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Review Article

HDAC11: The Lone Mystic Member of Class IV HDAC

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Histone deacetylases (HDACs) are the members of Histone deacetylase superfamily that play an essential role in epigenetics by modifying (deacetylation) histone and non-histone proteins and thereby regulating transcription of genes. In humans, the 18 HDACs are divided into four classes, namely Class I to IV. Among the four classes of HDACs, the lesser known Class IV has a single member, HDAC11. Although few reports indicate the physiological role of HDAC11 in immune tolerance *via* the regulation of IL10 production, cell cycle arrest and cell death in cancer cells, its role concerning the cellular physiology remains unexplored. According to the Cancer Atlas database, HDAC11 shows high mutations in many cancer patients and thereby acting like a potential candidate for targeted drug therapy. Also, due to the overlapping functions between the HDAC isoforms belonging to various classes, several toxicities are reported with HDAC inhibitors in clinical trials. However, HDAC11 being the only member of class IV is unique and a potent drug target for carcinomas. In this review, we summarise the existing knowledge on HDAC11 and the need to explore its structure, function and evolutionary significance.

Keywords: HDAC11; HDAC Inhibitors; Cell Survival

Introduction

Histone deacetylases (HDACs) are the members of histone deacetylase superfamily along with acetylpolyamine amidohydrolases and acetoin utilisation protein. HDACs mediate the removal of the acetyl group from the ε-N-acetyl of lysine residues present on the N-terminal tails of histone proteins resulting in compact chromatin and thus repress the genes. Apart from histone proteins, several non-histone proteins are also the substrates for HDACs and hence are also called lysine deacetylases (KDACs) (Choudhary *et al*., 2009). HDACs are implicated in several cellular physiological functions (Haberland, Montgomery, and Olson 2009) (Fig. 1). In the nucleus, HDACs generally function in a large multiprotein complex and thus form part of several repressor complexes along with other proteins (co-repressor molecules) like NuRD, CoREST, and Sin3A that are involved in transcriptional repression and chromatin remodelling.

In humans, there are 18 HDAC proteins identified and divided into four classes (Fig. 2). Class I with members HDAC 1, 2, 3, 8 are mostly nuclear in origin. They have a yeast homologue called Rpd3-like protein. Class II family has six members namely HDAC4, 5, 6, 7, 9, 10 that usually shuttles between nucleus and cytoplasm depending on their phosphorylation states and are thought to be involved in regulation of non-histone proteins also (Gregoretti, Lee, and Goodson 2004). Hda1-like proteins are the structurally similar proteins to HDAC Class II proteins found in yeast. Class III is the Sirt-like proteins including members Sirt1 to 7. These are the only members that are dependent upon NAD+ for the activity, unlike other classes which require Zn+ as a co-factor (Frye 2000). All HDACs except HDAC8 usually form a complex and work as a unit of DNA modifying enzyme. Post-translational modification of HDACs is essential for their functioning. Phosphorylation mostly at serine/threonine residues plays a crucial role in the enzymatic activity of HDACs. HDAC Class IV includes the only member HDAC11, a zinc-dependent protein having a large

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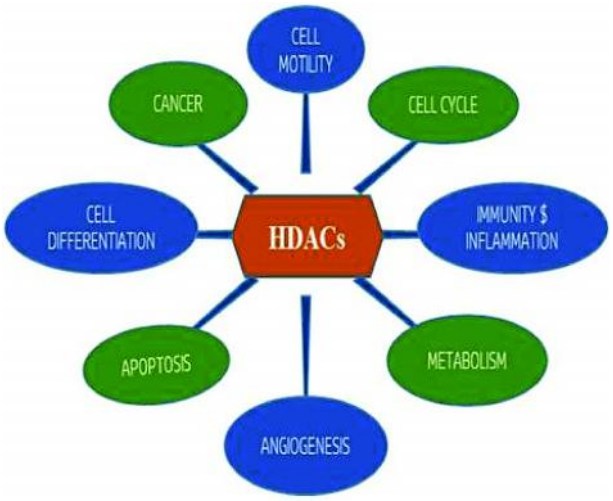


Fig. 1: Role of Histone deacetylases in cellular physiology and metabolism. HDACs in general form repressor complexes regulating gene function leading to cell motility and differentiation, apoptosis, angiogenesis, cell cycle, immunity and inflammation, cancer

deacetylase domain. It is thought to be similar to Class I and II but functionally doesn't overlap, thus having a separate place as class IV. It is known to interact well with HDAC6 (Cheng *et al*., 2014), but the structural domains of HDAC11 are not yet identified. Due to its limited knowledge in structure and function, this review will highlight known facts about its role in cell metabolism and disease physiology and the future of it being one of the important HDACs for gene and immunotherapy.

