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Review

Epigenetics of IgA Nephropathy: A Brief Review

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Abstract:

Immunoglobin A Nephropathy (IgAN) is the most common primary glomerulonephritis worldwide. Its development is characterized by the deposition of immune complexes that consist of abnormally galactosylated IgA1 molecules and IgG or IgA autoantibodies in the mesangium and the subsequent induction of renal injury. Recent research has shed light to many aspects of the pathogenesis of the disease, including the contribution of epigenetic modifications in its onset and progression. This review aims to present some of the most important epigenetic mechanisms mediating IgA1 development, including alterations in DNA methylation and histone modifications. Though a lot of progress has been made in this field, there is still much to be uncovered to have full understanding the full understanding of the epigenetics involved in IgAN, which can finally lead to a new, more promising approach to IgAN patients.

Keywords

IgA nephropathy (IgAN); epigenetics; DNA methylation; histone modifications; histone methylation; histone deacetylaces (HDACs); micro-RNAs (miRNAs)

1. Introduction

Immunoglobin A Nephropathy (IgAN) is the most common primary glomerulonephritis and its pathogenesis is mediated by a multi-hit process. Production of galactose-deficient IgA1 molecules (Gd-IgA1) by a subset of IgA1-secreting cells seems to play a key role in the development of the disease. In susceptible individuals, abnormal IgA1 glycosylation triggers the synthesis of anti-glycan IgG and IgA autoantibodies that recognize epitopes on the aberrantly galactosylated O-glycans in the hinge region of the heavy chains of IgA1. Circulating Gd-IgA1 forms immune complexes with the O-glycan-specific autoantibodies (Gd-IgA1-auto-Ab immune complexes), some of which deposit in glomeruli. This immune complex deposition is responsible for the activation of mesangial cells and the subsequent induction of cellular proliferation and overproduction of extracellular matrix and cytokines or chemokines, which gradually leads to the development of renal injury [1-3].

Epigenetics is defined as "the study of changes in gene function that are mitotically and/or meiotically heritable and that do not entail a change in DNA sequence" [4]. The term comprises all the processes that affect and modify gene activity without altering the DNA sequence and can be transmitted to daughter cells [5]. A great number of epigenetic mechanisms, such as DNA methylation and chromatin modification (e.g. through acetylation, phosphorylation, methylation, ubiquitination, and ADP ribosylation), have already been described, though a lot more progress in this field is expected to be made through future research [5, 6].

In this review we examine some of the epigenetic mechanisms that are involved in the development and the progression of IgAN.

2. DNA Methylation

In eukaryotic cells, cytosine methylation changes the chromatin state and is generally responsible for gene downregulation [7]. A whole-genome DNA methylation screening performed in CD4+ T-cells of IgAN patients demonstrated low methylation levels on Dual Specificity Phosphatase 3 (DUSP-3) and Tripartite Motif Containing 27 (TRIM27) genes, as well as Vault RNA 2-1 (VTRNA2-1) hypermethylation in comparison to healthy controls [8].

The DUSP3 gene encodes dual-specificity phosphatase (DUSP) 3, also known as Vaccinia H1-Related (VHR) phosphatase, which dephosphorylates and deactivates both members of the MAP kinase (MAPK) family (Extracellular Signal–Regulated Kinases 1/2 [ERK1/2], c-Jun N-terminal kinases [JNK], and p38 MAPK) and non-MAPK substrates (such as Signal Transducer and Activator of Transcription [STAT] 5, Epidermal Growth Factor Receptor [EGFR], and Erythroblastic Leukemia Viral Oncogene Homolog 2 [ErbB2]), thus being an important regulator of signaling pathways involved in cell survival, proliferation, differentiation, and cytokine production [9]. In T-cells, VHR inhibits the ERK and JNK activation caused by T-cell antigen receptor (TCR) and CD28 interaction [8].

TRIM27 is thought to be a negative regulator of CD4+ T-cells. It acts as a really interesting new gene (RING) E3 ubiquitin ligase and is responsible for the deactivation of Class II Phosphatidylinositol 3 Kinase C2β (PI3KC2β), which is an enzyme activated by the TCR, through polyubiquitination of lysine 48. Decreased PI3KC2β activity leads to inhibition of the KCa3.1 K^+ channel, which is important for CD4+ T-cell activation as it permits Ca^{2+} influx [8, 10].

