Polycomb-like Proteins in Gene Regulation and Cancer

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Polycomb-like proteins (PCLs) are a crucial group of proteins associated with the Polycomb repressive complex 2 (PRC2) and are responsible for setting up the PRC2.1 subcomplex. In the vertebrate system, three homologous PCLs exist: PHF1 (PCL1), MTF2 (PCL2), and PHF19 (PCL3). Although the PCLs share a similar domain composition, they differ significantly in their primary sequence. PCLs play a critical role in targeting PRC2.1 to its genomic targets and regulating the functionality of PRC2. However, they also have PRC2-independent functions. In addition to their physiological roles, their dysregulation has been associated with various human cancers.

Keywords: Polycomb-like ; PHF1 ; MTF2 ; PHF19 ; cancer ; transcription ; leukemia

1. Introduction

Failures in chromatin and gene regulatory mechanisms can be the source of various human diseases [1]. Polycomb repressive complex 2 (PRC2) is a key component of the chromatin regulatory machinery of the cell [2][3]. The primary function of PRC2 is to add methyl groups to lysine 27 of histone H3 (H3K27) to establish H3K27 trimethylation (H3K27me3), which induces gene repression. PRC2 is particularly relevant for maintaining the correct gene expression pattern during development [2] and is often associated with cell differentiation [3].

Given its central role in gene regulation, dysregulation of PRC2 is commonly observed in various cancer types [2][4][5]. In solid tumors, such as prostate cancer, bladder cancer, and melanoma, high PRC2 activity is typically associated with aggressive and advanced disease progression [5]. Thereby, overexpression of PRC2 leads to the repression of tumor suppressor genes, which can contribute to the development and progression of these cancers [5]. In contrast, in some cancer types, such as in T-ALL (T-cell acute lymphoblastic leukemia) [6][7] and breast cancer [8], PRC2 activity is reduced, leading to enhanced expression of oncogenes.

In some cancer types, loss- or gain-of-function mutations of the core components of PRC2 are observed. Many mutations affect the histone methyltransferase EZH2, such as in hematologic malignancies [7][9][10][11], which globally influence the chromatin landscape [7][12]. Furthermore, the target of PRC2, the amino acid K27 of histone 3, can be altered. In pediatric glioblastoma, a mutation to methionine (H3K27M) is commonly observed [13][14] and prevents the efficient spread of H3K27me3, a requirement for tumorigenesis in this cancer type [15].

The activity of PRC2 is mainly determined by the expression of its core components, which facilitate the enzymatic deposition of the H3K27me3 mark. However, not only the PRC2 core determines the activity of PRC2 but also the associated factors influence the composition, recruitment, and functionality of PRC2.

2. Polycomb-like Proteins Are Key Components of the PRC2.1 Subcomplex

Research in recent years has demonstrated that mammalian PRC2 represents not a single complex but a variety of alternative complexes that possess a common core complex but differ in the accessory factors [16]. The number of PRC2 components has also considerably increased during evolution, leading to a greater variety of possible compositions of the mammalian PRC2 compared to nonvertebrate PRC2 [17].

The catalytic core of PRC2 consists of four components: The histone methyltransferase EZH2 is responsible for the deposition of the majority of the H3K27me3 histone mark. EZH1, the homolog of EZH2, is structurally similar to EZH2 but is less essential for H3K27me3 deposition [18]. Instead, EZH1 may play a role in chromatin compaction by establishing dimeric PRC2 [19]. EZH2 alone cannot perform efficient H3K27me3 methylation but requires additional factors [20]. Another critical component of PRC2 is SUZ12, which acts as a scaffold that brings all necessary proteins together [16][21]. It allows the binding of EZH2, EED, and one of the two highly homologous proteins, RBBP4 and RBBP7 [21]. RBBP4/7 are

structural components of the PRC2 complex, but are not required for its enzymatic activity [20]. EED also has a structural function [22]; additionally, it also recognizes the substrate of PRC2, H3K27me3, which is vital for the activity of PRC2 on chromatin [23]. Only the combination of EZH2, SUZ12, and EED establishes the necessary structural conformation that allows efficient methylation of histone proteins [16][22].

The PRC2 core complex is associated with additional proteins, establishing alternative subcomplexes [16][17]. The two major PRC2 subcomplexes are named PRC2.1 and PRC2.2 and are defined based on the proteins that are associated with the PRC2 core. The PRC2.2 subcomplex possesses JARID2 and AEBP2 [16][17] and will not be further addressed here. The defining characteristic of PRC2.1 is the presence of one of the PCL proteins, which is mutually exclusive to the binding of JARID2 and AEBP2 [17][24]. In the mammalian system, three PCL proteins exist: PHF1, MTF2, or PHF19 (alternative names are PCL1, PCL2, and PCL3, respectively). These three PCL proteins have evolved from the same ancestor protein, called Polycomb-like (Pcl) [25], and consequently have a similar domain composition [17]. They contain five different conserved domains.

