Epigenetic Mechanisms in Inflammation

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ABSTRACT

Epigenetic modifications occur in response to environmental changes and play a fundamental role in gene expression following environmental stimuli. Major epigenetic events include methylation and acetylation of histones and regulatory factors, DNA methylation, and small non-coding RNAs. Diet, pollution, infections, and other environmental factors have profound effects on epigenetic modifications and trigger susceptibility to diseases. Despite a growing body of literature addressing the role of the environment on gene expression, very little is known about the epigenetic pathways involved in the modulation of inflammatory and anti-inflammatory genes. This review summarizes the current knowledge about epigenetic control mechanisms during the inflammatory response.

KEY WORDS: epigenetics, histone modifications, DNA methylation, inflammation.

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INTRODUCTION

Epigenetics is defined as the study of mitotically and meiotically heritable changes in gene function that are not dependent on DNA sequence (Feinberg, 2007). The molecular basis of epigenetic processes is complex and involves modifications of histones, methylation of DNA, positioning of histone variants, and gene regulation by non-coding RNAs. Epigenetic modifications are potentially reversible, and, therefore, a thorough understanding of these changes may identify new therapeutic targets for disease.

The epigenome, the overall epigenetic state of an organism, is just as important as the genome to normal development. Importantly, environmental factors (nutrients, toxins, infections, hypoxia) can have profound effects on the epigenetic signature (Fig. 1) and trigger susceptibility to disease (Barros and Offenbacher, 2009; Safronova and Morita, 2010). For example, recent studies have shown that the fetal environment can cause changes in the epigenome, with long-term consequences for gene regulation and age-related diseases (Thompson and Einstein, 2010). The studies by Bobetsis *et al.* (2006) showed that periodontal infection can lead to placental-fetal exposure and, when coupled with a fetal inflammatory response, leads to preterm delivery.

INFLAMMATION

Inflammation is a complex physiological response of an organism to harmful stimuli, such as pathogens, damaged cells, or irritants. In acute inflammation, the initial response of the body to a stimulus is achieved by increasing the migration of leukocytes and plasma from the blood to the injured areas. When inflammation has a slow onset and persists for a long period of time, it becomes chronic. The symptoms in chronic inflammation are not as severe as in acute inflammation, but the condition is persistent. Chronic inflammation underlies many diseases, including periodontal disease and diabetes mellitus (Dunning, 2009).

The complexity of the inflammatory response requires the development of a sophisticated regulatory network to carry out functions at signal-specific and gene-specific levels (Medzhitov and Horng, 2009). This network involves the activation of specific genes for antimicrobial defense, immune response, and tissue repair and remodeling (Medzhitov, 2008). Macrophages play critical roles in diverse chronic diseases, including cancer and allergic responses, and analysis of recent data indicates that chromatin modifications are mechanistically important in the acquisition of the macrophage phenotype (Khansari *et al*., 2009). Transcription factors of the NF-κB, FOXP3, IRF, and STAT families along with epigenetic phenomena, including DNA methylation and covalent histone modifications, have been shown to be critical in the regulation of inflammatory genes (Medzhitov and Horng, 2009). In addition, several of these regulatory factors are controlled by epigenetic mechanisms in T-cells and monocytes (Lal *et al*., 2009; Wells, 2009; Wierda *et al*., 2010).