HDAC11 Gene and Its Regulation

Although HDAC11 has been identified and cloned 15 years ago, very few studies have been carried out on its functions, substrates, binding partners etc. Based on fluorescent-labelled *in situ* Hybridization (FISH) studies, it was identified that HDAC11 gene is located on chromosome 3p25, encoded by 10 exons (Fig. 3). The 5' flanking region of the gene consists of a TATA and CCAT box-less promoter with 1-kb CpG-island

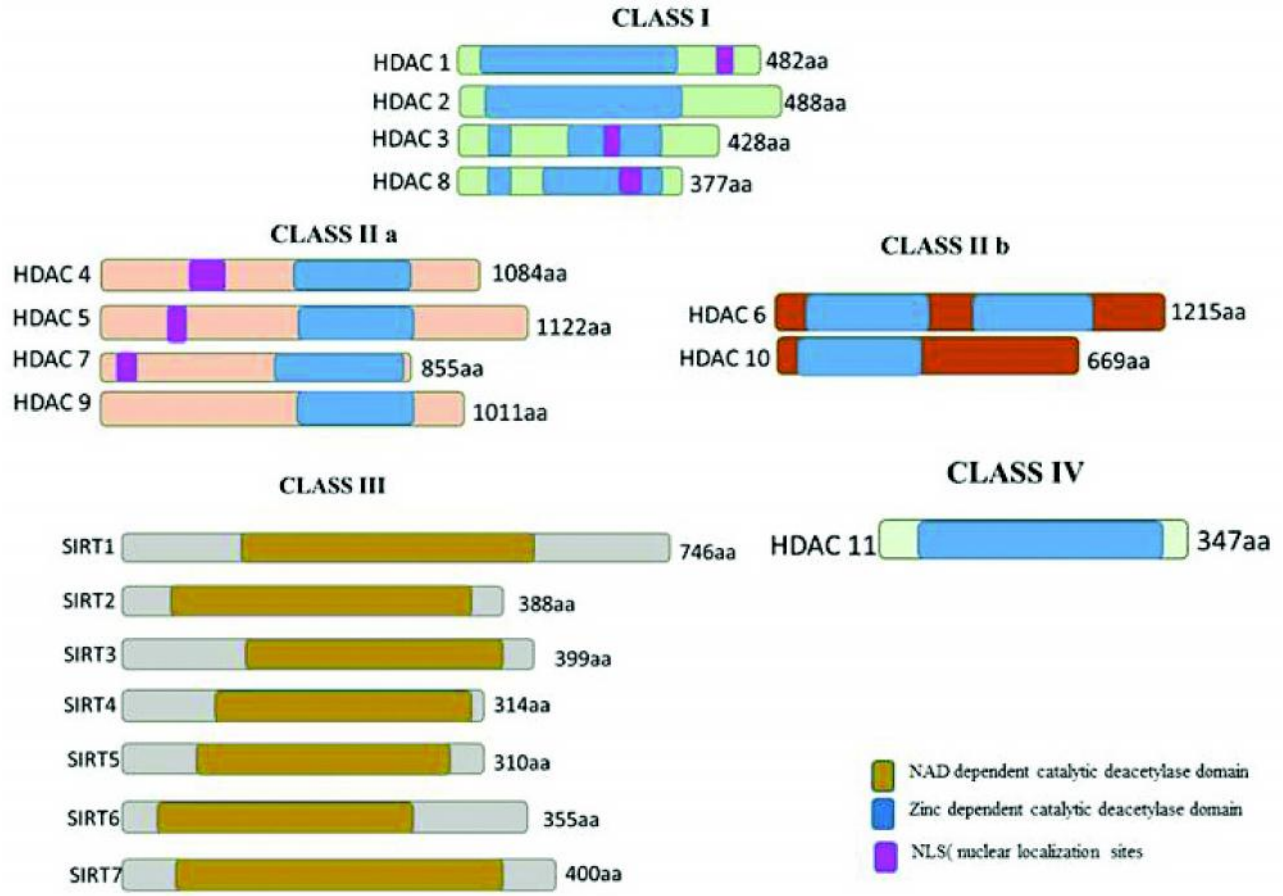


Fig. 2: Different classes of HDACs on the basis of their structural similarity and catalytic domain. Class I, II and IV have Zinc dependent catalytic domain, whereas Class III has NAD-dependent catalytic domain

