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Histone deacetylase: A potential therapeutic target for ovarian dysfunction

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1. ABSTRACT

Post-partum uterine disorders and reproductive tract infections cause ovarian dysfunction and infertility. Histone deacetylases (HDACs) prevent the relaxation of chromatin, and positively or negatively regulate transcription. Hence, HDACs play a pivotal role in altering the gene expression that impact different signalling pathways underling ovarian dysfunction. Thus, HDAC inhibitors (HDACi) may act as potential therapeutic targets in the treatment of an array of disorders impacting ovarian function.

2. INTRODUCTION

Ovarian dysfunction is a major cause of infertility in females both in humans and animals. Some common causes of ovarian dysfunction are repeated breeding, anoestrus, ovarian cyst and the infectious diseases such as, metritis, submetritis, endometritis and mastitis, which are collectively called as postparturient disorders. The incidence of reproductive disorders varies in different dairy animals. For instance, reproductive disorders in buffaloes range from 4.66% to 12.66% (http://www.buffalopedia.cirb.res.in/). Similarly, genital tract disorders appear at different time intervals of postpartum. Metritis may occur within a week of postpartum in nearly 40% of cattle (1), endometritis can occur beyond 3 weeks of postpartum in 15 to 20% of cattle (2) and subclinical endometritis, a chronic inflammation of uterus without clinical signs, may occur in about 30% of cattle (2–4). Such disorders predominantly with microbial infections can cause infertility by disrupting uterine and ovarian functions. Metagenomic analysis with 16S rRNA identified a wide population of bacteria in normal and postpartum

endometritic buffaloes (5). Bacterial endotoxins, DNA and lipids are known to initiate a signaling cascade in host cells via Toll-like receptors (TLR4), resulting in the production of various pro-inflammatory cytokines, chemokines, anti-microbial peptides and various transcription factors. Activation of pro-inflammatory cytokines as a result of TLR response was reported to modulate the primary function of granulosa cells, such as steroidogenesis (6,7). Such changes could slow down the follicular development and lead to ovarian dysfunction.

Transcriptional regulation plays a central role in the molecular mechanism of any pathophysiology, including the ovarian dysfunction. It is influenced by the manner in which DNA is packed. Histone is the building block of chromatin, a protein-DNA complex into which the DNA is packed. Post-translational modifications of histones affect the chromatin structure. Acetylation, the most widespread of such modifications, is a key modulator of chromatin structure and thus, it is a modulator of gene expression. On the other hand, deacetylation of histones acts against acetylation and thus opposes the changes brought by the acetylation of histones. Different classes of histone deacetylases (HDACs) play a crucial role in TLR mediated signalling and inflammation (8). This available information is not surprising if one considers the central role of HDACs as key regulators of chromatin structure and post-translational modifiers of numerous key proteins in cells and tissues. Various HDAC inhibitors (HDACi) have roles in inflammation and ovarian dysfunction, but the mechanism of their action is not understood.. The present review aims to discuss the questions “how microbial infection and reproductive disorders induced ovarian dysfunction leads to infertility in females?” and “how HDACs are involved in fertility?” Towards this aim, the present review accounts for the role of different HDACs in TLR signalling, inflammation and ovarian function. Finally, the review discusses the selectivity of currently used HDACi and their molecular mode of action in the treatment of different diseases.

3. OVARIAN DYSFUNCTION AND ITS CAUSES

Ovarian dysfunction is the most frequent cause of female infertility. It denotes a problem related to timely release of an egg or ovulation. It can be categorized into three groups namely anovulation, oligovulation and late ovulation. Anovulation means the absence of ovulation, in which fertilization is not possible. Oligovulation is irregular ovulation, which reduces the chances of fertilization. Late ovulation seems to produce low quality eggs, which lowers the fertility. Cattle, which fail to ovulate by the voluntary wait period of 40 to 60 days of postpartum, and those initiate ovulation but entering into a phase of anovulation prior to a breeding period, are said to be suffering from ovarian dysfunction. The following are some of the major causes responsible for ovarian dysfunction.

3.1. Anestrus

Anestrus, a common functional disorder of the reproductive cycle, is characterized by the lack of expression of heat or estrus signals in dairy animals at proper time which ultimately leads to ovarian dysfunction (9). Its incidence is more in buffaloes than in cattle during severe summer. It is a multifactorial problem. It signals the problems, like inadequate nutrition, environmental stress, uterine pathology, scarce peripartum nutrition and improper managemental practices. During postpartum, initial stages of ovarian follicular growth are usually not affected by anestrus, but the subsequent stages of follicle development are affected. However, a healthy periparturient period and proper treatment can prevent this problem to an extent. Many hormonal and non-hormonal therapeutic agents have been used to treat this condition. However, no treatment is available for permanent cure of this condition. Better understanding of its etiology and prevention needs research in the following three areas: the role of peripartum disease conditions that influence reproduction, genes involved in ovulation, and the influence of proteins (e.g., leptin) that appear to be important links between metabolic signals and the neuroendocrine axis (10).

3.2. Ovarian cyst

Ovarian cyst is one of the most common postpartum ovarian diseases responsible for ovulation failure and infertility in dairy animals (11–15). In dairy cows, it is currently defined as cystic ovarian follicular structure of at least 17mm diameter which persists for at least 6 days in the absence of corpus luteum (13,16–25). Uterine infections and endometritis lead to ovarian cysts. Endotoxins released by pathogens in the uterine lumen are reported to perturb the LH surge in cattle, resulting into ovarian cyst formation (26). Different diagnostic approaches used to detect an ovarian cyst include the history of animals, clinical signs, transrectal palpation (27), ultrasonography (28) and plasma or milk progesterone assay (29). Some of the earliest treatments of ovarian cyst include: manual rupture, ovariectomy, injections of ovarian extract and CL extract, uterine infusions of antibiotics or antiseptics and injections of adrenaline chloride and pituitrin (30–33). Endocrine based treatments include the administration of steroids (34), gonadotropins (33,35–37) and GnRH (36,38–40).