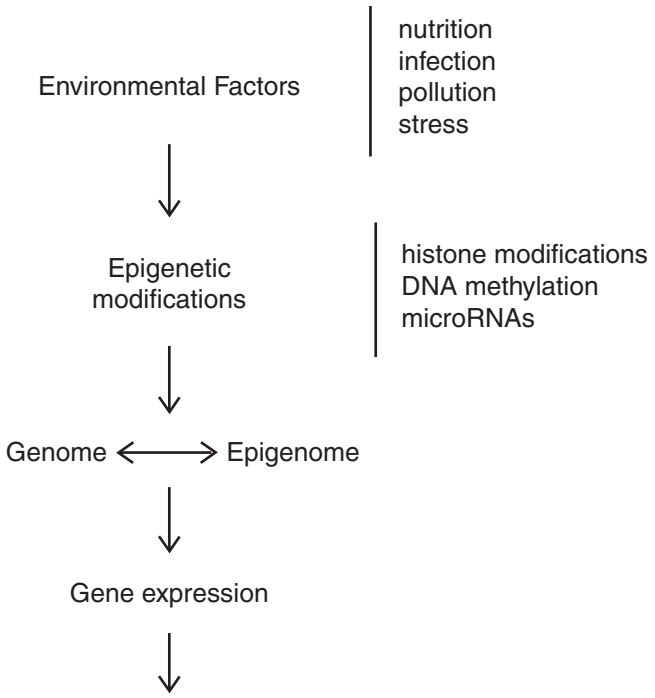

Figure 1. Environment and the epigenome. Differential expression of genes is dependent on chromatin organization. This organization is composed of DNA, nucleosomes, non-histone proteins, transcription factors, chromatin-modifying enzymes, and regulatory RNAs collectively known as the epigenome. The epigenome is sensitive to stress, toxins, nutrition, infections, and other environmental factors with long-term consequences for gene regulation and age-related diseases.

HISTONE MODIFICATIONS

The basic unit of chromatin, the nucleosome, consists of a short segment of DNA wrapped around core histones made up of two copies of H2A, H2B, H3, and H4. This organization provides a rigid structure to chromatin (Campos and Reinberg, 2009). The covalent modification of histones is an essential epigenetic mechanism of gene regulation. These post-translational modifications (methylation of lysines and arginines, acetylation, phosphorylation, ubiquitination, SUMOylation, and ADP-ribosylation) occur most frequently at the N-terminal tails of the core histones (Fuchs *et al*., 2006).

Acetylation of histones is associated with an "open" chromatin conformation that facilitates transcription (Campos and Reinberg, 2009; Cheng and Blumenthal, 2010). The acetylated N termini protruding from the nucleosome core provide reduced affinity for the DNA, allowing the chromatin to adopt a more relaxed structure for the recruitment of the basic transcription machinery. For example, the acetylated histone marks H3K4ac and H3K39ac are associated with transcriptional activation. Histone acetyltransferases (HATs) such as CREB-binding protein CBP and its close homolog p300 carry out these modifications (Timmermann *et al*., 2001). Histone deacetylases (HDACs) reverse HAT activity by making chromatin more condensed and by promoting gene repression. Histone methylation, in contrast, can keep chromatin in either an activated or a repressed state. Tri-methylation of histone H3 on lysine 4 and 36 (H3K4me3 and H3K36me3) facilitates an open chromatin for active transcription (Barski *et al*., 2007). By contrast, histone methylations on lysines 9 and 27 (H3K9me3 and H3K27me3) are generally associated with a condensed chromatin and gene silencing (Lan and Shi, 2009). Genes with bivalent modification (H3K4me3 and H3K27me3) are typically important developmental regulators in pluripotent embryonic stem (ES) cells or multipotent progenitor cells which are silenced, but are poised for activation, as differentiation proceeds (Bernstein *et al*., 2006; Mikkelsen *et al*., 2007). Enhancers, which determine tissue-specific gene expression, are marked by histone H3 lysine 4 mono-methylation (H3K4me1) and by the histone acetyltransferase co-factors CBP/p300 binding (Heintzman *et al*., 2007; Visel *et al*., 2009). Methylation of histones is carried out by histone methyltransferases (HMT) and demethylation by histone demethylases (HDM) such as members of the Jumonji protein family (Cheng and Blumenthal, 2010).