As a result of the observed hypomethylation of the DNA regions encoding DUSP3 and TRIM27, these genes were overexpressed in the CD4+ T-cells of IgAN patients [8].

The VTRNA2-1 gene product is a non-coding vault RNA and has been identified as a precursor of micro-RNA-886 (pre-miR-886). Low pre-miR-886 levels (resulting from VTRNA2-1 hypermethylation) cause a decrease in the CD4+ T-cell proliferation rate following CD3/CD28 TCR stimulation, through interaction with Protein Kinase RNA-Activated (PKR). Moreover, downregulation of VTRNA2-1 leads to enhanced Transforming Growth Factor β (TGFβ) expression, which in turn reduces the effect of CD3/CD28 activation and impedes normal Ca^{2+} influx, thus having a negative impact on TCR strength and CD4+ T-cell proliferation and activation while promoting a T-cell anergy status [8]. At this point, it would be of great interest to mention that TGFβ1 has already been linked to IgAN pathogenesis, as it is known to be involved in IgA and IgG2 switching and increased IgA1 and IgA2 secretion in B-cells [8, 11]. The reduced TCR strength and the T-cell anergy-like status are consistent with the Th1 shift observed in several IgAN patients. That shift is partially responsible for the immunoglobin deposits in IgAN; additionally to IgAs (whose production is favored by the IgA-IgG2 switching caused by TGFβ overexpression), there are also IgG1 and IgG3 molecules (which are Th1 isotypes) found in the mesangium of those patients [8]. However, due to the wide range of the involved immunopathogenic parameters, clarifying the mechanism through which the Th1/Th2 ratio divergence contributes in the pathogenesis of human glomerulonephritis is often difficult. In IgAN, the precise role of Th1/Th2 imbalance is still a matter of controversy, as severe proliferative disease is associated with a Th1-predominant response, while the onset of IgAN may be related to a Th2-predominant environment [12]. Thus, more research needs to be done in order to define the involvement of aberrant DNA methylation in IgAN development via immune disorder.

Core 1 β3GalT specific molecular chaperone (Cosmc) is an endoplasmic reticulum (ER)-localized molecular chaperone, required for O-glycosylation of the correct protein [13]. Decreased Cosmc expression has been linked to IgA1-aberrant glycosylation observed in IgAN [14, 15]. Sun et al. [16] investigated the methylation levels of CpG islands (CGIs) of the Cosmc gene promoter as a possible factor involved in its downregulation. In their research, they proved that Interleukin 4 (IL-4) enhances the divergence in Cosmc mRNA levels between IgAN patients (who already demonstrate lower Cosmc mRNA expression) and healthy subjects or patients with other renal diseases. It also significantly increases Cosmc promoter methylation in B-lymphocytes of IgAN patients when compared to the other two groups where the increase is more moderate. These findings were consistent with those of Yamada et al. [17], who indicated that in IgAN, IL-4 production (possibly resulting from aberrant immunoregulation) downregulates both Core 1 β3-Galactosyltransferase (C1β3Gal-T) and its molecular chaperone, Cosmc. In addition, according to He et al. [18], the IL-4/STAT6 signaling pathway is overactivated in the tonsil tissues of IgAN patients. On the contrary, treatment with 5-Aza-2'-deoxycytidine (AZA) (which increases Cosmc mRNA levels) has a stronger impact on IgAN patients than in healthy controls and patients with other renal diseases and therefore reduces the differences in the mRNA levels among the three groups. AZA is a DNA methyltransferase (DNMT1) inhibitor. Interestingly, even though the elevation of Cosmc mRNA levels it induces is more significant in IgAN patients, the decrease it causes in Cosmc promoter methylation is less remarkable in the IgAN group in comparison to the other two groups. Furthermore, in the IgAN group (conversely to the other two) there is a very strong negative

correlation between Cosmc DNA methylation and Cosmc mRNA expression, thus indicating that the degree of methylation could possibly be a crucial element in the regulation of the mRNA levels [16]. However, according to Sun et al. [16] results, Cosmc promoter methylation is not significantly different in IgAN patients compared to controls, possibly suggesting that Cosmc mRNA production is not determined by the level of methylation of the promoter, but by the change in the methylation status.