3.3. Post-parturient disorders and infections

Mastitis, metritis, submetritis and endometritis are post-parturient disorders. Mastitis

is the infection of the mammary gland or udder (41). Metritis is the infection of the uterine wall, its underlying glandular tissues and the muscular layer (42–44). Endometritis is the infection of the functional lining of the uterus (45–47). The later two disorders usually lack systemic signs (48). Prolonged endometritis can lead to endometriosis, which can also lead to premature ovarian failure that further leads to ovarian dysfunction. Pathogenic organisms like gram negative bacteria adhere to the uterine mucosa, penetrate into the epithelium and release endotoxins like lipopolysaccharides (LPS) into the blood circulation. Endotoxins thus carried into ovarian follicular fluid cause ovarian dysfunction and prolonged acyclicity. Persistence of infections can lead to ovarian carcinoma, which increases the degree of problems with ovarian dysfunction. This review mainly focuses on the infection induced ovarian dysfunction. Therefore, microbial infections leading to infertility and their mechanisms are dealt in detail in the following part.

4. UTERINE INFECTIONS LEAD TO OVARIAN DYSFUNCTION

Bacterial infections of the genital tract and mammary gland are responsible for many diseases of dairy animals (49–52) that can lead to ovarian dysfunction. Postpartum uterine infection is one such global problem, mostly in high yielding dairy animals. It causes inflammation of the uterus like metritis and endometritis. Usually, mammalian uterus is prone to bacterial infections during coitus and parturition (53) mainly during the first 5 weeks of postpartum (54). Moreover, infections of the reproductive system at calving cause prolonged acyclicity and reduced fertility upon artificial insemination, resulting in enhanced calving interval. Pathogenic organisms, mostly gram negative bacteria, in such infections adhere to the uterine mucosa, penetrate into the epithelium and release endotoxins like LPS into the circulation. These chemicals enter into ovarian follicular fluid to cause ovarian dysfunction and prolonged acyclicity (54). Persistent uterine infection reduces immune efficiency (55), which results into impaired functioning of the uterus and poor embryonic development (44). Moreover, the uterine bacterial inflammation interrupts the hypothalamo-pituitary function, ovulation, ovarian follicle development and luteal function (49,55–57). Slower follicular growth, scarcer ovulation, and lower estradiol concentration are the chief characteristics of the inflammatory diseases, like metritis and endometritis. In addition, infections in the mammary gland lead to mastitis in dairy animals which play a role in reducing the conception rates and infertility.

Uterine infections also depend upon the load and the type of attacking bacteria, animal species and their immunity. A wide range of bacterial species, both Gram-positive and Gram-negative along with aerobes and anaerobes, were isolated from the early postpartum infected uterus (58). Infections with pathogens like *Escherichia coli*, *Corynebacterium pyogenes*, *Streptococcus*, *Staphylococcus*, *Pseudomonas*, *Bacillus*, virus, fungi and mycoplasma are known to cause uterine infections. *Archanobacterium pyogenes*, *Fusobacterium necrophorum* and Bacteroides species are also associated with uterine infection in dairy animals. These organisms either alone or in combination with other bacteria cause uterine inflammation (58).

5. MICROBIAL INFECTIONS AND INFERTILITY: MECHANISM

Microbial infections of the genital tract cause infertility by disrupting uterine and ovarian functions. Many mechanisms which trigger the recognition of microbial pathogens by innate immune system have been identified in mammals during the last few years. Bacterial infections mediate their effects on host via Pathogen Associated Molecular Patterns (PAMPs), like peptidoglycans and LPS etc. present on their surface. Bacterial endotoxin, LPS, a major component of gram-negative cell wall is reported to accumulate in follicular fluid during infection (52). Bacterial endotoxins, DNA and lipids are recognized by TLR4 in host cells in an efficient manner and initiate a complex signaling cascade to activate pro-inflammatory cytokines (TNF-alpha, IL6, IL1beta), chemokines (IL8, CCLS, CXCL5 and (CXCL8) and anti-microbial peptides, including TAP, DEFB5 and DEFB1 (53,59) and also various transcription factors. Our studies and several other studies indicate the possible evidence of the expression of TLR4 on granulosa cells (7). LPS, through TLR4, activated the pro-inflammatory cytokines production and thus modulated the primary functions of granulosa cells, such as steroidogenesis (6,7).

According to the recent reports, estradiol production is chiefly affected by LPS due to the down-regulation of *CYP19A1*, a candidate gene encoding aromatase enzyme that catalyzes the final rate-limiting step in E2 biosynthesis, in bovine (52) and buffalo granulosa cells (60). The down-regulation of *CYP19A1* leads to slower follicular development and fertility impairment. In infected animals, luteal phases are often extended as the endometrial epithelial secretion of prostaglandins switches from the F to E series by a phospholipase A2 mediated mechanism, which would disrupt luteolysis. The endometrial immunity regulation mainly depends on estrogen, progesterone, somatotrophins and local regulatory proteins production (1). Ovulating dairy animals with uterine infections have lower peripheral plasma progesterone concentrations, which can reduce the chances of conception.