HISTONE METHYLTRANSFERASES

The Polycomb Group (PcG) proteins play an essential role during development and differentiation (Kerppola, 2009; Morey and Helin, 2010). In mammals, there are two classes of complexes, designated Polycomb Repressive Complexes 1 and 2 (PRC1 and PRC2). PRC1 is formed from 4 proteins, RING1, CBX family, PHC, and BMI1/MEL18. The core components of PRC2 are EZH2/EZH1, EED, RBAP48/46, and SUZ12 (Simon and Kingston, 2009; Morey and Helin, 2010). PRC2 regulates transcriptional repression by catalyzing the di- and tri-methylation of lysine 27 on histone H3 (H3K27me2/3). Recent genome-wide mapping studies revealed that PRC1, PRC2, and H3K27me3 occupy the same sites at the regulatory regions of several developmentally important genes, including members of the *Dlx, Hox, Pax, Sox, Gata,* and *Tbx* families (Kerppola, 2009; Simon and Kingston, 2009; Morey and Helin, 2010). The binding of PRC1 to chromatin is usually dependent on the activity of PRC2. However, PRC2 may use different recruitment mechanisms to target different downstream genes (Peng *et al*., 2009; Shen *et al*., 2009; Landeira *et al*., 2010; Li *et al*., 2010; Pasini *et al*., 2010). PRC2 forms a stable complex with the transcriptional repressor JARID2, a member of the Jumonji C (JmjC) and ARID domain protein family (Cheng and Blumenthal, 2010). JARID2 binds to the PcG-responsive sites through the DNA-binding domain ARID (Fig. 2B) for many PRC2-regulated genes. PRC2 can also be recruited to target promoters by non-coding RNAs (Zhao *et al*., 2008; Khalil *et al*., 2009).

DNA METHYLATION

DNA methylation is the covalent transfer of a methyl group from S-adenosyl-L-methionine to cytosines in CpG dinucleotides (Herman and Baylin, 2003; Weber and Schübeler, 2007). Mammalian genomes are punctuated by DNA sequences containing a high number of CpG sites termed CpG islands, which

