Zebrafish Model to Understand Epigenetics

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Contributor: Janina Müller-Deile

Epigenetic modifications are able to alter gene expression and include DNA methylation, different histone variants, and post-transcriptional modifications (PTMs), such as acetylation or phosphorylation, and through short/long RNAs, respectively. In this review, we focus on current knowledge concerning epigenetic modifications in gene regulation. We describe different forms of epigenetic modifications and explain how epigenetic changes can be detected. The relevance of epigenetics in renal diseases is highlighted with multiple examples and the use of the zebrafish model to study glomerular diseases in general and epigenetics in renal diseases in particular is discussed. We end with an outlook on how to use epigenetic modifications as a therapeutic target for different diseases. Here, the zebrafish model can be employed as a high-throughput screening tool not only to discover epigenetic alterations contributing to disease, but also to test novel substances that change epigenetic signatures in vivo. Therefore, the zebrafish model harbors the opportunity to find novel pathogenic pathways allowing a pre-selection of potential targets and compounds to be tested for renal diseases.

Keywords: zebrafish model ; epigenetics ; renal diseases ; microRNAs

1. Epigenetic Modifications

The term epigenetics describes patterns of modifications of the DNA, resulting in differential gene expression, while the genomic sequence is not altered. In general, there are three different modes of epigenetic modifications—DNA methylation, histone modifications, and posttranscriptional modifications through short/long RNAs (**Figure 1**).

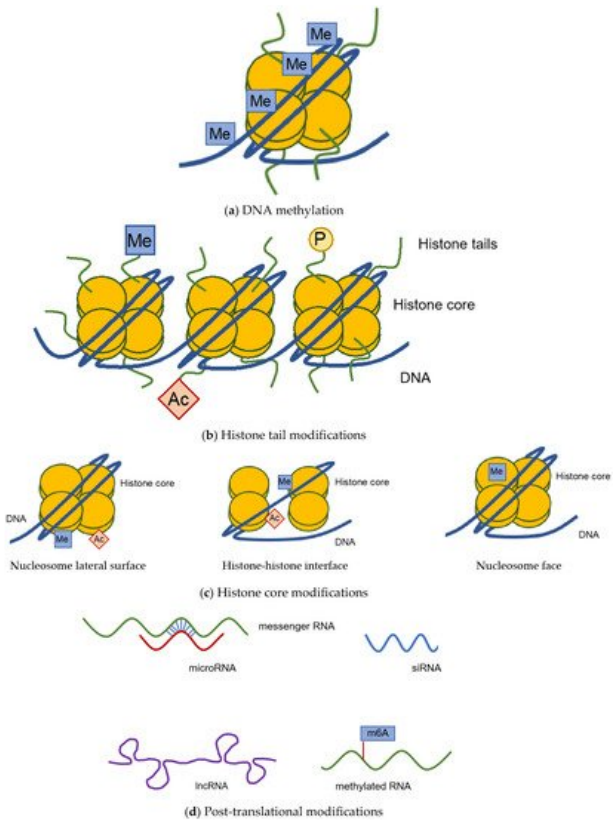

Figure 1. Schematic depiction of epigenetic modifications. Epigenetic modifications describe a set of different chemical alterations to either DNA, histones, or RNA that influence gene expression, without changing the genomic sequence. DNA is methylated (**a**) and the status of this methylation, as in hyper- or hypomethylation, has an impact on gene expression [1]. Furthermore, histones can be chemically modified on either their tails (**b**) or on the histone core itself (**c**). For histones, several modifications have been described, in addition to methylation, acetylation, phosphorylation, and SUMOylation

have also been found. Histone cores can be modified on their lateral surface, the histone–histone interface, or the nucleosome face [2]. (**d**) Post-translational modifications of RNA are mediated by microRNAs, small RNAs, such as siRNAs, or long non-coding RNAs. Methylation of mRNA molecules has also been described [3][4]. Figures adapted from [2][5].