6. HISTONE DEACETYLASES (HDACs) AND THEIR BASIC MECHANISM OF ACTION

Histone deacetylases (HDACs) are a part of a complex family of multi-subunit enzymes. They deacetylate the histone proteins and compact the chromatin, and thus, restrict the binding of transcription factors at the gene specific promoter regions, which in turn prevents the gene expression (61). Thus, they play multi-faceted roles to control and coordinate the interactions of intracellular signaling pathways. These controls are influenced by the manner in which DNA is packaged with chromatin (62), a highly organized and dynamic nucleoprotein complex, which acts as a binding site for various transcriptional modulators. The accessibility of DNA to regulatory elements is controlled by these transcriptional modulators, which modify the chromatin structure. The basic structural unit of chromatin (63), the nucleosome, contains a histone octamer that consist of two copies of each H2A, H2B, H3, H4 ((H3-H4)2 tetramer flanked by H2A and H2B dimers), attached by 146bp of linker DNA (64,65). The presence of amino acid residues (lysine and arginine) within histone tails is associated with a variety of modifications that modulate chromatin structure, and thus gene transcription. Therefore, these modifications can have positive as well as negative effects (66,67). Architecture of chromatin is directly influenced by post translational modification of histones such as methylation, acetylation and phosphorylation. Deacetylation by HDACs counters acetylation, and thus it acts as an important modulator of chromatin and transcription.

Histone acetylation is a complex dynamic and reversible process, which reduces the affinity of the histones for DNA. The acetylation possibly reduces the interaction among nucleosomes, leads to the formation of the 30 nm chromatin fiber and promotes an open chromatin conformation, which facilitates transcription (68,69). Acetylation of ε-amino groups of lysine residues within histone tails neutralizes their positive charge, which in turn allows the chromatin to adopt a more relaxed structure for the recruitment of basic transcriptional machinery. On the other hand, deacetylation of lysine residues within histone tail is associated with chromatin compaction, leading to transcriptional gene silencing (62,64,65,70). Both acetylation as well as deacetylation of transcription factors can have positive as well as negative impacts on gene expression. Acetylation of histones creates a docking site for binding of other proteins containing a bromodomain. Histone acetylation is controlled by two large families of enzymes namely, the histone acetyltransferases (HATs) and the histone deacetylases (HDACs). The enzymes of these two families are antagonistic in their action. The balance between their actions plays a crucial role in chromatin remodeling and gene transcription (62). These enzymes, thus, are assumed to regulate various biological processes, like epigenetic changes, inflammation, ovarian function, fertility and a disease state.

7. CLASSIFICATION OF HISTONE DEACETYLASES (HDACs)

There are 18 histone deacetylases (HDACs) broadly grouped under two families, named as “Classical” and “Sirtuins” (also called Silent information regulator 2 or SIR2). Classical HDACs have different phylogenetic classes, namely class I (HDAC1, HDAC2, HDAC3, HDAC8), class IIa (HDAC4, HDAC5, HDAC7, HDAC9), class IIb (HDAC6, HDAC10) and class IV (HDAC11) (71,72). Sirtuin HDACs are also called as class III HDACs (SIRT1–7) (73).

7.1. Classical: Class I

Class I HDACs (HDAC1, 2, 3 and 8) are closely related to RPD3 (reduced potassium dependency 3), which is a transcriptional regulator found in yeast (*Saccharomyces cerevisiae*). Due to the presence of a nuclear localization sequence, this class of HDACs (except HDAC3) (74) is reported to be localized in the nucleus (75). A nuclear export signal found in HDAC3 indicates that its presence is also in the cytoplasm apart from the nucleus (76). This class mostly functions as histone modulator and transcriptional repressor. The expression of Class I HDACs is found in majority of the organisms and it is ubiquitous in human.

7.2. Classical: Class II

Class II HDACs (HDAC4, 5, 6, 7, 9 and 10) share domain similarity to histone deacetylase 1 (HDA1), another deacetylase found in yeast (71). Based on the domain organization, this class is divided into two groups, namely class IIa (HDAC 4, 5, 7 and 9) and class IIb (HDAC 6 and 10). The presence of tandem deacetylase domains in class IIa distinguish it from class IIb. Class II HDACs have both N and C terminal domains with different properties. The N-terminal domains interact with the transcription factors such as myocyte enhancer factor 2 (MEF 2) families, whereas C-terminal with nuclear export signals enables shuttling between the nucleus and cytoplasm. Class IIa HDACs can act as transcriptional repressors as well as transcriptional activators. These enzymes control gene expression by recruiting others proteins (coactivators and corepressor)at the transcriptional machinery.

7.3. Classical: Class IV

HDAC11, a newly identified member of the HDAC family is the lone member of class IV HDACs (77). It shares the common functional properties of class I and class II HDACs.

7.4. Sirtuins: Class III

Sirtuins (Class III HDACs) are also known as nicotinamide adenine dinucleotide (NAD+) dependent histone deacetylases (HDACs). They may have a variety of substrates like structural proteins, metabolic enzymes and histones (78, 79). Primarily, all sirtuins remove acetyl groups from cellular proteins, which significantly affect protein localization and function. The acetyl group from the acetylated substrate is transferred to the ADP-ribose portion of NAD, releasing 2'-O-acetyl-ADP-ribose, nicotinamide, and the deacetylated substrate as products. Seven members of this family have been identified in mammals (SIRT1–7) and each member has own specific subcellular localization, function, and substrate specificity (80). All members of this famuly, except SIRT4, exhibit deacetylase activity. The SIRT4 exhibits only ADP-ribosyltransferase catalytic activity (77). SIRT1 and SIRT2 are localized in both the nucleus and cytosol; SIRT3, SIRT4, and SIRT5 are reported to be present exclusively in mitochondria; whereas SIRT6 and SIRT7 are found only in the nuclear compartment (78,81,82).

8. FUNCTIONS OF HDACs

The functions of different HDACs in gene expression, TLR signalling, inflammation and ovarian functions are described below along with an illustration (Figure 1) and table (Table1), which can help to understand the role of HDACs and its relation to infertility.