3. Polycomb-like Proteins in PRC2 Chromatin Recruitment and Mammalian Gene Regulation

PCLs are crucial in targeting PRC2 to chromatin and, thus, important for gene repression. Deleting all three PCL homologs substantially reduces the chromatin association of PRC2 [26][27], suggesting that PRC2 chromatin binding strongly depends on the PCLs.

The PRC2 recruitment function of the PCLs particularly relies on the DNA-binding ability of their winged helix (WH) domains. The WH domain recognizes explicitly unmethylated CpG motifs via a positively charged region that reaches deeply into the major groove of the DNA [28]. The presence of methylated cytosine leads to a steric clash, preventing DNA binding [28]. This binding property is consistent with the common presence of PRC2 at unmethylated CpG islands in the genome [29]. Notably, the three PCLs proteins differ in their ability to interact with DNA. While MTF2 and PHF1 can strongly bind to DNA, the DNA binding function of PHF19 is more subtle [28]. Consistently, in mouse embryonic stem cells, the recruitment of PRC2 to CpG islands is particularly dependent on MTF2 [26], the most strongly expressed PCL protein in these cells. Consequently, mutation of the DNA-binding ability of MTF2 substantially reduces the PRC2 recruitment function of MTF2 in these cells [28].

The role of the other domains is less well understood. The Tudor domains of all three mammalian PCLs form a hydrophobic cage and have a high affinity for trimethylated lysine 36 of histone H3 (H3K36me3) [30][31][32][33]. PHF1 and PHF19 can also recognize the K27 trimethylation of the testis-specific histone variant H3t [34][35]. However, the binding strength of the Tudor domain to this modification is substantially lower than that for H3K36me3, suggesting that H3K36me3 is the preferred target of the Tudor domain. Nonetheless, the relevance of the H3K36me3 binding function of the Tudor domain remains controversial, given that H3K36me3 is a transcription elongation mark found in the gene body, and PRC2 typically does not colocalize with H3K36me3 in the genome. Thus, it is unclear whether this histone-binding ability is important for the chromatin recruitment of PRC2 or whether it may have another function related to H3K36me3. Given that H3K36me3 has been found to inhibit the enzymatic activity of PRC2 [36][37], the H3K36me3-binding function of the Tudor domain could potentially also play a role in inferring with the activity of PRC2 at active genes.

To recruit PRC2 to its target genes, the PCL must tightly interact with the PRC2 core complex. This function is facilitated via the very C-terminal chromo-like domain of the PCLs, which is necessary and sufficient for interaction with PRC2 [21][38]. The C-terminal domain is sequence-wise and similar between MTF2 and PHF19, consists of one helix and two β sheets, and shares some similarities with the chromodomains of HP1 (heterochromatin-protein 1) [38]. The C-terminal domain of PHF1 lacks the α helix [38], which may suggest some alternative structural functionality.

4. Polycomb-like Proteins in Human Cancer

An investigation of the role of the PCLs in cancer using publicly available databases suggests that the three PCLs have nonoverlapping roles in cancer. First, the expression changes in cancer versus normal tissue considerably differ between the proteins. PHF1 is predominantly downregulated in cancer, while PHF19 is largely upregulated [39], implicating a potentially opposing role of these two proteins. Indeed, when looking at all cancer types, high PHF1 expression is associated with a better prognosis, while high PHF19 expression is typically linked to a worse outcome. MTF2 expression is not strongly affected in most cancer types, and its expression does not correlate with patient survival. Notably, however, the pattern of the gene expression changes, and the correlation with patient survival is variable and dependent on the individual cancer type and on the investigated PCL protein. For example, a high PHF1 expression is linked to a worse

prognosis in colon adenocarcinoma (COAD) but a better prognosis in pancreatic cancer. In addition, only a few cancer types, such as ovarian cancer (OV) and thymoma (THYM), show a similar pattern for all three PCLs. In most other cancer types, the role of the PCLs is highly individual. In addition to changes in gene expression, all three PCL proteins are also commonly mutated in cancer [40].