1.1. DNA Methylation

By adding methyl groups to the DNA, transcription of the respective DNA segment is altered (**Figure 1**a). While most invertebrates display a mosaic pattern of DNA methylation throughout their genome, vertebrae genomes are predominantly methylated at CpG dinucleotides. Due to the high mutagenic potential of methylcytosine, which can deaminate spontaneously and cause cytosine to thymine transitions, the genome of vertebrates is in general CpG-poor. Yet, there are so-called CpG islands, which have a content of more than 50% of guanines and cytosines and are longer than 200 bp, that are usually unmethylated and represent key regulatory units. These are found predominantly in promoter regions of developmental and housekeeping genes. High DNA methylation is found in heterochromatin and repeat elements, while gene-distal regulatory elements, such as enhancers, which have a moderate CpG content, are differentially methylated depending on the type of cell. DNA methylation is involved in several physiologic processes, such as genomic imprinting, inactivation of the X chromosome, and aging and has been shown to be essential for development [1][6][7][8].

Methyl groups can be added to either adenine or cytosine, however, in mammals the most common and most studied form of methylation is that in CpG dinucleotides. Recently also non-CpG methylation has been described e.g., in embryonic stem cells, hematopoietic progenitor cells, or brain development [9][10][11].

DNA is methylated in defined regions spanning several 100 kb via DNA-methyltransferases (DNMTs). DNMT3A, DNMT3B, and DNMT3C are de novo methylation enzymes, which contain a highly conserved MTase domain and two chromatin reading domains. DNMT3L is catalytically inactive, but stimulates DNMT3A and B activity and interacts with those enzymes in the germline. Symmetrical CpG methylation is maintained in replication of DNA, this is facilitated by DNMT1 together with an E3 ubiquitin-protein ligase named UHRF1. Ten-eleven translocation (TET) enzymes are able to actively demethylate DNA and it has been shown that both DNMTs and TETs can be co-expressed, causing turnover of DNA methylation, a feature that has recently been described in the differentiation of pluripotent stem cells [7][8].

1.2. Histone Modification

In contrast to DNA methylation, modification of histones is more variable, as in addition to methylation, acetylation, biotinylation, SUMOylation, phosphorylation, and other chemical modifications can occur and the changes of these modifications are reversible, which means that gene transcription is repressed or enhanced. Enzymes involved in these processes include e.g., histone-deacetylases (HDACs), histone-acetyltransferases (HATs), and histone-methyltransferases (HMTs).

Histone modifications can alter the structure of the chromatin, making it more or less accessible for transcription [12].

Each histone represents an octamer of core histones, with two H2A–H2B dimers and one H3–H4 tetramer. DNA is wrapped around the core histone in 1.65 turns (~146 bp), forming a higher order structure, which is stabilized by H1, the linker histone.

Histone proteins are highly conserved and post-translational modifications occur on both the N-terminal tails and on globular domains. Histone tail modifications (**Figure 1**b), such as methylation at lysine 4 of histone H3 (H3K4), have been described to be involved in DNA repair, replication, and transcription, as well as indicating enhancer regions. However, these modifications do not affect chromatin structure itself, but are believed to either recruit or ward off proteins that bind specifically to post-translational modifications, which then facilitate the observed biological effects. Recently, histone core modifications (**Figure 1**c) on the histone lateral surface (e.g., H3 K122), histone–histone interface (e.g., H4 K91) and the solute-accessible face (e.g., H4 K59) have been identified. These are proposed to directly regulate the accessibility of nucleosomal DNA to regulatory factors and thereby contribute to changes in chromatin-dependent processes, such as DNA damage repair, transcription, and chromatin assembly [2][13][14].

1.3. Post-Transcriptional Modification

Gene expression can also be modified posttranscriptionally by non-coding RNAs (**Figure 1**d). These include microRNAs (miRNAs), short RNAs, and long RNAs. Short noncoding RNAs can be divided into three classes, namely microRNAs (miRNA), small interfering RNAs (siRNA), and piwi-interacting RNAs (piRNA). Long non-coding RNAs (lncRNAs) modify

gene expression on the chromatin level [3]. Short RNAs and lncRNAs interact with each other with reciprocal consequences for their fates and functions. piRNAs induce epigenetic and post-transcriptional silencing of transposons [15].