8.1. Control of gene expression

Histone deacetylases (HDACs) are responsible for specific gene alterations and the maintenance of gene expression during numerous biological processes. In eukaryotic cells, the distinctive gene expressions are associated with the modulation of specific gene transcription. This modulation acts in response to various physiological and pathological signaling, which require various levels of transcription control.

8.2. Regulation of TLR signalling

HDACs can act as both positive and negative controllers of TLR signaling. Their inhibitors can oppose this control, leading to alterations in the expression of TLR target genes (83). These include a number of genes that encode key inflammatory molecules, like cytokines such as interleukin (IL)-6, tumor necrosis factor (TNF-alpha), IL-1beta, IL-12, and IFN-β; chemokines including chemokine (C-C motif) ligand (CCL2, CCL7, chemokine (C-X-C motif) ligand (CXCL10), and other secreted inflammatory mediators like MMP-9 and endothelin-1 (84–86). Some studies find various HDACs promoting TLR responses by regulating the function of transcription factors, and there are evidences of deacetylation of molecules in TLR signalling pathway. However, the molecular basis behind the involvement of specific HDACs in the expression of these TLR target genes is still obscure.

Lipopolysaccharide (LPS) mediated TLR4 signaling triggers acetylation of the phosphatase mitogen activated protein kinase phosphatase (MKP)-1/dual specificity protein phosphatase 1. This in turn attenuates the activation of mitogen activated protein kinase p38 and pro-inflammatory cytokine responses (87). Thus, deacetylation of MKP-1 by HDACs (specific HDACs unknown) can help in the sustainability of p38 activation and promote TLR inducible inflammatory responses. Members of the interferon regulatory (IRF) transcription factor family impart cell-type specificity and are required for the production of various inflammatory mediators, including TLR-inducible production of type I IFN (84). IRF1 and IRF7 promote MyD88 (myeloid differentiation primary response gene (88) dependent production of type I IFN in conventional dendritic cells (cDCs) and plasmacytoid dendritic cells (pDCs), respectively (88).

HDAC activity in macrophages and dendritic cells was reported to influence TLR inducible expression of several IRF target genes (85,89). Hypoxia-inducible factor (HIF)-1α is a key pro-inflammatory transcription factor in TLR4-dependent inflammatory responses in macrophages (86), and is essential for myeloid dependent inflammation (91). In response to hypoxia, HDAC1, HDAC3 (92), HDAC4, HDAC6 (93) and HDAC7 (94) are reported to interact with HIF-1α and regulate its function. Role of HDACs in TLR-mediated activation of other transcription factors is unknown. Some studies have also reported HDACs as negative regulators of TLR-mediated NF-κB activation.

Through chromatin remodeling, different HDACs are involved in the silencing of TLR4-target genes and endotoxin tolerance in macrophages (95). Classical HDACs are primarily responsible for transcriptional repression through histone modulation and thus show negative regulatory effects on TLR responses. HDAC1 inhibits TLR and/or pathogen inducible activity of numerous inflammatory gene promoters, including IL-12p40 (96), Cox-2 (97) and Ifn-β (98). Moreover, HDAC1 interacts with activating transcription factor (ATF) 3, an inducible attenuator of the TLR responses required for Histone H4 deacetylation. It was also reported that TLR4 induces Hdac1 mRNA in primary mouse macrophages (64). This indicates the probable action of HDAC1 as a feedback regulator of TLR responses by promoting histone deacetylation (99).

HDAC1 is reported to exert negative regulatory effects through the inhibition of NF-κB