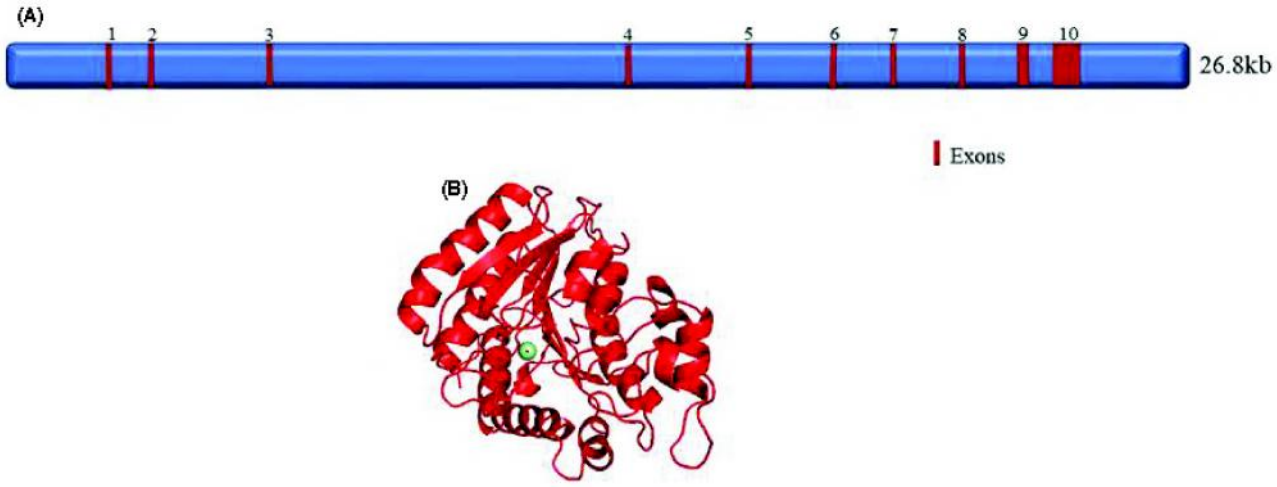


Fig. 3: (A) A pictorial representation of HDAC11 gene of length 26.8Kb having 10 exons. (B) A constructed protein model of HDAC11 formed using protein sequence via I-TASSER online tool

(Voelter-Mahlknecht, Ho and Mahlknecht 2005). It has 15 protein-coding transcripts and 3660 variants mostly intron variants (gene cards database). Though the significance of these protein-coding splice variants is not yet elucidated and is a part of our research interest too as it is important to know the functionality of such protein-coding variants if present in the cell and when. According to single nucleotide polymorphisms (SNP) database (dbSNP), it is observed that the HDAC11 genomic region is prone to various mutations in different cancer types (Fig. 4). However, in-depth analysis in large patient samples is required to call this region as a "hotspot".

Based on *in silico* analysis, it was predicted that the 5'UTR of the HDAC11 gene has GATA-1, NF-κB, AML1a, STAT5 putative transcription factor binding sites. However, experimental validation remains elusive. A study has identified a sequence-tagged site (STS) marker, RH92585, within exon 9 of HDAC11, indicating the uniqueness in the coding sequence of HDAC11. The conserved HDAC family signature sequence lies between exons 5 and 7 of HDAC11 (Gao *et al*., 2002).

Tissue-specific Expression of HDAC11

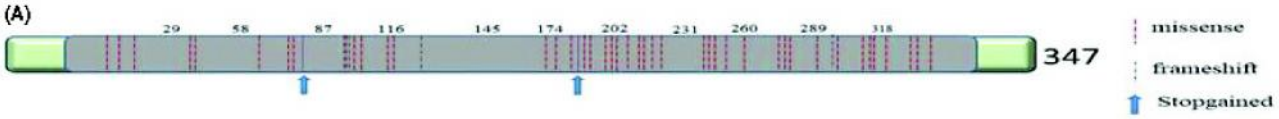
According to the study of the 68FANTOM5 project in human adults, HDAC11 is highly expressed in tissues of the brain (brain meninx, frontal lobe, occipital cortex, and temporal gyrus), heart, CD4+ T-cells (Keedy *et al*., 2009), smooth muscle tissue. HDAC11 RNA expression is more found in Testis and cerebral cortex. Moreover, various differential expression studies of HDAC11 also have been carried out which related its expression to disease phenotype in cancer cells vs normal (Expression Atlas).