Other areas that demonstrate a degree of aberrant methylation include Tyrosine-Protein Phosphatase Non-Receptor Type 2 (PTPRN2) and Interleukin 1 Receptor Accessory Protein-Like 1 (IL1RAPL1) genes, which are hypermethylated in IgAN patients. As we will mention below, these genes also present decreased levels of trimethylated histone H3 at lysine-4 (H3K4me3) [19].

3. Histone Methylation

Histone methylation controls gene transcription through alterations in the chromatin structure. H3K4me3 has been associated with gene activation [20].

The majority of human gene promoters lie within non-methylated CpG CGIs. It has been proposed that CGIs interact with CXXC Finger Protein 1 (CFP1) and other CpG-binding proteins, thus playing a crucial role in the trimethylation of H3K4 [20]. Sites of H3K4me3 are recognized by certain transcription-activating effector proteins and promote gene expression [19, 21]. It has been shown that in IgAN patients there are several sites that present aberrant H3K4me3 levels [19]. Four key relevant genes are analyzed below.

It has been found that in peripheral blood mononuclear cells (PBMCs) from IgAN patients, Fc Receptor-Like 4 (FCRL4) and Galactokinase 2 (GALK2) genes present greater accumulation of H3K4me3 in comparison to normal controls. FCRL4 is one of the several FcRL gene members clustered on the long arm of chromosome 1 and encodes FcRL4 glycoprotein, a bona fide Fc receptor that binds to IgA molecules [23]. It has been shown that Fc alpha Receptor I (FcαRI) activation is involved in the influx of macrophages and T-cells observed in the kidneys of IgAN patients and in the disease progression towards renal failure in an Fc Receptor Gamma (FcRγ)-dependent manner, possibly by inducing Tumor Necrosis Factor alpha (TNF-α) production [22]. Thus, Qi et al. suggested that the FCRL4 glycoprotein may have a similar function as FcαRI in IgAN pathogenesis [19].

As for GALK2, it encodes N-acetylgalactosamine (GalNAc) kinase, an enzyme that can catalyze the conversion of α-d-galactose to galactose 1-phosphate, although its most favorable substrate is GalNAc, against which it exhibits greater activity [24]. Biosynthesis of the hinge-region O-linked glycans of IgA1 begins with the addition of GalNAc and continues with the addition of galactose [25]. Qi et al. hypothesized that since GALK2 is important to normal galactose metabolism, its enhanced activation (which results from the presence of high H3K4me3 levels) could induce the low concentration of galactose and result in the undergalactosylation of IgA1 [19]. As stated before, poorly galactosylated serum IgA1 stimulates the production of glycan-specific IgG and IgA autoantibodies, which are essential to the creation of circulating IgA1 immune complexes that finally deposit in the glomerular mesangium [26].

On the other hand, low levels of H3K4me3 are found in PTPRN2 and IL1RAPL1. The enzyme produced by PTPN2 expression is a member of the Protein Tyrosine Phosphatase (PTP) family and opposes Protein Tyrosine Kinase (PTK) actions [19]. However, as some PTKs seem to participate in

the pathogenesis of several types of immune-mediated glomerulonephritis, possibly including IgAN [27], we could assume that PTPN2 downregulation plays a role in IgAN progression [19]. IL1RAPL1 encodes a member of the IL-1 Receptor (IL1R) family; despite the poor levels of H3K4me3, it is upregulated in IgAN patients, perhaps as a result of some other epigenetic mechanism. IL-1 cytokine family members seem to be involved in the deterioration of IgAN [19], as several IL-1 gene cluster Single Nucleotide Polymorphisms (SNPs) have been associated with increased susceptibility to IgAN in children (specifically rs1143627, rs3917356, and rs1143633 in the IL1B gene, and rs928940, rs439154, and rs315951 in the IL1RN gene), while rs1143627, rs3917356, and rs1143633 of IL1B also seem to be linked to the presence of podocyte foot process effacement. Moreover, development of proteinuria in IgAN is perhaps related to IL1A [28]. Since the action of IL-1 family members is mediated by IL1Rs, high expression levels of IL1RAPL1 might contribute to the disease progression [19].