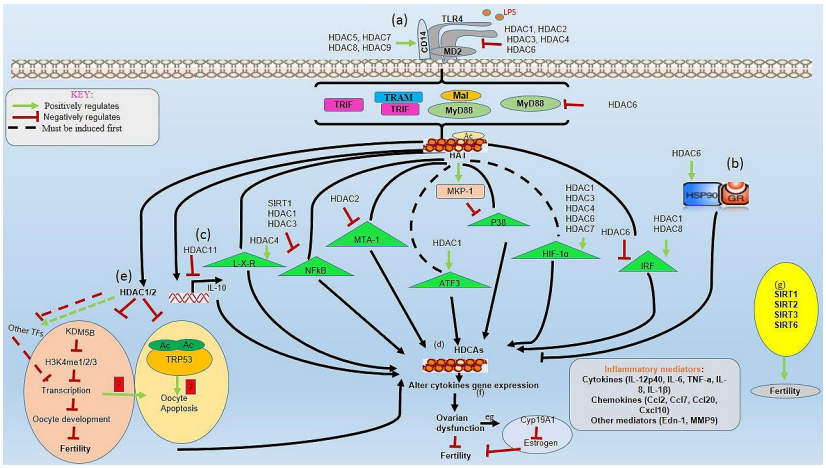

Figure 1. Summary of regulation of the key inflammatory pathways and fertility by HDAC and HAT. HATs and HDACs can both positively (green line) and negatively (red line) regulate these pathways by targeting histones and non-histone proteins. (a) TLR signalling. TLR signalling is positively regulated by HDAC5, HDAC7, HDAC8, HDAC9 and negatively regulated by HDAC1, HDAC2, HDAC3, HDAC4, HDAC6. MyD88 enrolment is inhibited by HDAC6 (100), whereas NF-κB and MTA-1 can be repressed by SITR1, HDAC1, HDAC3, HDAC2 (96–98, 101,102) and HDAC2 (104), respectively. Whereas, liver-X-receptor (L-X-R) positively regulated by HDAC4 (99). LPS induces HIF-1α (a transcription factor) expression (indicated by the dotted line) and its activity is enhanced by many HDACs (although whether this occurs in response to TLR signalling remains to be determined) (91–93). Acetylation increases MKP-1 (a phosphatase that negatively regulates TLR signalling) activity, which inhibits p38-mediated inflammatory responses (82). IRF, a transcription factor function is enhance by HDAC6 whereas repress by HDAC1 and HDAC8 (83). Other HDACs might also promote TLR-mediated nuclear translocation and/or DNA binding of IRF family members (164, 165). (b) Signalling crosstalk with TLR responses. Deacetylation of HSP90 by HDAC6 enables GR maturation to attenuate inflammatory pathways (86). (c) HDAC11 negatively regulates Il-10 expression, thus blocking its suppressive effect on co-stimulatory molecule expression (87). (d) Chromatin remodeling. HDACs act as feedback regulators to switch off TLR-inducible gene expression through histone deacetylation (7), and the inducible transcription factor ATF3 is involved in this process (99). Histone deacetylation also prevents reactivation of specific inflammatory genes in the context of endotoxin tolerance (94). (e) Fertility. Oocyte deficient with HDAC1 and HDAC2 perturbs the transcriptome and induce apoptosis. Absence of HDAC1 and 2 not only affects expression of transcription factors (TFs; proteins that affect the transcribing of genes) but also increases expression of the Kdm5b gene, which in turn decreases H3K4 methylation, an activating mark. This decreases global transcription, which may cause apoptosis, which could also result from hyperacetylation of TRP53 observed in these mutants. Ultimately development beyond secondary stage does not occur and that's result infertility in females (127). (f) Altered expression of cytokine genes is mainly cause's ovarian dysfunction that responsible for infertility in females. For eg. LPS induced pro-inflammatory cytokines by increasing HDAC activity and nuclear translocation of NF-kB down regulate CYP19A1 and E2 production in buffalo GCs (7). (g) SIRT1, SIRT2, SIRT3, SIRT6 all play important role in maintenance of fertility in females (189).

p65 (100,101). Specifically, it promotes the repressive effects of the NF-κB p50 homodimer on the promoters of inflammatory genes (102). Similarly, other class I histone deacetylases are also known to function as negative regulators. HDAC3 deacetylates NF-κB p65, which promotes a complex formation with IκBα and nuclear transport to inhibit the expression of pro-inflammatory cytokines (103). HDAC2 interacts with the transcriptional activator MTA1 (metastatic tumor antigen 1) to block its ability to activate pro-inflammatory cytokine genes in macrophages (104). HDAC6 impairs TLR4 responses by promoting ubiquitin-dependent MyD88 aggregation that inhibits MyD88 signaling. In LPS stimulated mouse macrophages, HDAC4 is required for liver X receptor (LXR) mediated repression of inflammatory gene expression (105). Other studies also revealed that deacetylation of HSP 90 (heat shock protein 90) by HDAC6 are essential for maturation and signaling through glucocorticoid receptor (GR), a well-known negative regulator of inflammatory genes expression. Thus, various studies have identified the signaling systems employing HDACs for positive and negative regulation of TLR responses which in turn regulate the levels of pro-inflammatory cytokines. However, there are many such systems yet to be determined.

8.3. Role of HDACs in inflammation

A substantial body of evidence has documented the roles of HDACs in inflammatory pathways. Inflammation, a complex pathophysiological situation of an organism, is a primary response to harmful stimuli like pathogen and cell damage. It is achieved due to increased migration of leukocytes and plasma from blood to the injured areas. Inflammation becomes prolonged and insistent when it has slow inception and continues for a long period. A number of cellular functions, including the regulation of inflammatory gene expression, cell proliferation and DNA repair are known to be regulated by modification of histone and non-histone proteins (acetylation). Various mammalian diseases, particularly related to inflammation are reported to be associated with varied patterns of histone acetylation. Moreover, unusual expression and activation of histone acetyltransferase (HAT) in inflammatory diseases is reported to act as a transcriptional co-activator. Functional inhibition of histone deacetylases (HDAC) is now gaining therapeutic importance in the treatment of various diseases. Current studies have indicated that HDAC inhibitors may act as anti-inflammatory tools due to their broad spectrum of action. But, this broad

Table1. Functions of different classes of HDACs

Class	HDACs	Specific cell	Function	Reference
I	1	Macrophage as well as Non-immune cells	Enhance HIF-1α function	92
			Repress NF-κβ function	93, 100–102
			Inhibits TLR- and/or pathogen-inducible activity	96–98
		Endometrium	Endometriosis lesion	132
		Embryonic stem cells	Critical for pre implantation development in mouse	126
			Oocyte development	127
		Ovarian cancer tissues	Ovarian cancer and proliferation	130, 131
	2	Embryonic stem cells	Oocyte development	127
		Ovarian cancer tissues	Ovarian cancer	130, 131
		Endometrium	Endometriosis lesion	132
		Macrophages	Repress MTA1 function	104, 171
			Promote GR-mediated repression of NF-κB	172
			Repress NF-κB-dependent inflammatory genes	114
	3	Macrophage and Non-immune cells	Repress NF-κB signalling	103
			Enhanced in histone deacetylation of IL-12b promoter by IL-10 and attenuates transcription of IL12b	118, 173
			Control of pro-inflammatory cytokine gene expression, via inhibiting MAPK11/ ATF-2 signalling	121
			Positive regulator of IL-1-induced gene expression	120
			Enhance expression of IL-1β	174
			Enhance HIF-1α function	92
		Ovarian cancer tissues	Ovarian cancer, Cell migration and adhesion	138, 139
		RA[1] FLS[2]	Enhance inflammatory gene expression, including type I IFN production	174
	8	Human blood monocytes	Enhance inflammation	124
IIa	4	Macrophage	Control LXR-mediated repression of TLR-inducible genes	105
			Enhance HIF-1α function	93
	5	FLS[2], Macrophage	Pro-inflammatory cytokines enhancement via NF-KB signalling	123, 125
		Monocytes/ macrophages	Unknown	175
	7	Macrophage	Enhance HIF-1α function	94, 176
	9	Macrophage	Positive regulator of TLR signalling,	116
IIb	6	Macrophage	Enhance LPS-induced activation of macrophages and production of pro-inflammatory cytokines.	115
			Enhance expression of IL-1β	174
		Unknown	Promote HSP90 chaperone function	177
	10	Tregs	Decreased Foxp3, Granzyme-B, IL-10, Decreased acetylation of NF-kB/p65 at lysine 310	178