The principle of RNA interference mediated by siRNAs and miRNAs is based on three steps. First, long double-stranded RNAs are enzymatically processed into smaller fragments by RNase III enzymes (Dicer and Drosha). These double-stranded fragments are then separated, and the leading stand is loaded to the RNA-induced transcriptional silencing complex (RISC). The RISC is then able to find its targeted RNA and either inhibit or degrade it, whereas the small RNAs give the specificity and the Argonaut protein within the RISC conveys repression of translation. For siRNAs, Argonaut proteins cleave target RNA in several cycles, while the guide strand is bound. In the case of miRNAs, Argonaut proteins inhibit translation by staying associated with the target RNA or induce degradation of the poly-A tail of the target RNA, resulting in RNA degradation [16][17].

Furthermore, similar to DNA, RNA molecules can also be chemically modified. Here, N6-methyladenosin (m6A) was shown to be the most abundant from of modification in eukaryotic RNA. It is involved on many levels in mRNA processing, e.g., in mRNA degradation, but also in promoting mRNA translation and export from the nucleus. It has also been linked to human disease, e.g., neuronal disorders, viral infection, and inflammation [4][18]. In addition to mRNAs, functional RNAs, namely transfer RNAs (tRNAs) and ribosomal RNAs (rRNAs) are also chemically modified for stabilization and proper biological functions. While the exact pathological mechanisms are still elusive, changes in these modifications or their mediators have already been linked to human disease, e.g., dyskeratosis congenita [4][18].

2. Using the Zebrafish Model to Study Epigenetics in Renal Diseases

In recent years, the zebrafish (*Danio rerio*) model has been used to study glomerular function and disease [19][20][21][22][23]. The zebrafish larvae's pronephros, which is composed of two bilateral pronephric ducts linked with fused glomeruli in the midline of the larvae, is very similar to the human metanephros [24][25]. The pronephros tubular epithelium is composed of two proximal convoluted tubules, two proximal straight tubules, two distal early and distal late tubule segments, and a pronephric duct [26]. The main difference between the pronephros of the zebrafish and the mammalian partner is that the pronephros does not have a thin limb segment between the proximal straight tubule and the thick ascending limb. The glomerulus of the pronephros contains podocytes, glomerular basement membrane fenestrated endothelial cells, and mesangial cells [21]. Glomerular filtration begins as early as 48 h post-fertilization (hpf) and a fully functioning pronephros of zebrafish larvae is fully developed within 72 hpf [27][28].

At least 70% of zebrafish proteins have a human orthologue [29]. Furthermore, the zebrafish is very amenable to genetic manipulations though microinjections of morpholinos, DNAs, RNAs, and microRNAs [19][21][22][23][30][31][32][33][34].

Given its high genetic and renal similarity to humans the zebrafish has been used to study different renal diseases such as FSGS [35][36][37][38], polycystic kidney diseases [39][40][41], diabetic nephropathy [38][42], and renal cancer [43].

However, these manipulations can have effects on the developing embryo and observed phenotypes might not be specific to the tissue or organ of interest. Furthermore, injection of these molecules often has off-target effects, which are sometimes difficult to identify.

For more specificity, genetic editing techniques such as transcription activator-like effector nucleases (TALENs), zinc finger nucleases, and clustered regularly interspaced short palindromic repeat (CRISPR)-Cas9 can also be performed in the zebrafish [44][45][46].

The zebrafish has already served as a model to investigate epigenetic changes in hearing loss [47], development [48], and cancer [43][49][50] and in propagating secondary complications observed in diabetes mellitus [51]. However, though the zebrafish model has been used abundantly in kidney research, so far only few studies have focused on the epigenetic contribution to renal diseases in this versatile in vivo model [19][22][23][52].