It is clear that in IgAN patients there are significant differences in the H3K4me3 pattern [19], and there is a strong possibility that the genes mentioned above are involved in the disease pathogenesis. However, the exact mechanisms through which they mediate IgAN development have not been clarified yet and deserve further investigation.

4. Histone Deacetylaces and Fibrosis

The development of glomerular and tubule-interstitial scarring in the course of IgAN is a strong indicator of progression into end-stage renal disease [29]. Renal fibrosis is induced by several growth factors and cytokines that stimulate intracellular signaling pathways, such as the STAT3 pathway, or the SMAD2/3 pathway, which are responsible for the activation and proliferation of renal interstitial fibroblasts [30, 31]. It has also been observed that deposition of polymeric IgA1 (P-aIgA1) that occurs during IgAN increases the expression of Histone Deacetylace (HDAC)-1, -2, and -8 [31, 32].

HDAC mediates STAT3 pathway activation, as it is essential for STAT3 phosphorylation at tyrosine 705 and the subsequent formation of active STAT3 homodimers and heterodimers that translocate into the nucleus and control gene expression. The genes influenced by this regulatory mechanism are associated with tissue fibrosis and include α-smooth muscle actin, fibronectin, and collagen I genes [30].

SMAD2 and SMAD3 are proteins involved in signaling by TGF-β and activin and are also activated by HDAC [31, 33]. SMAD2 is a TGF-β-receptor-regulated signal transducer (R-SMAD) which, after activation, forms a heterocomplex with SMAD4, a co-mediator SMAD (Co-SMAD), and transfers into the nucleus, where it acts as a transcriptional modulator. SMAD3 is another R-SMAD that presents a great sequence identity with SMAD2, but as it has a different basal state, the state of the heterocomplexes it forms with SMAD4 differs, as well as its biological functions [33].

Therefore, HDAC inhibitors, such as trichostatin A (TSA) and valproic acid (VPA), can prevent fibroblast proliferation and activation by impeding STAT3 and SMAD2/3 action, thus delaying the development of fibrosis [30, 31].

5. Micro-RNAs and Epigenetics

Micro-RNAs (miRNAs) are small, single-stranded RNA molecules that bind to the 3'-untranslated region (3'-UTR) of their target mRNAs, thus negatively regulating their protein production [34, 35]. Over the past few years, there has been great progress in the research regarding miRNAs in the nephrology field, as they could possibly serve as non-invasive biomarkers for various kidney diseases [36, 37]. Nevertheless, it is still unclear whether divergence in their expression is tissue- and disease-specific or represents more general pathologies like inflammation. Their potential contribution in clinical practice needs to be further clarified [37].

In a study performed by Wu et al. aiming to find differentially-expressed miRNAs in peripheral plasma from IgAN patients, four miRNAs (miR-148a-3p, miR-150-5p, miR-20a-5p, and miR-425-3p) were found to be significantly upregulated in IgAN patients compared to healthy subjects. The study consisted of three phases (screening, training, and testing phase) and the diagnostic value of the four miRNAs in distinguishing IgAN patients from normal controls was assessed by the area under the receiver operating characteristic (ROC) curve (AUC), which was calculated by combining the data from the training and the testing stage. The AUCs were 0.66, 0.69, 0.65, and 0.64 for miR-148a, miR-150, miR-20a, and miR-425, respectively, while the combination of the four miRNAs increased the AUC value to 0.75. Moreover, the authors pointed out that there is a greater positive correlation between this miRNA upregulation and the presence of histological findings consistent with the earliest stages in the development of IgAN (IgAN grade I and II) than more advanced histological damage (IgAN grade III and IV). Therefore, they proposed that miR-148a, miR-150, miR-20a, and miR-425 could be candidate biomarkers for the clinical assessment of the disease, serving as potential indexes that would facilitate the early diagnosis of IgAN [38]. Of course, since the levels of some of the previously mentioned miRNAs may also be deregulated in other renal disease, more research needs to be done regarding their specificity for IgAN. For example, miR-148a and miR-150 expression levels are elevated in the blood serum and renal tissue biopsies of several patients with lupus nephritis (LN) [39-41].