III (Sirtuin)	SIRT1	Ovary	Folliculogenesis	148–150
			Proliferation and Activation of steroidogenesis	179
		Granulosa Cells	Proliferation and Secretory activity	180, 181
			Mediation of FSH action and Activation of steroidogenesis	182
		KGN (cell line)	Cell homeostasis, Response to Metformin, Activation of steroidogenesis, and Proliferation	179, 183–185
		COV434 (cell line)	Cell homeostasis	151, 183
		Oocyte	Chromatin configuration and Maturation, Oxidative stress response and Aging process	186, 187
			Maturation	150
		Embryo	Embryo development and Regulation of apoptosis	152
		Periodontal ligament (PDL) cells	Anti-inflammatory	188
	SIRT2	Oocyte	Metaphase II spindle assembly, Chromosome alignment and Aging process	151 143
		Embryo	Embryo development and Regulation of apoptosis	152
	SIRT3	Granulosa cells	Follicle metabolism, Aging process, Folliculogenesis, Luteinization, Progesterone secretion, Oxidative stress response	145, 146
		COV434 (cell line)	Folliculogenesis, Luteinization and progesterone secretion	146
		Cumulus Cells	Follicle metabolism and Aging process	145
		Oocyte	Oxidative stress response and Maintenance of mitochondrial functionality	151
		Embryo	Embryo development, Oxidative stress response and Maintenance of mitochondrial functionality	151
			Embryo development, Regulation of apoptosis, and Marker of embryo potential	152
	SIRT4	Oocyte	Function unknown	151
	SIRT5	Oocyte	Function unknown	151
	SIRT6	Ovary	Folliculogenesis	148–150
		Oocyte	Follicle development	150, 151
	SIRT7	Oocyte	Function unknown	151
IV	11	Antigen Presenting Cells (dendritic cells)	Inhibit *Il10* and promote expression of co-stimulatory molecules *in vitro*	117
HDACs (not specified)		Granulosa cells	Histone H3 acetylation at Lys 9/14 is important for CYP19A1 gene regulation during follicular development.	142
			HDAC inhibitor (TSA) prevents LPS induced inhibition of CYP19A1 expression and 17b-estradiol production	7

[1]Rheumatoid arthritis [2]Fibroblast-like synoviocyte,
Known functions of individual HDACs in inflammation and fertility are listed along with their references

spectrum hinders the quest for the identification of important HDAC enzymes related to inflammation.

The complexity of the inflammatory response requires the development of a sophisticated regulatory network to carry out functions at different levels (106). This network involves the activation of specific genes for antimicrobial defense, immune response, tissue repair and remodeling (107). Recent studies have highlighted the mechanistic importance of chromatin modifications in the acquisition of phenotypes in macrophage (108), a major immune cell playing critical role in inflammation and other chronic diseases. Transcription factors of the NF-κB, FOXP3, IRF and STAT families, along with chromatin remodeling, DNA methylation and covalent histone modifications, are reported to be critical in the regulation of inflammatory genes (106).

Histone acetylation by HATs and the diminished activity of HDACs promote the activation of inflammatory gene expression. Histone deacetylation by HDACs represses inflammatory gene expression. For example, promoter regions of several pro-inflammatory cytokines (IL-1, IL-2, IL-8 and IL-12)

are rapidly acetylated by CBP/p 300, leading to transcriptional activation and thus reduced HDAC activity (109). The recruitment of HDACs, in contrast, leads to histone deacetylation and gene repression. HDACs regulate the 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 (109). NF-κB is controlled by the IκB kinase complex, IKK-α, in response to cytokine treatment (110). IKK-α along with Polymerase II complex and CBP binds to the NF-κB-dependent promoters, where it acetylates histone H3 at Lys9 (111) and phosphorylates the same at Ser10 (112). This cytokine-induced phosphorylation is critical for the subsequent CBP-mediated acetylation of histone H3 on Lys14 (113). 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 (114). Glucocorticoid receptor (GR) and HDAC2 can reverse this process, and thus can promote the repression of NF-κB-dependent inflammatory genes (114).

HDACs regulate the functions of the innate immune cells, like mature macrophages and dendritic cells (DC), by controlling the production of inflammatory mediators such as cytokines, chemokines and matrix metalloproteinases (MMPs). TLR signaling pathways are also modulated by HDACs in these immune cells. Various studies reported that HDAC6 is involved in lipopolysaccharide (LPS) induced macrophage activation. Down regulation or inhibition of HDAC6 expression compromises LPS induced macrophage activation. It indicates that targeting HDAC6 might hold a potential promise for the management of inflammatory diseases (115). HDAC9 is supposed to act as a positive regulator of TLR signaling as macrophages with HDAC9−/− are reported to be less sensitive to LPS. Thus, HDAC9 inhibition can have potential to prevent inflammation and atherosclerosis (116). HDAC11, the sole member of class IV, is reported to inhibit the "*in vitro*" expression of interleukin (IL)-10 in dendritic cells (117).

