REVIEW

Role of Histone Deacetylases (HDAC) & Histone Deacetylases Inhibitors (HDACis) in Oral Cancer: A Literature Review with Concept-Centric Approach applying Synthesis Matrix Framework (SMF).

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Abstract

Introduction: Based on the Synthesis Matrix Framework, this narrative review with concept-centric approach was conceptualized with the aim to pen down the existing knowledge regarding Histone Deacetylases and Histone Deacetylases inhibitors in oral cancer by synthesizing few evidence-based research studies applying time-ordered matrix framework and role-ordered matrix framework design.

Material and Methods: Google scholar and PubMed search engine were implemented with search strings using Boolean keywords such as "oral squamous cell carcinoma", "OSCC", "oral cancer", "etiological factors of Oral Cancer", "diagnosis of Oral Cancer", "HDAC in Oral cancer", HDACis in Oral cancer", "HDAC in OSCC", "HDACis in OSCC". The review was further assessed by using a three category rubrics of literature review (coverage, synthesis and significance) uncovering the normal function of Histone Deacetylases, classification, molecular mechanism, future directions in research with challenges that can be encountered before the Histone Deacetylases inhibitors are applied in clinical practice.

Conclusion: This review highlights a brief overview on importance of applying Synthesis Matrix Framework as a guiding principle in the field of scientific writing and hence should be included as a modification in curriculum design by educationalist and policy reformers in higher education as quality enhancement initiative in the discipline of research.

Keywords: Histone Deacetylases, Histone Deacetylases Inhibitors, Literature Review, Oral Cancer, Synthesis Matrix Framework

Introduction

One of the most challenging malignancies, enlisted as top ten on global index worldwide, is Oral Cancer/Oral Squamous Cell Carcinoma (OSCC).[1] The morbidity and mortality rates of OSCC demands for much deeper diagnostic accuracy and prognostic accuracy studies to be considered as interventional pristine therapy modalities before surgical intervention.[2] The evolution of field cancerization phenomena,[3] second primary tumours (SPT's),[4] recurrence rate and survival index has made researchers to relook into the genetic-epigenetic changes that occur in a malignant cell. Apart from being multifactorial in nature caused due to chronic use of Tobacco in Smoke/Smokeless forms,[5-10] synergistic effect of alcohol[11], genetic mutations[12], immune deficiencies[13], viral oncogenesis involving Human Papilloma Virus (HPV), Epstein Barr Virus (EBV), Hepatitis C, Nutritional deficiencies (Vitamin A, Vitamin C) and Candida infections[13-15], the oral carcinogenesis is a multi-step complex process involving the interplay between genetic-epigenetic level in a malignant cell, thereby influencing the onset and spread of oral cancer.

Based on the Synthesis Matrix Framework (SMF), we designed this comprehensive narrative review with the

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aim to discuss the role of Histone Deacetylases inhibitors (HDACis) in oral cancer. The primary objective (SMF-O1) was to discuss on the link between human chromatin and HDAC's. The secondary objectives (SMF-O2) were set to discuss on the HDAC's and HDACis by synthesizing few evidence-based research studies applying time-ordered matrix framework and role-ordered matrix framework design. The third objective was to implement rubric framework as an objective assessment process (OSP) to verify the coverage, synthesis and significance of the literature review.

Before initiating this framework, a brief summary on the various molecular pathways of cell dysregulation, inactivation of tumour suppressor genes, enhanced angiogenetic mechanisms and immune invasion with chronic inflammatory mechanism that have influenced the complex genetic -epigenetic role in oral cancer needs to be revised as there is a strong interlink between the HDAC and chromatin structure of a normal cell, without which the objectives of the SMF would not be effective.