Phylogenetic Evolution of HDAC11

All HDACs, except Class IV, are found in all free-living eukaryotes. Class IV HDAC is found in very few prokaryotes and ancestral eukaryotes (Ledent and Vervoort 2006). This suggests that all classes of HDACs existed even before the evolution of eukaryotes. The conservation of these proteins in evolution indicates the non-redundancy of the HDACs in cell and its basic biological processes. Even though there are specific overlapping functions observed, the significant prevalence of such genes over time suggests a selective pressure attributing to their unique function. (Lynch and Conery 2000; Force *et al*., 1999). This is significant taking into consideration the findings that HDACs often form a complex and appear to have similar interacting partners.

There are orthologues of HDAC11 found in different phyla and classes of the eukaryote-like mouse, chicken, lizard, zebrafish etc. (Fig. 5). HDAC11-like proteins are mostly seen in eubacteria and higher eukaryotic organisms. However, when we carried out multiple alignments using CLUSTALW followed by BLAST analysis, we identified that it is similar to an uncharacterized protein sequence found in *C. elegans*. Its structurally similar sequences are found in eubacteria, plants, algae and higher metazoans

(A)



(B)

SNP	Allele	Study populations	Associated phenotype
rs2290194	C/T	ESN	serum cholestrol, systolic blood pressure, glucose tolerance, prion diseases
rs2290196	A/G	BEB, CDX	no signicant disease phenotype
rs2655218	T/C	ASW	Hodgkin lymphoma
rs2655222	A/G	ASW, GIH, GWD, IBS, ITU, MXL, PEL, PUR, STU,TSI,YRI	Breast cancer, insulinresistance,
rs2655224	A/T	ASW, GWD, LWK, YRI	glucose tolerance
rs2675231	G/A	CEU, FIN,GBR, GIB,IBS,ITU,KHV,PEL ,PUR,STU,TSI	Glucose tolerance
rs2738168	T/C		height
rs4648513	T/C	CHS, CLM,MXL	systolic blood pressure, antipsychotic effects
rs17038236	G/A	CEU,FIN,GBR	kuru(prion diseases), upper lip thickness.
rs3732670	C/T	ASW, CLM, ESN, LWK, MSL, MXL, PUR, TSI, YRI	hodgkin lymphoma, schizophrenia(but with p=0.06)
rs75944917	C/G	CEU, FIN, GBR,	Upper lip thickness
rs76917434	C/T	CEU, FIN, GBR	upper lip thickness
rs112195459	G/A	ASW, CEU, FIN, GBR, GWD, MSL, YRI	upper lip thickness
rs11711996	G/A	BEB, CDX, CHB, CHS	cystic fibrosis lungfunction
rs12107323	C/T	CEU, CLM, GBR, FIN, GIH, IBS, LWK, MSL, YRI	Upper lip thickness
rs12633341	C/T	KHV, ITU, STU, GIH	glucose tolerance

Fig. 4: (A) Schematic representation of the various SNPs reported in HDAC11 gene. There 49 missense, 4 frame shift and 2 stop gained mutations observed in protein. (B) The table depicts the HDAC11 SNP found in different population group and their associated phenotype as taken from 1000 genome browser dbSNP for SNP data analysis

describing its evolutionary history (Ledent and Vervoort 2006; Bradner *et al*., 2010). It is predicted via phyletic distribution that it has undergone gene duplication followed by horizontal gene transfer possibly during evolution, though the donor and acceptor species have not been explored yet. In Fig. 5, we have diagrammatically shown the evolution of HDAC11 in the animal kingdom. The protein is conserved through the diverging lines of the kingdom Animalia yet the functional significance of its prevalence in most of the classes of Phylum Arthropoda, Ecdysozoa and Nematode are not yet known. The darker Phyla are the ones having HDAC11 in most of the organisms in particular. So, the question is why it is frequently found in higher organisms? Alternatively, was there any loss in function in the lower organism or has it modified its function in higher animals under specific pressure? Answers to these will give us lead to its evolutionary significance and also will help us to understand better the non-redundant role of HDACs in cell metabolism.