2.1. DNA Methylation

It has been observed that loss of DNA methylation in developing zebrafish embryos upregulates LTR transposons, which were shown to be highly methylated in control larvae. This hints a direct contribution of DNA methylation in suppression of this type of transposable element [53]. Furthermore, dysregulated expression of stem cell transcription factor POU5F1 is part of a larger pattern of gene expression changes in renal cell cancer that may be induced by HIF-dependent reactivation of dormant promoters embedded within endogenous retroviral LTRs [54].

2.2. Histone Modifications

Ito et al. have demonstrated that in podocytes Wolf–Hirschhorn syndrome candidate 1-like 1 long form (WHSC1L1-L) acts as a histone methyltransferase and suppresses nephrin gene expression by binding to its promoter, probably by reducing H3K4 trimethylation. This alteration of nephrin expression might be involved in both acquired and congenital nephrotic syndrome [55]. The zebrafish model was also used to generate a bioinformatic pipeline in dissecting functions of kidney-disease-associated variants based on cell-type-specific epigenome including transcription-centered 3D chromatin organization and histone modifications [49].

2.3. Post-Transcriptional Modifications

Data on post-transcriptional regulation is more abundant concerning renal disease. siRNA-mediated gene-silencing techniques have been used to examine e.g., heart regeneration in zebrafish. In the study of Xiao et al., nanoparticles, which encapsulated a siRNA specific to *Aldh1a2* (aldehyde dehydrogenase 1 family, member A2), were injected into zebrafish hearts after resection of the apex of the ventricle and knock-down of the target gene was observed [56]. This method provides an alternative approach for determining gene functions in zebrafish and might be extended to other organs such as the kidney. Recently, we have shown that e.g., microRNA-26a-5p is increased in urine of preeclamptic patients, compared to healthy controls, and that miRNA-26a-5p overexpression in zebrafish leads to a phenotype comparable to that of preeclampsia, including proteinuria, edema, and podocyte foot-process effacement [23]. Among others, vascular endothelial growth factor A (VEGF-A) is an important target of miRNA-26a-5p and reduced VEGF-A levels are a hallmark of preeclampsia. We not only showed that overexpression of miRNA-26a-5p in zebrafish reduces vegf-A but also that injection of human VEGF-A protein was able to partially rescue the miRNA-26a-5p-induced phenotype [23].

We also observed that miRNA-143-3p decreased syndecan 3 and 4, as well as versican mRNA after overexpression in zebrafish larvae. These components of the glycocalyx that are produced by podocytes and glomerular endothelial cells have an important role in a well-functioning glomerular filtration barrier. Overexpression of miRNA-143-3p in zebrafish, by injection of a miRNA-143-3p, mimicked the one to four cell stage causing edema, podocyte effacement, loss of plasma proteins, and endothelial damage [22].

MiRNA-378a-3p targets podocyte nephronectin (NPNT), an extracellular matrix protein in the GBM. miRNA-378a-3p mimic injection, as well as npnt knockdown by a morpholino caused a similar phenotype consisting of edema, proteinuria, podocyte effacement, and widening of the glomerular basement membrane in zebrafish. Murine Npnt constructs containing a mutated 3′UTR region prevented the phenotype caused by miRNA-378a-3p mimic injection and indicated that the miRNA-induced changes in npnt caused the pathological findings. Biopsies from patients with FSGS and MGN showed increased miRNA-378a-3p expression and reduced glomerular levels of NPNT suggesting miRNA-378a-3p-mediated suppression of NPNT as a novel mechanism for proteinuria in glomerular diseases [19].