Human chromatin constitutes the nuclear DNA that is coiled together by histone proteins and non histone proteins. The core histone proteins include type H3, H2B, H2A and H4, wrapping around the DNA substrate and initiating series of reactions such as transcription, replication, recombination, and repair, thereby playing a crucial role in gene transcription mechanism. This process is initiated when the chromatin structure is in its relaxed state. This phenomenon of chromatin flexibility allows the chromatin to freely interact with the DNA binding factors. Two major events are commenced at this stage. Firstly, the chromatin remodelling factors that are ATP dependent interact with the histone proteins making them accessible to the second event of exposing the amino terminal tails of histone proteins to post transitional modifications such as acetylation, phosphorylation, methylation, ubiquitination, and ADP-ribosylation. They further lead to the process of epigenetic modifications which are the critical regulators of various gene expressions in malignant cells. "Epigenetic modifications are physical or chemical alterations that impact gene accessibility, thus regulating how the genes are read and expressed, without changing the actual DNA sequence".[16]

Histone acetylation is the most studied post translational modification and is the main primary epigenetic modification

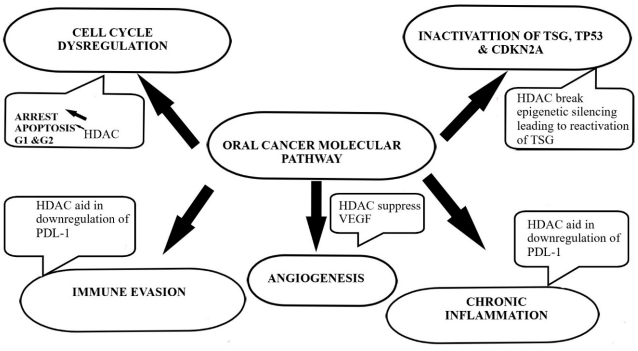

Fig.1: Mind mapping approach to depict the major role of Histone Deacetylases with its HDAC enzymes in coordinating epigenetic changes in oral cancer cells.

that is linked to transcriptional activation. Being regulated by two sets of enzymes i.e histone acetyltransferases (HATs) and histone deacetylases (HDACs), this process involves the transfer of an acetyl group to the ε-amino group of lysine residues in histone tails.[17] This mechanism is meant to neutralize the positive charges present on histones so as to generate a permissive structure for easy binding of the DNA proteins. Since this process is reversible, the delicate balance of this reaction can be easily catalysed by histone deacetylases, thereby initiating the deacetylation process.

The deacetylation process is dependent on HDAC's enzymes which functions to remove the acetyl group from the histone proteins (repressive chromatin), thereby playing a role in epigenetic level of gene expression. It further gets catalysed by histone acetyltransferases (HATs) resulting in acetylation (active chromatin). This balanced phenomena between acetylation and deacetylation helps in maintaining the structural integrity of the chromatin structure, thereby leading to normal gene expression. Any imbalance in this controlled mechanism can lead to abnormal gene expression profiles, paving its path to neoplastic process.[18] Epigenetic changes involve three major dynamic events conscripted as DNA methylation followed by histone modifications and non coding RNA modifications. DNA methylation is a process wherein, there is addition of methyl groups to cytosine residues in CpG dinucleotides. In malignant cell, this undergoes hypermethylation resulting in suppression of tumour suppressor genes and transcriptional silencing. Histone modifications involves Histone methyltransferases (HMTs) and demethylases (HDMs) that promote gene expression by removing methyl groups. In case of non-coding RNA, the micro-RNA's work by deacetylating the miRNA biogenesis-related proteins wherein the HDACs can indirectly affect miRNA expression. On the other hand, miRNAs can target HDACs and set up a feedback loop. A mind mapping approach to depict the major role of Histone Deacetylases with its HDAC enzymes in coordinating epigenetic changes in oral cancer cells is shown in Figure 1.

Biomarkers such as Histone Deacetylases with its HDAC enzymes have played a major role in coordinating epigenetic changes in oral cancer cells as shown in figure 1.[17] HDAC enzymes constitutes four major classes of proteins that are characterized based on its structural moiety, homology and functions. The class I group includes HDAC1, HDAC2, HDAC3 and HDAC8, located in the nucleus, are important for embryonic development and are crucial players for tissue specific differentiation phenomena. They function to provide deacetylation process with transcription repression mechanism. The class II group includes HDAC4, HDAC5, HDAC6, HDAC7, HDAC9 and HDAC10, located in the cytoplasm, are important for cardiac and skeletal muscle development. The class III group, commonly known as Sirtuins (Sirtuins, SIRT1-SIRT7) are dependent on NAD + co factor, function in DNA repair mechanism and control the process of ageing and longevity. The class IV group includes HDAC 11 that function in immunomodulatory mechanism and inflammatory processes. Any dysregulation in any of the four groups is directly corelated to the imbalance in the genetic-epigenetic

level that leads to disease process and carcinogenesis.