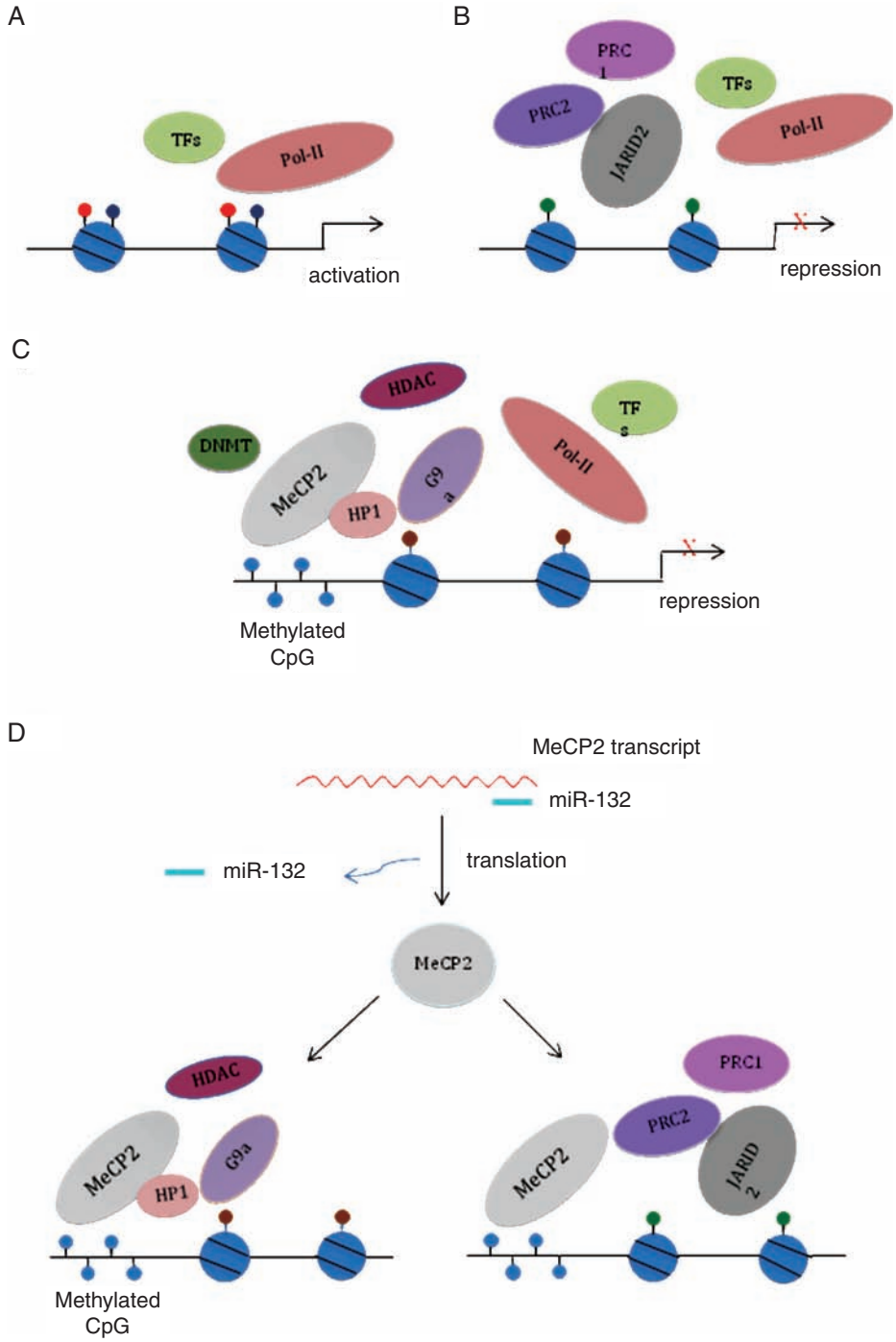

Figure 2. Epigenetic mechanisms of gene repression. **(A)** The open chromatin structure of an active gene with an unmethylated promoter region. The nucleosomes have activation marks such as acetylation (red circles) and H3K4 methylation (blue circles). The RNA Polymerase complex (Pol-II) and transcription factors (TFs) bind to the promoter and initiate transcription. **(B)** Gene repression by the Polycomb repressive complexes (PRC1 and PRC2) is mediated by the DNA-binding protein JARID2 and accompanied by H3K27 methylation (green circles), loss of H3K4 methylation, and deacetylation of nucleosomes. **(C)** DNA methylation (light blue circles) is mediated by the HP1-dependent recruitment of DNA methyltransferases (DNMTs) and the H3K9 methyltransferase G9a. Methyl-binding proteins (MeCP2 or members of the MBP family) bind to the methylated DNA and recruit histone deacetylase complexes (HDACs). Brown circles indicate H3K9 methylation. Overall, gene silencing is accompanied by the chromatin compaction, loss of histone activation marks, and removal of transcription factors. **(D)** An epigenetic mechanism dependent on microRNA, MeCP2, and Polycomb. In hepatic stellate cells, translation of the MeCP2 transcript is blocked by miR-132. Upon myofibroblast transdifferentiation, down-regulation of miR-132 enables activation of MeCP2, which binds to the PPARγ promoter and recruits H3K9 histone methyltransferases and the HP1 repressor. In addition, MeCP2 stimulates chromatin condensation by recruiting PRC1 and PRC2. This eventually leads to repression of the PPARγ transcription.

lack DNA methylation and associate with the majority of known gene promoters (Illingworth and Bird, 2009). In eukaryotes, the methylated CpG islands are found in non-coding regions of the genome associated with transcriptional repression (Jones and Liang, 2009), including developmental genes, repetitive sequences, and germ-line specific or imprinted genes. The changes in DNA methylation, such as hypomethylation, very often are associated with chromosome instability and activation of transposable elements in human cancers (Cheung *et al*., 2009). DNA methylation is catalyzed by a family of closely related DNA methyltransferases (DNMT1, DNMT3a, and DNMT3b) (Hermann *et al*., 2004). DNMT1 is a maintenance methyltransferase and is the most abundant DNA methyltransferase in mammals. It predominantly adds methylation to DNA when one strand is already methylated (hemi-methylated) (Jeltsch, 2006). The methylated DNA can recruit the methyl-CpG-binding domain proteins Kaiso, MeCP2, and members of the MBD family (Fig. 2C), which recognize 5-methylcytosines in CpG islands and participate in chromatin silencing (McCabe *et al*., 2009).

It is important to note that DNA methylation and histone methylation are tightly controlled events in eukaryotes (Cheng and Blumenthal, 2010). The histone H3 N-terminal tail with an unmethylated lysine 4 (H3K4) is required for DNA methylation (Hu *et al*., 2009). In addition, tri-methylation of histone H3 on lysine 9 (H3K9me3) participates in DNA methylation mediated by DNMT1 (Rottach *et al*., 2010). The NP95 protein, which contains SET-, Ring-, and Tudor domains, is responsible for linking DNMT1 with DNA and histone H3 methylation (H3K9me3). Therefore, NP95 coordinates two major epigenetic silencing pathways, DNA methylation and histone methylation (Rottach *et al*., 2010).