Histone deacetylation of the IL-12b promoter by HDAC3 is known to mediate homeostatic effects of IL-10 in macrophages. IL-10 partially counters RNA pol. II recruitment to IL-12b promoter through inhibition of chromatin remodeling at the IL-12b promoter and thus it attenuates transcription of IL-12b (118). HDAC3 deficient macrophages, when stimulated with LPS, were unable to activate almost half of the inflammatory gene expression (119). In another study, HDAC3 acted as a co-activator in inflammatory gene signaling pathways. HDAC3 is a positive regulator of IL-1-induced gene expression. This effect is mainly mediated by the removal of inhibitory NF-κB p65 acetylations at K122, 123, 314 and 315 (120). HDAC3 is also reported to play an important role in the control of pro-inflammatory cytokine, like TNF, gene expression, via inhibiting the MAPK11/ATF-2 signaling (121). In rheumatoid arthritis associated fibroblast-like synoviocytes (FLS), deficiency of class I HDAC3 and class IIb HDAC6 activity reduced the expression of IL-1-beta-induced inflammatory genes expression (122). TNF and IL-1-beta in these cells suppress the expression of HDAC5 which leads to an increase in the production of inflammatory mediators by FLS (123). Specific inhibition of HDAC8 was reported to reduce inflammation with low cell toxicity (124). In macrophages, HDAC7 acts as a positive regulator of TLR responses and also promotes HIF-1α-dependent LPS-induced inflammatory responses (90,94). HDAC5 acts as a positive regulator of TLR4 and TLR9 responses and regulates the inflammation caused by PAMPs, including LPS and CpG, or bypassed by IFN-y. Macrophages with HDAC5 are reported to enhance pro-inflammatory cytokines via NF-κB signaling (125).

8.4. Role of HDACs in ovarian function

There are some evidences related to the roles of HDACs in the maintenance of ovarian function. HDAC1 plays an exclusive role in embryonic stem cells, and it is considered as a critical factor for pre-implantation development in mouse (126). Similarly, a few studies have identified that both HDAC1 and HDAC2 could play major role(s) in oocyte development (127). Oocytes lacking specific enzymes that catalyze histone posttranslational modification are infertile due to some changes in the gene expression as well as the activation of apoptosis. Studies in oocytes have reported that the deletion of both the genes together produce infertile female mice, whereas deleting either one gene had no effect on fertility. It was found that deletion of both HDAC genes disrupts the formation of a complex containing HDAC1 and HDAC2 proteins. The decrease in the ovary size related to this problem leads to the premature arrest of follicle development at secondary stage and the oocyte present in these follicles undergo apoptosis (127). Moreover, Hdac1:2−/− oocytes result in developmental arrest that causes a global decrease in transcription and histone H3K4 methylation. Such cells generally undergo apoptosis by hyperacetylation of TRP53, which occurs in mutant oocytes as observed during infertility. Oocytes deficient with HDAC and methylated H3K4 have an overexpression of KDM5B, a transcription repressors in various systems (128,129).

HDACs, like HDAC1-HDAC3, genes are reported to be over-expressed in ovarian cancer tissues than normal tissue, indicating their role in ovarian carcinogenesis (130,131). While HDAC1 and HDAC2 play an essential role in the proliferation of ovarian cancer cells, HDAC3 functions in cell adhesion and migration (131). Studies indicated that

the expression levels of HDAC1/2 are significantly correlated with endometriosis lesions (132). Immunostaning showed a large portion of HDAC1 in ovaries, skin, and gastrointestinal lesions. Similarly, HDAC2 was localized in skin lesions and endometrium from patients with endometriosis (132).

Studies in buffalo granulosa cells have observed that HDAC inhibitor (TSA) prevents LPS induced inhibition of CYP19A1expression and 17β-estradiol production (7), which is a major cause of infertility underlying postpartum uterine infection. Presence of LPS in uterine lumen, peripheral plasma and ovarian follicular fluid indicates it as the key bacterial molecule responsible for uterine infections and eventual ovarian dysfunction (52). Therefore, transient increase in pro-inflammatory cytokines, like TNF-alpha, IL6, IL1B, IL8 etc. is associated with HDACs. The granulosa cells are not only steroidogenic cells, but also exhibit the phenomenon of phagocytosis and expression of TLRs (133). This behavior is similar to innate immune cells. Moreover, granulosa cells also produce pro-inflammatory cytokines in response to the binding of LPS to TLR4 receptor complex, which is also similar to the activities in case of immune cells.

TLR4 initiates a downstream signaling cascade and allows nuclear translocation of NF-κB to produce pro-inflammatory cytokines and chemokines (41). These pro-inflammatory cytokines (IL-1b, IL-6, IL-8 and TNF-alpha) directly affect steroid generation in granulosa Cells (GCs) (134–136). Moreover, TNF-alpha also prohibits estradiol production in bovine granulosa cells (137,138). IL-6 is known to suppress estradiol production in human granulosa cells (139). Thus, LPS stands to be responsible for the down regulation of estradiol production in granulosa cells. It was observed that LPS down-regulates CYP19A1 gene expression in bovine (52) and buffalo GCs (60). The CYP19A1 is the candidate gene encoding aromatase enzyme that catalyzes the final rate limiting step in the biosynthesis of estradiol (140), which plays a pivotal role in female reproduction (141). Recently, it was reported that histone H3 acetylation at Lys 9/14 is important for CYP19A1 gene regulation in buffalo GCs during follicular development (142).

SIRT1 is mainly responsible for NF-κB deacetylation and inactivation, which lowers the cellular ROS load by promoting the resolution of inflammation (143,144). Sirt1−/− mice show a number of early embryonic developmental defects, which may be further evidence for ovarian dysfunction, compromised oocyte development and infertility. SIRT3 is reported to exert a positive role in the folliculogenesis and luteinization processes in GCs. Reduction in SIRT3 expression is associated with a less active deacetylated glutamate dehydrogenase (GDH) form, leading to the altered metabolism of follicle cells during aging (145). Finally, SIRT3 depletion was reported to result in down regulation of steroidogenic enzymes, and thus a decreased progesterone secretion from human GC (146). A lower SIRT2 protein level in the oocytes of aged mice suggests the roleof SIRT2 for contributing the age-dependent deficits of oocytes (147). SIRT6 also plays a vital role in follicle development (148–151).

