Drosophila*, only Pho and Pho-like (Phol) proteins have sequence-specific DNA-binding ability. It was shown that all PREs contain binding sequences for Pho (Brown et al., 1998; Ringrose et al., 2003) and that Pho directly recruits the ESC-E(Z) complex to PREs (Polycomb Response Elements, see below) (Wang et al., 2004). dSfmbt selectively binds to mono- or dimethylated lysine 9 of histone H3 or lysine 20 of histone H4 (Klymenko et al., 2006). Since PhoRC targeting to PREs depends on the Pho DNA-binding ability, it is thought that binding of dSfmbt to methylated histones is not required for PhoRC targeting but is needed for repression (Klymenko et al., 2006; Muller, Kassis, 2006).

(2) The **ESC-E(Z)** (**e**xtra **s**ex **c**ombs-**E**nhancer-of-**z**este) complex (also known as PRC2) contains Esc, E(z), a PEV suppressor Su(z)12, a histone-binding protein Nurf55 (also a component of the chromatin remodelling complex NURF) and a histone deacetylase Rpd3 (present in some forms of the complex) (Ng et al., 2000; Tie et al., 2001; Czermin et al., 2002; Muller et al., 2002; Nekrasov et al., 2005). The ESC-E(Z) complex functions as a histone methyltransferase (HMT) that specifically methylates histone H3 at lysine 27 *in vitro* (Czermin et al., 2002; Muller et al., 2002; Orlando, 2003; Muller, Kassis, 2006) . Although this activity is provided by the E(z) SET domain, the noncatalytic subunits are also critical for the functioning of this complex: it was shown that the activity of a recombinant four-subunit ESC-E(Z) complex is over 1,000 fold greater than that of E(z) alone (Muller et al., 2002).

(3) The **PRC1** (**P**olycomb **r**epressive **c**omplex 1) contains Polycomb (Pc), Polyhomeotic (Ph), Posterior sexcombs (Psc), Sexcombs extra (Sce, also known as dRing1), Sex combs on midleg (Scm) and components of basal transcriptional machinery (Franke et al., 1992; Shao et al., 1999; Saurin et al., 2001; Ringrose, Paro, 2004). The Pc protein has a chromodomain which specifically recognizes histone H3 methylated at lysine 27 (Fischle et al., 2003) and thus directs the PRC1 complex to the binding sites created by the ESC-E(Z) complex. It was also shown that PRC1 is able to inhibit the nucleosome remodelling ability of the SWI/SNF complex *in vitro* (Shao et al., 1999; Francis et al., 2001; Levine et al., 2002).

Thus, binding of PcG proteins to PREs occurs in the following way: PhoRC complex recognizes specific Pho-binding sites and recruits the ESC-E(Z) complex, which in turn creates methylation mark recognized by the PRC1 complex.

PcG PROTEINS AND THEIR PARTNERSHIPS ARE EVOLUTIONARY CONSERVED

After PcG proteins were found in *Drosophila*, numerous studies have been performed to identify their homologues in other species. Some proteins, like the E(Pc) (Enhancer of Polycomb) and E(z), have homologues in a wide range of species, from yeast to mammals (Table 1; the phylogenetic tree was taken from (Roger and Hug, 2006) with minor modifications) (Stankunas et al., 1998; Shimono et al., 2000; Boudreault et al., 2003; Ceol, Horvitz, 2004); others are less studied in this regard. At the moment, mammals are the only group where homologues of all core members of the PcG complexes were identified (Table 1).