EPIGENETIC EVENTS IN INFLAMMATION

Histone Methylation and Inflammation

Jmjd3, a member of the Jumonji family, is an inducible enzyme that erases histone marks. This protein was recently found to control differentiation and cell identity in macrophages, and therefore provides a link between inflammation and reprogramming of the epigenome (Ishii *et al*., 2009). Jmjd3 is induced in macrophages exposed to bacterial products and inflammatory cytokines, where it binds the PcG target genes and regulates their H3K27me3 levels and transcriptional activity (De Santa *et al*., 2007). Continuous IL-4 treatment leads to activation of Jmjd3 and the release of H3K27me3 repressive marks from the STAT6 promoter. Activated STAT6 positively regulates Jmjd3 by binding to its promoter. Removal of H3K27 methylation marks by Jmjd3 triggers expression of specific inflammatory genes.

However, work by De Santa *et al*. (2009) revealed that Jmjd3 acts also through a H3K27 demethylation-independent mechanism. According to this study, Jmjd3 is preferentially recruited to transcription start sites characterized by the presence of the activation marker H3K4me3 and the presence of RNA Polymerase II complex. This study found that the binding of Jmjd3 to target genes is not accompanied by H3K27 demethylation. These findings indicate that reciprocal exchange in H3K4 and H3K27 methylation can be an important epigenetic process for the control of genes.

The mammalian genome contains several PcG target genes critical in development and differentiation (Bernstein *et al*., 2006; Mikkelsen *et al*., 2007). It was reported recently that some of these targets are subject to aberrant DNA methylation following chronic inflammation (Hahn *et al*., 2008). It was shown that PcG proteins bind to the regulatory regions of target genes and recruit DNMTs (Fig. 2D) for more efficient repression. Another pathway leading to gene repression was recently described for NF-κB/RelB-dependent silencing in severe systemic inflammation (SSI) caused by sepsis and other acute inflammatory processes (Chen *et al*., 2009). Induction of RelB by endotoxin activation is necessary and sufficient to repress acute pro-inflammatory genes. During SSI, RelB represses these genes by inducing heterochromatin formation through direct interaction with the histone H3 lysine 9 (H3K9) methyltransferase G9a. This interaction leads to trimethylation of histone H3 on lysine 9 (H3K9me3) and subsequent recruitment of heterochromatin protein 1 (HP1). HP1 and G9a form a repressive complex at the promoters of RelB-dependent genes (Fig. 2D) and lead to the recruitment of DNMT3a/b and CpG methylation. This cooperative interaction of histone methylation and DNA methylation in response to SSI was recently reported for the TNFα promoter in blood leukocytes (El Gazzar *et al*., 2008).

Histone Acetylation and Inflammation

Histone acetylation by HATs activates inflammatory genes, whereas increased HDAC activity results in inflammatory gene repression. In chronic obstructive pulmonary disease, airway biopsies, and alveolar macrophages, increased acetylation of histones at the promoter region of inflammatory genes is mediated by NF-κB. The increase in histone acetylation is associated with decreased histone deacetylase (HDAC) activity. For example, promoters of several pro-inflammatory cytokines (IL-1, IL-2, IL-8, and IL-12) are rapidly acetylated by CBP/p300, leading to transcriptional activation, and display reduced HDAC activity (Villagra *et al*., 2010). The recruitment of HDACs, in contrast, leads to histone deacetylation and gene repression. HDACs regulate transcription of both pro- and anti-inflammatory cytokines through their recruitment to gene promoters *via* co-repressor complexes and transcription factors such as FOXP3, STATs, GATAs, ZEB1, and NF-κB (Villagra *et al*., 2010).

NF-κB is tightly controlled by the IκB kinase complex IKK-α in response to cytokine treatment (Ghosh and Karin, 2009). IKK-α binds to the NF-κB-dependent promoters with the assistance of the Polymerase II complex and CBP, where it acetylates histone H3 at Lys9 (Yang *et al*., 2009) and phosphorylates histone H3 at Ser10 (Anest *et al*., 2003). This cytokine-induced phosphorylation is critical for the subsequent CBP-mediated acetylation of histone H3 on Lys14 (Yamamoto *et al*., 2003). Acetylation of histone H3 at the promoters of several cytokines and chemokines after inflammation results in the increased recruitment of NF-κB to these regions (Barnes, 2009). Glucocorticoid receptor (GR) and HDAC2 can reverse this process, thus

promoting repression of NF-κB-dependent inflammatory genes (Barnes, 2009).