HDAC11 Protein Structure and Function

The cloning and subcellular localisation studies by Gao *et al*. identified that the HDAC11 protein is a 347 amino acid protein (39kDa), primarily located in the nucleus, and shares its 9 deacetylase motifs with the members of both classes I and II HDACs (Gao *et al*., 2002). The protein with 6.88 pI constitutes of a catalytic domain at the N-terminus and Trapoxin can inhibit its activity. The HDAC11 protein crystal structure is not yet available, but several in silico models have been developed and validated by Ramachandran plot analysis (L R Samant 2015). We have also developed a protein model based on the homology with other HDACs using protein sequence via I-TASSER online tool (as shown in Fig. 3B). The protein models mainly show that HDAC11 has one large deacetylase domain with a 143rd amino acid as a putative active site residue. However, experimental evidence to this end at this point is lacking.

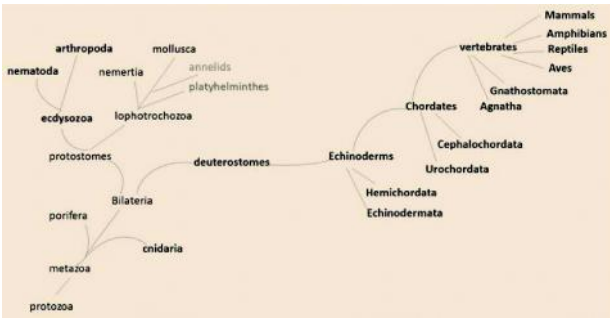


Fig. 5: Phylogenetic evolution of HDAC11 in animal kingdom. A pictorial representation of evolution of HDAC11 gene in animal kingdom. This tree has been made using information from BLAST and Clustal Omega. The darkened phyla are those having HDAC11 or similar gene in most of their respective members

As it is the member of the deacetylase family, it has a zinc-dependent deacetylase domain responsible for the removal of an acetyl group from the lysine residues of histone and non-histone proteins and thereby regulating the gene expression. Apart from deacetylase activity, it also acts as a fatty acyl-hydrolase with an efficiency equal to its acetylation activity (Moreno-Yruela *et al*., 2018). Using Affinity capture mass spectroscopy and yeast two-hybrid assay, a total of 166 protein-protein interactions of HDAC11 were identified (Fig. 6). Since Hdac11 interacts with various proteins, it was also found to be interacting with Dicer1 and hence associated with SMN complex regulating U-12 type splicing of mRNA in CEM T-cells (Joshi *et al*., 2013). However, further validation and experimental proof of all of these interactions need to be carried out. Not many studies have been done in delineating the function of HDAC11.

HDAC11 Role in Autoimmune and Metabolic Diseases

It is known to play a role in obesity by regulating metabolic homeostasis (Sun, Marin de Evsikova, Bian, Achille, Telles, Pei, *et al*. (2018); (Sun, Marin De Evsikova, Bian, Achille, Telles and Seto 2018). It plays a role in regulating IL-10 gene expression in myeloid cells (Sahakian *et al*., 2015) suggests it as a druggable target to treat autoimmune diseases (Yanginlar and Logie 2018; Woods *et al*., 2017). It is also thought to be a promising target for the development of drugs for inducing tolerance post clinical liver transplantation in gene therapy (Lian *et al*., 2012). A detailed analysis of the HDAC11 mutations in genome-wide association studies (GWAS) by several groups (Fig. 4B), clearly indicated its role in insulin resistance and thermogenesis (Bagchi *et al*., 2018).

HDAC11 Role in Cancer

The fact that it is highly expressed in several cancers and has several mutations of type frameshift, missense, and stop-gain indicates its role in the development and progression of cancer. It is observed that knockdown of HDAC11 in MCL cell line, down-regulated cyclin D1, p21 and bcl-2 genes, hence arresting the cells in G1 phase. On the other hand, overexpression of HDAC11 enhanced the cell viability, apoptosis and inflammation by regulating oxidative stress (Fan *et al*., 2018), neutrophil biology and hematopoiesis. (Sahakian *et al*., 2017). A study by Deubzer *et al*. showed that HDAC11 depletion was sufficient enough to cause cell death in various cancers like prostate, breast, colon and ovarian cancer (Deubzer *et al*., 2013).