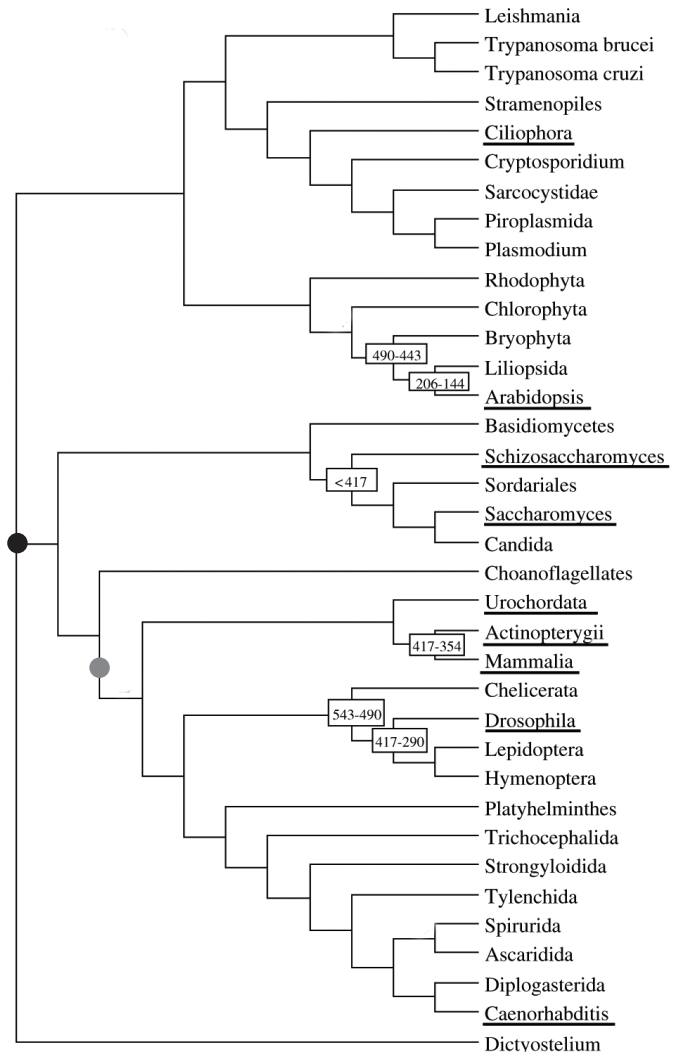
Although core components of both PRC1 and PRC2 complexes are conserved between flies and mammals (Table 1), mammalian PRC1 appears to lack most of non-PcG components (Levine et al., 2002; Ringrose, Paro, 2004). Mammals have multiple established or predicted orthologues of PcG genes; for example, there are up to five distinct potential Pc homologues and six potential Psc homologues (Martinez, Cavalli, 2006). In human PRC1 complexes, purified from HeLa cells (hPRC1), multiple homologues of most of the core proteins were found, although it is not clear whether they are present simultaneously in one complex or whether there exist different variants of this complex (Levine et al., 2002). This complex has the same ability to inhibit nucleosome remodelling as its *Drosophila* counterpart (Levine et al., 2002). Homologues of some PRC1 components were also found in other model animals, such as *Xenopus* and zebrafish (Strouboulis et al., 1999; Petrino, 2001), although they have not yet been identified in yeast or plants (Ketel et al., 2005; Saleh et al., 2007; Whitcomb et al., 2007). In *C. elegans* there is a complex named SOP-2/SOR-1, responsible for global repression of Hox genes and similar to the PRC1 complex of *Drosophila* (Yang et al., 2007).

In contrast, established or putative homologues of PRC2 components E(z) and Esc were found in both main phylogenetic branches: one that contains plants, Ciliophora and fungi (the "upper" branch of the tree), and another one with vertebrate and invertebrate animals (the "lower" branch of the tree) (Table 1) (Korf et al., 1998; Satijn et al., 2001; Ketel et al., 2005; Sun, 2005; Wang et al., 2006; Saleh et al., 2007; Whitcomb et al., 2007); and even possibly in *Dictyostellium*. In *Arabidopsis* also multiple homologues of the Su(z) protein were identified (Table 1) (Schubert et al., 2005; Makarevich et al., 2006). As the available data indicate, E(Pc) and E(z) proteins are found in the widest variety of species (Table 1). Different components of the PRC2 complex were found in such diverse groups as Ciliophora, Magnoliophyta, Basidiomycetes and in animals from worm to mammals (Birve et al., 2001; Levine et al., 2002; Thakur et al., 2003; Ringrose, Paro, 2004; Loftus et al., 2005; Lee et al., 2006; Wang et al., 2006; Liu et al., 2007; Saleh et al., 2007), and even in *Dictyostellium* there is a SET-domain containing protein, possibly related to E(z) (Glockner et al., 2002) (Table 1). This suggests that components of the PRC2 complex, particularly E(z), and the E(Pc) protein originated from some distant common ancestor (indicated by the black node on the phylogenetic tree). Since the E(z) protein is found in Ciliophora and Magnoliophyta , it is likely that homologous proteins also exist in other plants and, perhaps, in parasites Leishmania and Trypanosoma.

On the other hand, members of the PRC1 complex were so far identified only in some metazoan animals (Table 1). The grey node on the phylogenetic tree indicates a probable spot where they originated. Since these proteins were found in Chordata as well as in Insecta branches, it is likely that they also exist in the rest of insects and in worms, but not in Dictyostellium. Indeed, during an excellent research of evolutionary history of PcG proteins, Whitcomb and co-authors identified putative homologues of the Pc protein in sea urchin and *C. elengans* (Whitcomb et al., 2007).