DNA Methylation and Inflammation

DNA methylation is important in the regulation of inflammatory genes. Promoter hypomethylation of the Toll-like receptor 2 (*TLR2*) gene is associated with increased pro-inflammatory response to bacterial peptidoglycan in cystic fibrosis bronchial epithelial cells (Shuto *et al*., 2006). DNA methylation and histone acetylation regulate *TLR4* in intestinal epithelial cells (Takahashi *et al*., 2009). DNA methylation and histone modifications play an important role in the establishment of the epigenetic landscape across the TNFα locus (Sullivan *et al*., 2007). Environmental factors including bacterial infection were shown to contribute to the epigenetic status of the genome (Barros and Offenbacher, 2009). DNA methylation of imprinted genes plays an important role in fetal development. For example, bacterial infection induces hypermethylation in the promoter of the *Igf2* gene in mice (Bobetsis *et al*., 2007). Expression microarray studies in mice demonstrated that maternal infection was associated with changes in placental expression of key developmental genes, including several imprinted genes (Bobetsis *et al*., 2010). Chronic colonization of the human stomach by *Helicobacter pylori* (HP) causes inflammation within the gastric mucosa and activates multiple oncogenic pathways (Ding *et al*., 2010). HP induces alterations in the DNA methylation pattern in gastric epithelial cells (Niwa *et al*., 2010). Katayama *et al*. (2009) showed that HP-induced DNA methylation in the *Runx3* locus causes loss of expression in gastric epithelial cells.

MicroRNAs and Inflammation

MicroRNAs (miRNAs) are small non-coding RNAs that negatively regulate the expression of target genes at the post-transcriptional level. miRNAs are transcribed as long preliminary transcripts and, after cleavage by the Drosha and Pasha complexes in the nucleus, translocate to the cytoplasm to be processed by Dicer into 18- to 24-bp miRNA duplexes. The RNA-induced silencing complex (RISC) incorporates these short RNA duplexes and binds to the 3′ untranslated region (3′UTR) of specific messenger RNAs for subsequent degradation or translational repression.

Recent investigations implicated miRNAs in the regulation of development, differentiation, and disease (Friedman *et al*., 2009; Sonkoly and Pivarcsi, 2009). miR-146a limits Toll-like receptor signaling by blocking the signaling molecule TRAF6 (Taganov *et al*., 2006), and miR-155 targets the lipid phosphatase SHIP1 (O'Connell *et al*., 2009), an important signal for macrophage activation. miR-132 has anti-inflammatory effects by binding acetylcholine (ACH) mRNA, a critical inhibitor of peripheral inflammation (Shaked *et al*., 2009). The exposure of cultured macrophages to lipopolysaccharide (LPS) leads to up-regulation of miR-155, which targets the mRNA for CCAAT/enhancer binding protein Beta (C/EBP Beta), implicated in the regulation of pro-inflammatory cytokines during macrophage activation and the acute phase response (Worm *et al*., 2009). Studies by Liu *et al*. (2009) demonstrated that the induction of miR-147 by TLR prevents excessive inflammatory response through a negative-feedback loop mechanism. TLR stimulation induces miR-147 and requires activation of both NF-κB and IRF3. Furthermore, miR-147 attenuates the TLR-induced inflammatory response in macrophages (Liu *et al*., 2009). In another study, miR-105 was shown to modulate TLR-2 translation in human gingival keratinocytes (Benakanakere *et al*., 2009). It was recently suggested that the TLR4-dependent reprogramming of inflammatory genes is mediated by two distinct levels of regulation (El Gazzar and McCall, 2010). The first level is transcriptional control mediated by epigenetic modifications, and the second level is regulated by the TLR4-dependent differential expression of miRNAs (miR-221, miR-579, and miR-125b).