It is not surprising that these miRNAs seem to be involved in the regulation of several immunological parameters. As analyzed below, that regulation is often mediated by epigenetic mechanisms.

More specifically, miR-150 is involved in the differentiation of stem cells towards megakaryocytes rather than erythrocytes, as well as T- and B-cell differentiation and the defense reaction [38]. Interestingly, a possible binding site for miR-150 is located within the 3'-UTR of Specificity Protein 1 (Sp1) mRNA. Its product, Sp1, is a zinc finger protein that acts as a transcription factor, binding to GC-rich regions of promoters that affect various cellular processes including cell differentiation, cell growth, apoptosis, immune response, response to DNA damage, and chromatin remodeling [42]. As for its involvement in epigenetics, Sp1 interacts with HDAC1 and induces gene transcription inhibition and also affects DNA methylation. More specifically, it binds DNMT1, which finally represses the targeted genes; it also contributes to the maintenance of a methylation-free state in CGIs of several gene promoters [43].

MiR-148a is possibly involved in B-cell tolerance regulation by reducing the expression of growth arrest and DNA damage 45a (GADD45a), phosphatase and tensin homolog (PTEN), and BCL2-like 11 (BCL2L11) (which encodes the pro-apoptotic factor Bim) [44]. GADD45a is one of the

three members of the GADD45 family. GADD45 proteins play an important role in autoimmune and tumor suppression and are responsible for DNA gene-specific demethylation in response to stress, nuclear hormones, and induced differentiation. Their impaired expression has been linked to immune deficiencies and enhanced tumorigenesis [45]. PTEN is a well-known tumor suppressor protein. Among its other functions, it seems to affect gene expression profiles by preserving chromatin condensation through interaction with histone H1 and repression of acetylation of histone H4 at lysine 16 (H4K16 acetylation) [46]. Through suppression of GADD45a, PTEN, and BCL2L11, miR-148a averts immature B-cell apoptosis that is induced by B-cell receptor (BCR) engagement. As expected, miR-148a dysregulation contributes to the development of autoimmune diseases [44].

MiR-20a binds to the 3'-UTR of E2F transcription factor 1 (E2F1) mRNA and inhibits its action [47]. E2F1 is an activator of transcription and since many of its target genes are known to promote cell cycle progression, its role as a cell proliferation inducer has been primarily emphasized. However, recent studies have shown it exhibits a great functional diversity, as it also regulates processes such as apoptosis, DNA damage repair, stress response, differentiation, and metabolism. Among other functions, E2F1 has been found to recruit transformation/transcription domain-associated protein (TRRAP), a common component of many histone acetyltransferase (HAT) complexes, in order to promote H3 and H4 acetylation. Moreover, it associates with the AT-rich interaction domain 1B (ARID1B) subunit of SWItch/Sucrose non-fermentable (SWI/SNF) nucleosome remodeling complex (an ATP-dependent chromatin remodeler), thus engaging it to mediate the activation of some cell cycle genes [48]. As a regulator of E2F1, miR-20a is thought to be involved in the body's immune inflammatory response [38].

MiR-425 levels are also linked to cell-mediated inflammation and apoptosis [38], but there are not yet enough data regarding its exact interaction with epigenetic mechanisms.

Several other miRNAs have also been proposed as potential markers for IgAN. For example, a retrospective international study by Serino et al. highlighted the importance of a combined biomarker, miR-148b-3p and let-7b-5p, in the detection of primary IgAN. This study also consisted of three phases (training, validation, and testing stage) and the miR-148b and let-7b specificity for IgAN was supported by their ability to discriminate IgAN patients from patients with other forms of primary glomerulonephritis in the testing phase, using the combined measurement of their serum levels (AUC, 0.76). Of course, even though this combined miRNA signature presented a high diagnostic accuracy for IgAN, its clinical utility as a biomarker needs to be further assessed for reasons analyzed above.