4.1. Tumor-Suppressive and Oncogenic Roles of PHF1

Public data suggest that PHF1 is typically downregulated in many cancer types, and its low expression is often associated with a poorer prognosis. In addition, in some cancer types, such as carcinomas [40], frameshift mutations are commonly observed. This indicates a more tumor-suppressive role of PHF1. Indeed, several publications support this idea, and it has been shown that the tumor-suppressive function of PHF1 is linked to its ability to regulate p53-dependent pathways in cancer [41]. P53 is one of the most common tumor-suppressor genes in cancer, and inactivating mutations are often crucial for cancer development [42]. The interaction of PHF1 stabilizes p53 by preventing MDM2-dependent ubiquitination and proteasomal degradation [41]. Thus, the downregulation of PHF1 in cancer cells could be involved in reducing the protein level of p53 and thereby impairing its tumor-suppressor activity. Additional work suggests that the link between PHF1 and p53 depends on two unique serines in the N-terminal PHD finger of PHF1. These serines are not present in MTF2 or PHF19 [43], explaining why the interaction with p53 is restricted to PHF1. The PHF1–p53 axis is essential for inducing cellular quiescence and to prevent uncontrolled cell growth [43]. One mechanism that regulates PHF1 expression levels in cancer involves the RNA-binding protein FTO, which stabilizes the *PHF1* mRNA [44]. PHF1 has also been shown to be involved in DNA repair mechanisms via interaction with the Ku70/Ku80 heterodimer [32][45]. Therefore, PHF1′s tumor-suppressive role may also be linked to its ability to suppress DNA damage and thereby prevent harmful chromosome rearrangement.

4.2. PHF1 in Gene Fusions

In addition to the role of PHF1 itself, PHF1 is also commonly involved in gene rearrangements in some cancer types. To date, eleven in-frame gene fusions have been described. Most of these rearrangements were identified in ossifying fibromyxoid tumor (OFMT) or endometrial stromal sarcoma (ESS), both relatively rare cancer diseases.

OFMT is a soft-tissue tumor characterized by bone-like tissue formation within the tumor [46]. In approximately 50% percent of the OFMT cases, the PHF1 gene is rearranged [47], often with a transcription factor gene, such as *FOXR1* [48], *FOXR2* [48], or *TFE3* [49]. In these cases, the N-terminal chromatin-binding region of PHF1 is translocated to the transcription factor in frame, resulting in a transcription factor that possesses an additional chromatin-binding function. These fusion proteins lack the C-terminal PRC2-interacting domain of PHF1, suggesting that these fusion proteins act in a PRC2-independent manner. One could speculate that the fusion protein can be recruited to places normally targeted by PHF1, such as CpG islands [28]. The displaced transcription factor recruitment to these locations may lead to the dysregulation of target genes relevant to the development of OFMT. This idea is supported by the observed gene expression changes upon ectopic expression of a PHF1-TFE3 fusion protein [50].

4.3. A Predominantly Tumor-Suppressive Role of MTF2 in Cancer

To date, the physiological function of MTF2 has been predominantly linked to its role in stem cell maintenance and differentiation [28][51][52] and during hematopoiesis [53]. The cancer-related role of MTF2 appears rather versatile and can both promote and inhibit tumor growth.

In acute myeloid leukemia, a reduced level of MTF2 has been associated with increased chemotherapy resistance [54], thus resulting in a worse prognosis. In AML cells, it has been demonstrated that MTF2, together with PRC2, inhibits the expression of MDM2, a key regulator of the tumor suppressor p53. Consequently, it has been proposed that either overexpression of MTF2 or inhibition of MDM2 sensitizes the leukemic cells to chemotherapeutics [54], offering a potential new strategy for treating AML patients. A similar link between low MTF2 expression and increased resistance to chemotherapeutics has been shown in basal-like breast cancer cells [55]. Here, reduced activity of PRC2 led to the derepression of Nfat1c, which is important for epithelial–mesenchymal transition (EMT) and resistance to cytotoxic treatments.

4.4. The Oncogenic Role of PHF19

In contrast to PHF1 and MTF2, PHF19 has primarily been described as an oncogene in multiple cancer types [56]. Of note, in humans, but not in mice, PHF19 has a shorter isoform, which contains the Tudor domain and the first PHD finger but lacks the second PHD finger, the winged helix domain, and the PRC2-interacting chromo-like domain [57]. Consistently, this isoform does not interact with PRC2 [58], suggesting that this isoform has a distinct functionality from full-length

PHF19. Currently, many studies regarding PHF19 in cancer do not fully distinguish between these two isoforms, making the conclusion about the role of PHF19 in cancer less defined.

Initially, PHF19 was identified as a gene similar to Drosophila PCL, which shows elevated expression levels in cancer [57]. This upregulation is particularly evident for the short isoform but also measurable for the long isoform. The first functional study in cancer about PHF19 was performed in melanoma cells, where depletion of PHF19 leads to reduced proliferation but enhances invasiveness [59], suggesting a nontrivial role of PHF19. A similar role in regulating invasiveness was subsequently found in mammary tumors [60].

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