About 30% of all human genes are estimated to be potential miRNA targets (Lewis *et al*., 2005; Xie *et al*., 2005). Among them are genes encoding the epigenetic markers EZH2, DNMT3a and DNMT3b, and HDACs (Valeri *et al*., 2009). miR-29 can reverse aberrant methylation in lung cancer by targeting DNMT3a and DNMT3b (Fabbri *et al*., 2007), and miR-143 regulates DNMT3a in colorectal cancer (Ng *et al*., 2009). miR-29 promotes osteogenesis by targeting HDAC4 (H Li *et al*., 2009), and miR-2861 controls osteoblast differentiation by repressing HDAC5 (Z. Li *et al*., 2009). The cartilage-specific miR-140 regulates HDAC4 (Tuddenham *et al*., 2006), and MiR-449a targets HDAC1 in prostate cancer (Noonan *et al*., 2009). However, the action of microRNA on epigenetic markers can be indirect. One example of this is the viral microRNA K12–4-5p, which blocks the retinoblastoma (Rb)-like protein 2 (Rb12) transcript, a known repressor of DNMT1, 3a, and 3b mRNA levels (Lu *et al*., 2010). Expression of EZH2 is blocked by miR-101 (Varambally *et al*., 2008; Friedman *et al*., 2009), miR-26a (Sander *et al*., 2008; Wong and Tellam, 2008), and miR-214 (Juan *et al*., 2009). In the latter case, EZH2, the catalytic subunit of PRC2, and miR-214 establish a negative regulatory loop controlling PcG-dependent gene expression. PcG proteins repress transcription of miR-214 in undifferentiated skeletal muscle cells. Differentiation coincides with the PcG disengagement and activation of miR-214 transcription. miR-214, in turn, targets EZH2 (Juan *et al*., 2009).

In summary, we considered three different epigenetic processes of gene repression: DNA methylation, histone modifications, and targeting by microRNAs. Recently, an epigenetic relay pathway was described to explain the repression of PPARγ transcription (Mann *et al*., 2009). This pathway (Fig. 2D) is dependent on a precisely controlled mechanism, which involves MeCP2, EZH2, and miR-132. The authors showed that down-regulation of miR-132 caused the release of the MeCP2 translational block. Consequently, MeCP2 mediates histone H3 methylation on Lys9 and Lys27 (H3K9 and H3K27) through the recruitment of HP1/G9a and PRC1/2 complexes at the PPARγ promoter region (Mann *et al*., 2009).

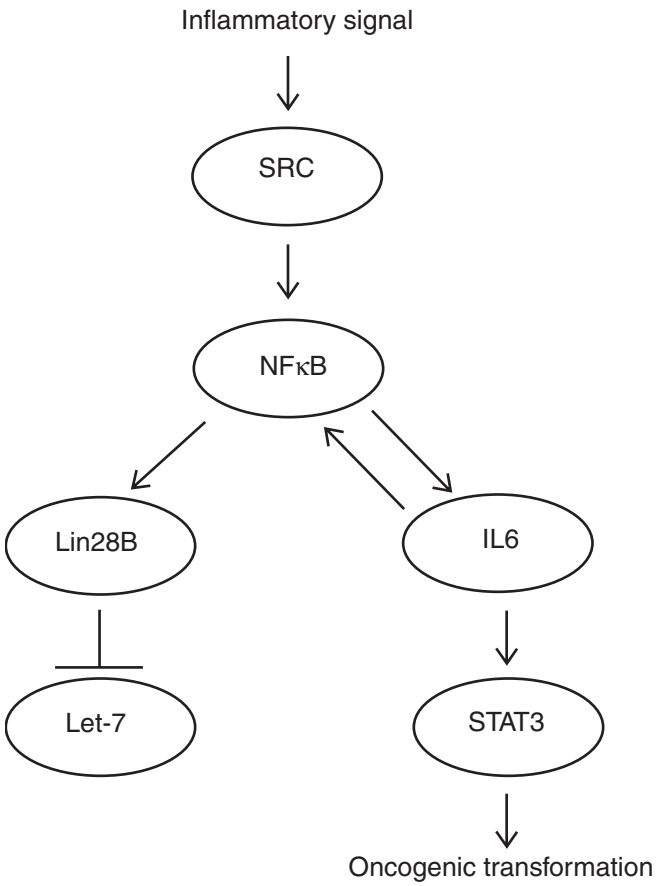

Figure 3. The regulatory circuit during oncogenic transformation. NF-κB, IL6, let-7 microRNA, and Lin28B are key components of the positive feedback loop underlying the epigenetic switch from normal to transformed cells. The switch is induced by an initial inflammatory signal (Src activation) that activates NF-κB, which turns on IL6 transcription and inhibits let-7 microRNA *via* Lin28B. The resulting high levels of IL6 activate NF-κB, thereby completing the positive feedback loop that maintains the transformed phenotype.