Various evidence based scientific studies have shown an association of increased expression of specific HDAC isoforms to malignancies including oral cancer. HDAC1, HDAC2 of class I and HDAC4, HDAC6 of Class II are particularly associated with oral cancer.[19-21] A concept mapping representation of the enigmatic role of HDAC's overexpression in the course of carcinogenesis is shown in Figure 2, Table 1

Based on the understanding of this mechanism, tailored made treatment approaches such as Histone Deacetylase Inhibitors (HDACis) have emerged as promising interventional pristine therapies along with the standard treatment strategies in the treatment of oral cancer. This revolution could be possible only due to, in depth understanding of these entities, thereby making it diagnostic and prognostic biomarkers. A concept mapping representation of mechanism by which these compounds exert their beneficial effects is by targeting the dysregulated activity of Histone Deacetylases (HDACs) is

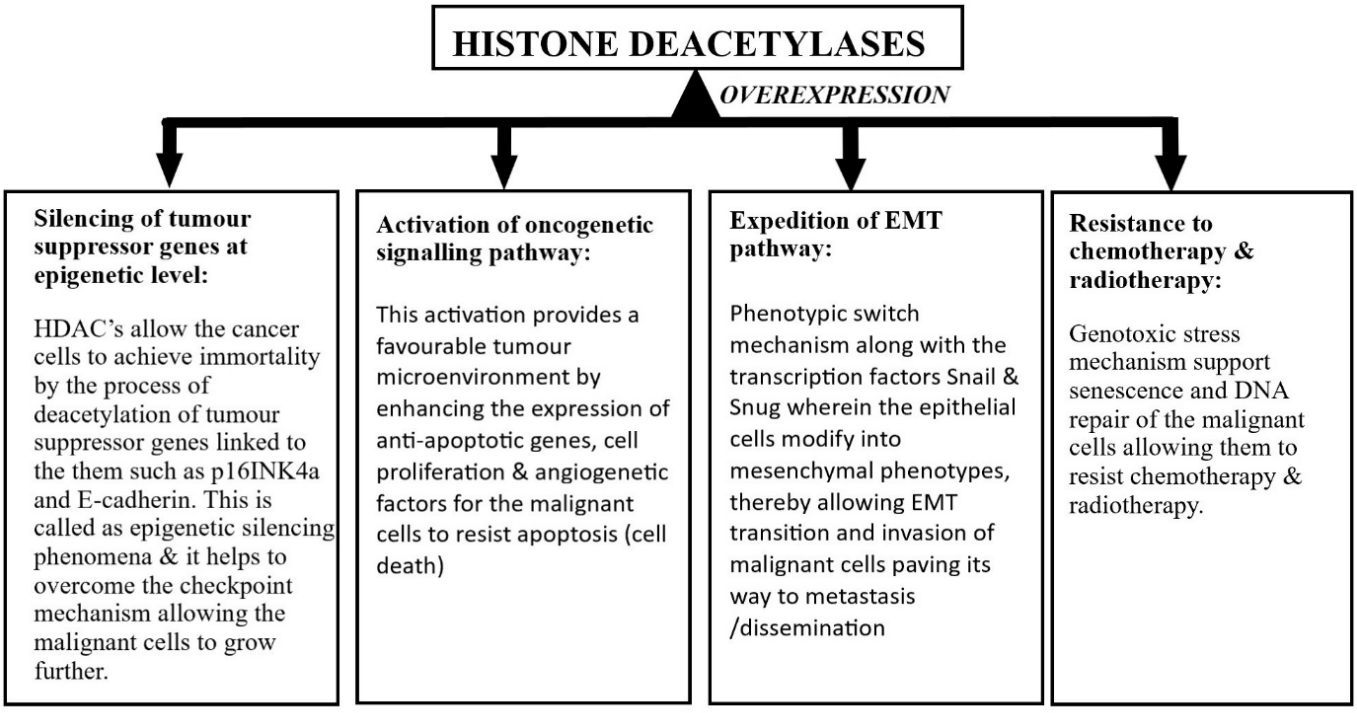

Fig. 2: Concept mapping of HDAC's overexpression in the course of carcinogenesis.