Epigenetic gene regulation and transcription-factor-mediated regulation share similarities, as usually both are involved in the regulation of gene expression. There is a tight interaction between epigenetic modifications and transcription factors as transcription factors can induce epigenetic changes and promoters of transcription factors have been found themselves to be modified by epigenetic regulators [57]. Several studies using the zebrafish model have been conducted to analyze transcription factor contribution to renal disease. For example, activation of P-TEFb by cAMP-PKA signaling was studied in autosomal dominant polycystic kidney disease (ADPKD) [58]. Furthermore, loss of vhl in the zebrafish pronephros recapitulates early stages of human clear cell renal cell carcinoma by stabilization of HIF1a and HIF2a, which up-regulates specific target genes involved in cell proliferation, angiogenesis, and erythropoiesis [58]. The transcription factor Dach1 was found to be important for podocyte differentiation and proper kidney function [59]. Finally, mutation in microphthalmia-associated transcription factor/melanogenesis-associated transcription factor (mitf) caused a significantly higher susceptibility for the disruption of the glomerular filtration barrier following puromycin treatment in zebrafish [52].

Table 1. Studies using the zebrafish model to study epigenetics and transcription factors in renal disease.

Study	Renal Disease	Epigenetic Mechanisms/Transcription Factors Involved	Results
“Overexpression of TGF-β Inducible microRNA-143 in Zebrafish Leads to Impairment of the Glomerular Filtration Barrier by Targeting Proteoglycans”; Müller-Deile et al. [22]	FSGS (focal segmental glomerulosclerosis)	Downregulation of versian and syndecan by miR-143-3p	Proteinuria, edema, and podocyte effacement
“Podocytes regulate the glomerular basement membrane protein nephronectin by means of miR-378a-3p in glomerular diseases”; Müller-Deile et al. [19]	Membranous glomerulonephritis	Downregulation of nephronectin by miR-367a-3p	Proteinuria, edema, podocyte effacement, and disrupted glomerular basement membrane
“Overexpression of preeclampsia-induced microRNA-26a-5p leads to proteinuria in zebrafish”; Müller-Deile et al. [23]	Preeclampsia	Downregulation of vascular endothelial growth factor A (VEGF-A) by miR-26a-5p	Proteinuria, edema, and glomerular endotheliosis
“Chromatin architecture reveals cell-type-specific target genes for kidney disease risk variants”; Duan et al. [49]	Risk variants for renal tumor and chronic kidney disease	Histone modifications of risk variants	Renal tumor and chronic kidney disease
“Activation of P-TEFb by cAMP-PKA signaling in autosomal dominant polycystic kidney disease”; Sun et al. [58]	ADPKD (autosomal dominant polycystic kidney disease)	cAMP-PKA signaling disrupts the inactive P-TEFb/HEXIM1/7SK snRNP complex	Cystogenesis
“Wolf–Hirschhorn syndrome candidate 1-like 1 epigenetically regulates nephrin gene expression”; Ito et al. [55]	Nephrotic syndrome	Wolf–-Hirschhorn syndrome candidate 1-like (WHSC1L1-L) acts as a histone methyltransferase and regulates nephrin gene expression	Reduction of nephrin mRNA
“Loss of vhl in the zebrafish pronephros recapitulates early stages of human clear cell renal cell carcinoma”; Noonan et al. [43]	Clear cell renal cell carcinoma	von Hippel-Lindau (vhl) inactivation leads to > Stabilization of hypoxia-inducible factors 1a and 2a (HIF1a and HIF2a) > Upregulation of specific target genes involved in cell proliferation, angiogenesis and erythropoiesis	Increased tubule diameter, disorganized cilia, cytoplasmic lipid vesicles, glycogen accumulation, aberrant cell proliferation, and abnormal apoptosis
“The transcription factor Dach1 is essential for podocyte function”; Endlich et al. [59]	Podocyte differentiation and proper kidney function	Transcription factor Dach1	Downregulation of nephrin, edema, and leakage of the filtration barrier
“Mutation of microphthalmia-associated transcription factor (mitf) in zebrafish sensitizes for glomerulopathy”; Müller-Deile et al. [52]	Glomerulopathy	Mutation in microphthalmia-associated transcription factor (mitf)	Increased susceptibility to edema, ptoteinuria, and podocyte effacement after puromycin treatment

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