INFLAMMATION AND CANCER

Inflammation contributes to the initiation and development of cancer (Rajput and Wilber, 2010). Until recently, the mechanistic aspects of this phenomenon were not clearly understood. The study by Iliopoulos *et al*. (2009) addressed this question by proposing a model that links inflammation to the oncogenic transformation. This model, based on a positive feedback loop mechanism, involves key molecular players: NF-κB, RNA-binding protein Lin-28, let-7 microRNA, and IL-6 cytokine (Fig. 3). Activation of the Src oncoprotein triggered the inflammatory response critical for cellular transformation *via* a NF-κB-dependent mechanism (Page *et al*., 2009). NF-κB activated transcription of Lin-28, which in turn inhibited the let-7 microRNA. let-7 repressed cellular transformation by blocking IL-6. Therefore, NF-κB activation and subsequent repression of let-7 resulted in a dramatic increase of IL-6, which is necessary for cellular transformation. STAT3 is a key IL-6 target that mediates oncogenic transformation.

EPIGENETICS IN HUMAN DISEASES AND AGING

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease characterized by the progressive destruction of articular cartilage and bone. Studies showed that epigenetic modifications such as genomic DNA methylation, histone acetylation, and miRNAs contribute to the pathogenesis of RA (Strietholt *et al*., 2008; Maciejewska Rodrigues *et al*., 2009; Brooks *et al*., 2010). The global DNA methylation pattern in RA synovial fibroblasts was shown to be reduced compared with that of cells derived from healthy controls (Karouzakis *et al*., 2009).

Several studies have suggested a central role for chronic inflammation in the pathogenesis of chronic obstructive pulmonary disease (COPD) and lung cancer (Bowman *et al*., 2009; Lee *et al*., 2009; Yao and Rahman, 2009). Recent evidence implicates epigenetic modifications in the development of tolerance in macrophages and T-cell function (Adcock *et al*., 2007). Reduced HDAC2 expression and activity are reported in lung macrophages, biopsies, and blood cells from patients with COPD, severe asthma, and smoking asthma (Adcock *et al*., 2007).

Age-associated changes in immune response increase the risk of infection and promote inflammation and increased reactivity to self-antigens and cancer. It has been suggested that age-associated hypomethylation of the DNA may be the cause of chronic inflammation and cancer (Agrawal *et al*., 2010). El Mezayen *et al*. (2009) showed the age-dependent up-regulation of the *IL-23p19* gene expression associated with H3K4 methylation in dendritic cells.

Periodontitis is a multifactorial infection characterized by inflammation and destruction of tooth-supporting tissues (Gomez *et al*., 2009). The levels of prostaglandin E and the prostaglandin-endoperoxide synthase-2 (PTGS2) increase in progressing periodontal lesions, but decrease in chronic disease. It was reported that expression of the *PTGS2* gene decreases in chronic periodontitis due to promoter hypermethylation (Zhang *et al*., 2010).

CONCLUSIONS

Knowledge about alterations in histone modifications, DNA methylation, and microRNA regulation will provide a better understanding of the molecular basis for various chronic inflammatory diseases. Progress in studies of epigenetic alterations during inflammatory response opens opportunities for the development of efficient medications for specific targets. Among the drugs currently proposed for epigenetic therapy are histone deacetylase inhibitors and demethylating agents, which target chromatin in rapidly dividing tumor cells and restore normal cell functions (Karberg, 2009). The integration of the latest technological achievements in whole-genome microarray expression profiling and chromatin immunoprecipitation-based sequencing (ChIP-seq) methods will be instrumental in the development of epigenetic drugs with greater specificity.

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