Table 1

Homologues of most of *Drosophila* PcG proteins in Eukaryota



"Free"		PRC1 complex					PRC2 complex			PhoRC complex	
E(Pc)	Pcl	Pc	Ph	Psc	Sce	Scm	E(Z)	Esc	Su(z)	Pho	dSfmbt
							?				
							?				
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+	—	—	—	—	—	—	?	—	—	—	—
							?				
—	?	?	?	+	+	—	+	—	?	?	—
+	?	+	+	+	+	—	+	+	+	+	?
+	+	+	+	+	+	+	+	+	+	+	?
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?	?	?	—	?	?	—	?	?	?	—	—
+	—	?	—	—	—	—	+	+	—	?	?
							?				

The table summarizes our current knowledge of PcG homologues in different species and taxa. Four groups of PcG proteins were analyzed: "free" proteins Enhancer of Polycomb (E(Pc)) and Polycomblike (Pcl) which were not found in multiprotein complexes, and components of the PRC1, PRC2 and PhoRC complexes (full names of their components are in the text). Each line of the table represents data for the corresponding branch of the phylogenetic tree (the tree was taken from (Roger and Hug, 2006) with minor changes). Underlined are the most popular model organisms where PcG proteins are studied best. In the table "+" indicates a positively identified homolog of corresponding *Drosophila* protein. "—" shows that no corresponding homolog was identified so far. "?" stands for either a putative homolog, a protein of similar properties (f. e. Enhancer of Polycomb-like) or a predicted protein. An empty cell means no available data. Explanations about the black and grey nodes are given in the text.

If members of the PRC1 complex are indeed absent in the branch with plants, fungi and *Ciliophora*, probably there are other proteins which fulfill their functions. However, while making this kind of analyses one always has to keep in mind that absence of data does not mean absence of proteins.

Members of the PhoRC complex are currently known in *Drosophila*, mammals and bony fishes (Table 1), so probably they originated at the same spot as PRC1 proteins (indicated by the grey node). In *Drosophila* the PRC2 complex is directed to PREs by the PhoRC complex which binds to DNA, and since the PRC2 complex is so conserved in evolution, we expect homologues of the Pho protein also to be found in all taxa. On the other hand, PREs were not yet identified and studied in mammals, plants or other non-insect groups, and it is possible that they have a different design and might require other proteins to attract the PRC2 complex.

Remarkably, not only are components of PRC1 and PRC2 complexes conserved in many different organisms,

but they also appear to function together as repressors in numerous developmental processes besides Hox-genes regulation. In *Arabidopsis* PcG proteins MEA, FIE, and FIS2 (homologues of E(z), Esc, and Su(z), respectively) work in a complex and control the initiation of seed development, flower organ development and vernalization (Wang et al., 2006). Whole mammalian PRC1 and PRC2 complexes and their individual members are implicated in hematopoiesis, X-chromosome inactivation, pluripotency and self-renewal of stem cells (Muller et al., 2002; Sun, 2005 Lee et al., 2006;), and their overexpression might result in various malignancies (Jacobs and van Lohuizen, 2002; Kuzmichev et al., 2005). MES-2 and MES-6 proteins of *C. elegans* (homologues of E(z) and Esc, respectively) form a stable complex and are required for gene silencing and germline development (Yang et al., 2007).

The mechanism of PcG repression is not yet decoded, but the fact that partnership of components of the PRC2 complex is conserved across the eukaryotic domain suggests that performed by E(z) methylation of H3K27 is crucial for PcG-mediated silencing. The main currently existing models of how PcG proteins maintain gene repression are shortly described in the next chapter.

PREs AND PROPOSED MECHANISMS OF PcG-MEDIATED REPRESSION

PcG proteins act on their target genes by binding to specific *cis*-regulatory elements called Polycomb Response Elements (PREs). Since these elements are able to maintain a defined state of gene activity during subsequent cell generations, they were also termed „cellular memory modules", or CMMs (Paro, Harte, 1996; Cavalli, Paro, 1998). In *Drosophila*, there are about 10 identified PREs like the Fab-7 and Mcp elements and over 100 PREs expected to be present, judging by the immunostaining data (Zink, Paro, 1989; Rastelli et al., 1993; Buchenau et al., 1998) and the results of a genome-wide sequence-based PRE prediction (Ringrose et al., 2003).

Functional versatility, evolutional conservation and abundance of PcG proteins suggest that PREs also exist in other taxa; however, so far no PREs were identified in mammals, worm or plants. Recently three genome-wide PcG profiling researches were made in mouse and human cells, using ChIP (chromatin immunoprecipitation) and high resolution oligonucleotide arrays (Boyer et al., 2006; Bracken et al., 2006; Lee et al., 2006). As a result, over 500 target sites of several PcG proteins have been identified, and although PRE elements were not found in these studies, these results will definitely speed up the search.