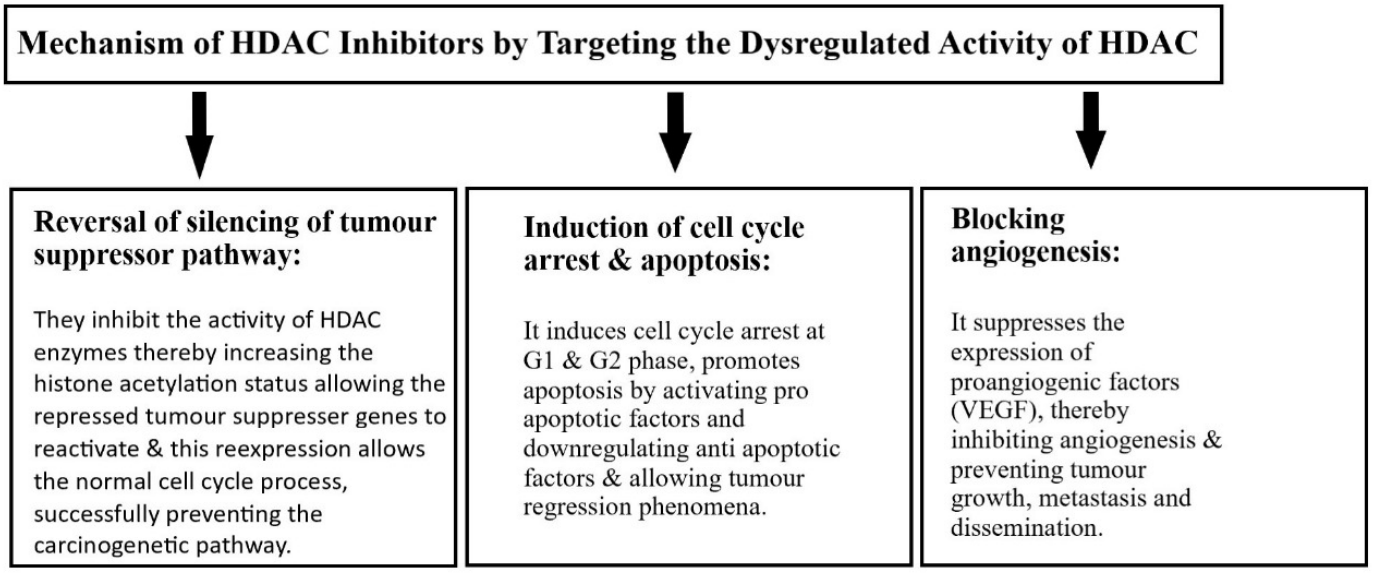

Fig. 3: Concept mapping of Beneficial effects of HDACis by targeting the dysregulated activity of Histone Deacetylases (HDACs)

shown in Figure 3, Table 2.

Rubrics were set for assessing the rubrics elements such as the total number of publications covered, synthesis of each publication and its significance, thereby making the assessment procedure more objective rather than subjective. [Table 3]

The type of rubrics applied was holistic type where the overall quick snapshot of impact of performance was evaluated as a single score applying level of performance classification using adjectives as Good, Fair and Poor. The categorical elements A1, A2, EE1, EE2 signifies Author 1, Author 2, External Expert 1and External Expert 2 respectively. The level of performance indicators reveals the degree of attainment of objectives set, thereby providing more objective assessment and feedback. The impact analysis was measured by involving the scrutiny of this narrative review by external experts who graded the quality of work conducted by the authors (A1 and A2). Google scholar and PubMed search engine was implemented by A1 and A2; EE 1 and EE2 with search strings using Boolean keywords such as "oral squamous cell carcinoma", "OSCC", "oral cancer", "etiological factors of OSCC", "diagnosis of OSCC", "HDAC in Oral cancer", HDACis in Oral cancer", "HDAC in OSCC", "HDACis in OSCC".