HDAC11 Inhibitors

Based on previous studies, it is apparent that the identification of HDAC11-specific small molecule pharmacologic inhibitors will prove beneficial for translational and immunological therapies (Huang *et al*., 2017). Moreover, it is also depicted by some studies that specific targeting of HDAC11 in cancerous cells decreases the viability of the cells and increase apoptosis (Deubzer *et al*., 2013). There are various pan-HDAC inhibitors such as Trichostatin, Quisinostat, Panobinostat (FDA approved drug for multiple myeloma), Pracinostat, Dacinostat, CUDC-101, BG45 that inhibit other HDACs along with HDAC11 but isoform selective HDAC11 inhibitors are not available yet. Currently, Mocetinostat (MGCD0103) a class 1 inhibitor of HDAC1, 2 and 3 also inhibiting HDAC11 is under phase I/II clinical trials for the treatment of Hodgkin's lymphoma (Fournel *et al*. 2008). Recently, a novel HDAC11 inhibitor has been discovered namely N-hydroxy-2-arylisoindoline-4-carboxamides and is thought to act specifically (Martin *et al*., 2018). Apart from other inhibitors, few researchers have also used the RNAi based HDAC11 inhibition strategy to suppress its activity but using it as a drug therapy is yet to be answered. Although there are patents filed for the

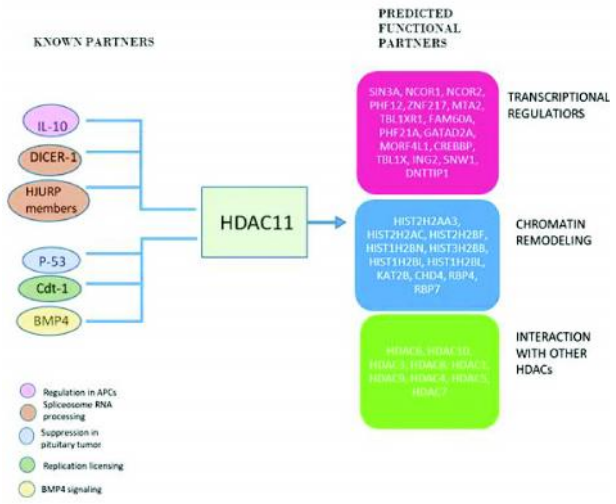


Fig. 6: A diagrammatic representation of the HDAC11 known interacting partners and partially compiled (out of 142 predicted interactions from STRING) predicted functional partners

RNAi based inhibitors, meant to be helpful in treatment of HDAC11 related disorders. Moreover, different individuals have different sensitivity towards the HDAC inhibitors (Halsall and Turner 2016), so the success of HDACi is yet to popularise in mass.

Summary

In this review, we summarise the literature focusing on HDAC11 structure and function in cellular physiology. HDAC11 being the sole member of Class IV HDAC has the least similarity with other HDACs, thus the functional difference and a separate class. All HDACs have a conserved catalytic domain making them a functional part of a repressor complex thereby involved in gene repression. Furthermore, the HDACs share common histone and non-histone protein substrates indicating their functional redundancy (Vanaja, Ramulu, and Kalle 2018). However, it is very well known that redundancy is not the rule of nature and if in humans, 18 HDACs are present, and their role must be precise in cell-type-specific manner and also depend on the upstream signalling event. This hypothesis of ours is best exemplified by HDAC11 showing low structural similarity with other HDACs, conserved in evolution and playing a role in immunity and metabolism via deacetylation. Therefore it becomes crucial to understand the evolutionary significance of such diversification from other HDAC members on the structural and functional basis. Here, we enumerate the role of HDAC11 in various metabolic pathways like immune tolerance, immune cell regulation (Yanginlar and Logie 2018), oncogenes, (Thole *et al*., 2017) cell differentiation (Powers *et al*., 2013) etc. proving it to be a potent target for drug therapy. As it is already known that it has tissue-specific expression and since it is involved in different immune responses, directly targeting this enzyme for therapeutic purposes cannot be considered at such an initial stage. Hence, more investigation is required on its structure-function relationship.

Future Perspectives

HDAC11 is known for its variable functioning in different cell-specific manner. Mostly it regulates cell cycle progression in cancer cells and lead them to apoptosis. There is no effect of change in hdac11 in normal cells. Thus there is a scope of it being a novel drug target for chemotherapy. The different isoforms of HDAC11 that are protein-coding needs to be validated for their significance inside the cell if so present. The domain study is not yet done to elucidate its role and catalytic efficiency overall. Therefore, it is essential to explore the primary structure-function relationship of this protein to have a better understanding of its role in cell metabolism. Our group aims to study the architecture of this gene and how it has been evolved as a separate class in HDAC family.

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