The detailed account on the structure of *Drosophila* PREs and their role in the maintenance of cell identity can be found in excellent papers written by Dr. Leonie Ringrose (Ringrose et al., 2003; Ringrose, Paro, 2004; Ringrose, Paro, 2007). However, despite our extensive knowledge about interactions of PcG proteins with their PREs and their role in gene regulation, the exact mechanism of PcG-mediated repression is not clear. Currently there exist several models of how PcG-mediated repression could be achieved; there are empirical and theoretical pros and cons for each model. Here we describe the main models and their background without attempting to judge which one is more likely than others. Basically, the existing models can be divided between *cis*- and *trans*- mechanisms of PcG regulation.

(**A**) The "*cis*" mechanism involves formation of repressive heterochromatin-like chromatin states and inhibiting the assembly or function of the transcription machinery (Busturia et al., 1997; Breiling et al., 1999; Francis, Kingston, 2001; Simon, Tamkun, 2002; Sengupta et al., 2004). This model has been the most popular one since the moment it was proposed. The Pc protein and the heterochromatin protein 1 (HP1) of *Drosophila melanogaster* have a common 30–50 amino acid domain — the chromo domain (Paro, Hogness, 1991; Koonin et al., 1995). They have different binding specificity: the chromo domain of HP1 binds with high affinity to histone H3 methylated at lysine 9 (Bannister et al., 2001; Lachner et al., 2001), while the chromo domain of Pc, which is more than 60 % homologous to that of HP1, specifically recognizes histone H3 methylated at lysine 27 (Fischle et al., 2003). It was also shown that Pc directly interacts with nucleosomal core particles *in vitro* (Breiling et al., 1999). Thus, it was suggested that PcG proteins package the DNA into a heterochromatin-like structure (Paro, Hogness, 1991; Messmer et al., 1992; Busturia et al., 1997; Breiling et al., 1999). Lately this model is not considered the most likely one (Stankunas et al., 1998; Wakimoto, 1998).

(**B**) The "*trans*-interaction" model proposes that PcG complexes assembled on PREs might interact with each other, bringing PREs together and thus forming nuclear subcompartments where the target genes are isolated from transcription factors and RNA polymerase (Pirrotta, 1995; Felsenfeld, 1996; Pirrotta, 1998; Breiling et al., 1999; Orlando, 2003). A modification of this model suggest that PRE DNA-looping interactions might change from promoter-enhancer to promoter-PcG interactions (Bienz, Muller, 1995; Pirrotta, 1998). Recently evidence of long-distance interactions between homologous CMMs and even of formation of so called "PcG bodies" in *Drosophila* (analogous to those in human cells) was published by two research groups (Bantignies et al., 2003; Grimaud et al., 2006; Vazquez et al., 2006). However, alternative data exist which suggest that such interactions are probably tissue- and development stage-specific (Rybakina, 2006; Fedorova et al, 2008;). Formation of so called "PcG bodies" in *Drosophila* nuclei also remains an open question, owing to pure technical difficulties of visualization and counting of tiny PcG foci which lead to controversial results (Buchenau et al., 1998; Ficz et al., 2005; Grimaud et al., 2006; Fedorova et al, 2008).

CONCLUDING REMARKS

Recent molecular phylogenetic studies allowed reconstruction of the phylogenetic tree of life of modern eukaryotes and demonstrated that their biodiversity is much greater than have been previously anticipated (Keeling et al., 2005; Roger and Hug, 2006). Metazoa and multicellular plants, which comprise most of the traditional objects in molecular biology, represent only two "apical branches" on the tree of life. They contain only the small part of eukaryotic biodiversity. Studying the evolution of genetic processes, and particularly evolution of the epigenetic transcriptional regulation, requires involvement of new objects. In the first place, these objects should be found among protozoan branches (lower eukaryotes, Table 1). Analysis of the phylogenetic tree indicates in which taxa we need to look for new model organisms for studies that will enable us to refine our current understanding of evolution of the epigenetic regulation and, possibly, will lead to discoveries of new mechanisms of this regulation.

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К пониманию механизмов эпигенетической регуляции: Часть I. Эволюционный взгляд на PcG-зависимую репрессию генов

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❀ **РЕЗЮМЕ: Эволюционно консервативные белки группы PcG обеспечивают стабильную эпигенетическую репрессию транскрипции, инициированную на более ранних этапах короткоживущими регуляторными белками. Точный механизм PcG-зависимой репрессии пока не расшифрован; в данной работе мы приводим существующие модели этой репрессии. Мы также кратко суммируем имеющиеся данные о белках группы PcG и их роли в различных процессах и рассматриваем эволюцию комплексов PRC1 и PRC2.**

❀ **КЛЮЧЕВЫЕ СЛОВА: белки группы PcG, эволюция, репрессия транскрипции, эпигенетическая регуляция**