Sirtuin inhibitors and siRNA-induced knockdown of Sirt3 promote ROS formation and a decrease in blastocyst formation. In porcine embryos, SIRT3 was found to regulate early embryo development by modulating essential gene expressions in concert with SIRT1 and SIRT3 (152). In addition, suppressing SIRT1 signalling and activating mTOR by high fat diet accelerated the rate of follicle loss and premature ovarian failure (POF) (150). The SIRT1-FOXO3A axis might be one of the signalling pathways with a main role in this process. The SIRT3 is essential in maintaining mitochondrial homeostasis, and preventing the activation of the ROS-p53 pathway responsible for developmental defects.

Possible role of SIRT1 and SIRT3 in folliculogenesis and luteinization processes has also been emerged as a result of various studies (145,146,148–150). SIRT1 is involved as a sensor of nutritional status and a regulator of cell cycle. It acts as the major nuclear deacetylase and plays a pivotal role in the transcriptional response to the changes in redox conditions. The SIRT3 acts as a guardian of the redox state and steroidogenic metabolism, the major mitochondrial deacetylaseand an "*in situ*" regulator of proteins, which ameliorate the damage in mitochondria, the major source of ROS in the cell. Protein acetylation regulates TLR mediated signalling pathways, inflammation and fertility.

9. HDACi AND ITS THERAPEUTICS APPLICATION

HDAC inhibitors may be the most promising therapeutic targets for infertility treatment due to their critical role in the regulation of transcription of key genes controlling important cellular functions. Histone deacetylase inhibitors (HDACi) are the molecules known to inhibit HDACs. Inhibition of HDACs can lead to the acetylation of histones followed by the transcriptional activation of certain genes due to the relaxation of the DNA conformation. Different types of HDAC inhibitors (HDACi) extending from intricated structures of bacterial or fungal origin like trichostatin to the very simple structures like butyrate are known. These are capable of inhibiting HDACs with a different range of efficiency at nanomolar to millimolar concentration. Those acting on Zinc dependent HDACs (HDAC1–11) are called "classical" HDACi. These include short chain fatty acids like sodium butyrate and valproic acid (VPA). "Pan-HDACis"

include hydroxamic acids like Trichostatin (TSA) and suberoylanilide hydroxamic acid (SAHA); benzamides such as MS275; and cyclic tetrapeptides such as trapoxin and depsipeptide, and others like M344 and Scriptaid.

"Classical" inhibitors are used in tumour cells for the treatment of cancer due to their abilities to promote tumour cell-cycle arrest, differentiation and apoptosis. On the other hand, 'pan-HDACi' such as the hydroxamic acid compounds may only block the HDAC activity of class I and class IIb HDACs. It may not block class IIa HDACs as they largely lack detectable deacetylase activity. Class I-selective HDACi such as MS275, 4-phenylimidazole62 and MC1293; class II-selective HDACIs such as MC1568 and MC1575, and HDAC isoform-specific inhibitors selective for HDAC4, HDAC6 or HDAC8 have been identified. Development of class I-specific HDACi may be particularly relevant in cancer. Anti-inflammatory mechanisms often involve targeting class II HDACs. Though the effect of HDACi on immune cells is less well understood, there are reports of their therapeutic use in immune cells, particularly against inflammation.

In CD4 T cells, pan-HDACi (Trichostatin A, N-Butyrate, Scriptoid, Vorinostat) and Class I HDACi (Romidepsin) were observed to reduce pro-inflammatory cytokine expression and proliferation (156–159). In CD8 T cells, pan-HDACi (Panobinostat and Trichostat A) were observed to increase pro-inflammatory cytokine production and cytotoxicity (153,157–159). In NK cells, pan-HDACi (Valproic acid) was observed to depress cell proliferation and cytotoxicity (160), whereas class I HDACi (Entinostat) was observed to improve cytotoxicity (161). In macrophages and DCs, pan-HDACi (Trichostatin A, Vorinostat, LAQ824, panobinostat and Valproic acid) and class I HDACi (Entinostat) were known to reduce pro-inflammatory cytokines (84,162–166). Pan-HDACi (Vorinostat and Givinostat) were reported to decrease pro-inflammatory cytokine production and inflammation in common (167–170). Histone inhibitors were also reported to reduce TLR-mediated recruitment of NF-κB p65 as inflammatory promoters (83,84). HDACi are known for the ability to reverse the LPS mediated down regulation of CYP19 gene. Experiments using Trichosanthin A (TSA), a HDACi, have observed that TSA attenuated LPS induced immune response, and thus could prevent the negative effects of LPS on CYP19A1 expression and estradiol synthesis in buffalo GCs (7).

Histone modifications are reported to play a role in the pathophysiology of endometriosis. HDACi decreases proliferation of endometriotic cell line by upregulating p21. Further, in case of endometriosis, histone deacetylase inhibition by HDACi results in reactivation of E-cadherin, attenuation of invasion, decreased proliferation of endometriotic cells and causes lesion regression in an animal model (132). In case of ovarian carcinoma cells, pre-clinical trials suggest that class I based HDACi decrease cell proliferation and increase apoptosis, likely through enhanced DNA damage and decreased DNA repair. New HDACi with less cellular toxicity may have potential as an anticancer agent (130).

10. CONCLUSION

Studies related to alterations in histone modification, particularly acetylation, can help to present a better understanding of the molecular mechanisms underlying various ovarian dysfunction and infertility related problems. Advances in studies of histone acetylation during inflammatory response have illuminated the path for the development of efficient therapies against infertility, and a lot of such achievements are expected. Histone deacetylase inhibitors can be a potential therapeutic against infertility, restoring normal reproductive functions.

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