Both miR-148b and let-7b are key modulators of the O-glycosylation process of IgA1 [49]. More specifically, miR-148b regulates the enzyme Core 1 β1, 3-galactosyltransferase 1 (C1GALT1), which catalyzes the second step in the biosynthesis of the hinge-region O-linked glycans of IgA1 (i.e. the addition of galactose). The G1GALT1 gene was found to be downregulated, while miR-148b levels were significantly higher in the PBMCs of IgAN patients compared to normal controls. Moreover, miR-148b levels negatively correlated with the G1GALT1 expression levels [25]. Let-7b negatively regulates the enzyme N-acetylgalactosaminyltransferase 2 (GALNT2), which is responsible for the addition of N-acetylgalactosamine (which is the first step in the glycan biosynthesis). Low expression of GALNT2 observed in PBMCs of IgAN patients was associated with high expression of let-7b [50]. Given their important role in the pathogenesis of the disease, further research

regarding miR-148b and let-7b function, including possible epigenetic mechanisms regulating their expression or mediating their actions, would perhaps provide new promising therapeutic targets.

6. Discussion

IgAN is characterized by abnormal galactosylation of IgA1 molecules, synthesis of IgG and IgA autoantibodies, deposition of Gd-IgA1-auto-Ab immune complexes in the mesangium, and induction of renal injury. Important steps have been made towards the understanding of the epigenetic mechanisms that contribute to the pathogenesis of IgAN.

Aberrant DNA methylation seems to contribute to the development of IgAN. In CD4+ T-cells derived from IgAN patients, the DUSP-3 promoter and TRIM27 3'-UTR are hypomethylated, while VTRNA2-1 demonstrates high methylation levels. These modifications lead to the overexpression of DUSP-3 and TRIM27 and downregulation of VTRNA2-1. These 3 genes are regulators of intercellular pathways involved in T-cell survival, activation, proliferation, differentiation, and cytokine production. PTPRN2 and IL1RALP1 are also hypomethylated in IgAN patient cells. Moreover, it is possible that changes in the methylation status of the Cosmc gene promoter (whose methylation levels, interestingly, are not significantly different in IgAN patients compared to healthy controls) determines Cosmc mRNA levels. The Cosmc gene codes for an ER-localized molecular chaperone and its decreased expression has been linked to IgA1 abnormal glycosylation.

Another possible mechanism includes alterations in the accumulation of H3K4me3 (which is considered responsible for gene activation) in several DNA sites. In IgAN patient cells, FCRL4 and GALK2 genes present high concentrations of H3K4me3 and are overexpressed. On the contrary, PDPRN2 and IL1RAPL1, encoding a protein tyrosine phosphatase and an IL-1 receptor respectively, exhibit low levels of H3K4me3. Interestingly, however, IL1RAPL1 is downregulated in IgAN.

The development of renal fibrosis in the course of IgAN is also partially mediated by epigenetic mechanisms. HDAC overexpression is induced by P-IgA1 deposition and activates pathways such as STAT3 and SMAD2/3 that promote the activation and proliferation of renal interstitial fibroblasts.

Lastly, miRNAs, such as miR-150, miR-148a, miR-20a, and miR-425 that are found at higher levels in the peripheral plasma of IgAN patients (and could be candidate non-invasive biomarkers for the assessment of the disease) can reduce the expression of factors that mediate cell differentiation and growth, apoptosis, metabolism, immune response, response to DNA damage, and chromatin remodeling through epigenetic modifications (including changes in DNA methylation and histone acetylation, interacting with nucleosome remodeling complexes, etc.).

Although the progress we have made in clarifying the pathogenesis of IgAN is remarkable, the future seems much more promising. Epigenetic modifications in IgAN patients need to be further examined, as they offer valuable information regarding mechanisms involved in the development of the disease and reveal possible targets for new treatments. We hope that future advances in the fields of epigenetics will eventually lead us to a more efficient approach towards IgAN patients.

Author Contributions

Stamatia Stai did all the research work for this study.

Competing Interests

The author has declared that no competing interests exist.

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