When compared to normal literature review without applying rubrics in SMF, the degree of quality assessment remains unpredictable. Hence, this review focusses on the importance of applying SMF with rubric design so as to enhance the quality of synthesis and coverage of articles.

All the three objectives (SMF O1, SMF O2 and SMF O3) are illustrative and serve as an conceptual guide for conducting more research with evidence based interventions and contribute to the development of new treatment regimens for early diagnosis of OSCC.

HDACis in Clinical Trials:

FDA (Food and Drug Administration) have approved Vorinostat, Romidepsin, Belinostat, Panobinostat, Givinostat, Abexinostat, Resminostat, Pracinostat, CUDC101, Quisinostat, Tefinostat, CHR-3996 for treatment of various solid and haematological malignancies as combination therapy.[44] However, adverse side effects such as thrombocytopenia, anaemia, neutropenia, fatigue, diarrhea, nausea, vomiting, anorexia, constipation and dehydration have been reported. Deaths due to the toxicity during the clinical trials have raised the curiosity to place amendments to curtail the toxicity induced by HDACis. The low therapeutic index is another major drawback of the above mentioned existing HDACis. Therefore, development of new HDACis with increased therapeutic index and efficiency is a need of an hour wherein more research needs to be conducted and explored.[45]

Significance of applying SMF for Literature Review:

Although the SMF concept was established long back, the application of this framework in Indian research has been scarce due to the fact of lack of understanding of importance of this framework in research. The importance of SMF is to synthesize and compare empirical studies efficiently so as to identify the research gap on a specific field of research topic already published, thereby leading to the development of conceptual framework and theoretical framework ideas in multiple dimensions in order to determine the scope of research across time. Acting as a strategic tool, this entire process, although time consuming and daunting, is far much rewarding due to the fact that it can spot both, differences and similarities, about a specific research topic published in different journal databases, hence skimming through the literature search in an organised and systematic approach.

SMF contributes in the development of conceptual framework (defined as a "framework that presents previous concepts/ideas on a particular study topic") and theoretical framework (defined as "a framework that presents a particular theory to be tested on a specific research topic").[46] Most research scholars fail to present both the above-mentioned framework.

Table 1: The SMF-O1 is to highlight the role of HDAC's in oral cancer and epigenetic changes that occur during carcinogenesis. The framework involves rows and columns. Each row represents Source information (SI) element time centred (Year of Publication), Role Centred (Author, Source/Citation) and Outcome of Each Paper. The column represents the Argument Matrix (AM) element

ARGUMENT MATRIX ELEMENT (AM)	"SMF O1 FRAMEWORK"		
	SOURCE INFORMATION ELEMENT (SI)		
Over expression of HDAC subtypes results in poor prognosis in OSCC but distinct variability in found in the mechanism of action and enigmatic role. This variability signifies the knowledge gap that needs to be explored	Year	References	Study Outcome
	2006	Sakuma et al.[30]	HDAC6 expression in OSCC was evaluated. Increased expression inferred poor prognosis.
	2009	Chang et al. [31]	Overexpression of HDAC2 in OSCC inferred poor prognosis.
	2011	Theocharis et al. [32]	Clinical importance of HDAC-1 and -2 protein expression in OSCC of tongue inferred poor prognosis.
	2016	Rastogi et al. [33]	Expression of HDAC9 in OSCC stimulated the cancer cells, thereby leading to cell dysregulation mechanism.

This can be attributed to the fact of lack of application of SMF in literature review writing by research scholars in higher educational institutes. Most research scholars assume literature review as a mere collection of previous published data and fail to critically analyse and synthesize the research topic. Literature review constitutes two main core domains i.e source information domain (SI) and argument matrix (AM) domain. Source information domain (year, authors, research outcome) is usually covered by research scholars during their thesis/dissertation presentation but the element of argument matric is lacking on a large scale. Sometimes being subjectively covered by few scholars, a more objective way of documenting the argument matric needs to be implemented.

Newer reforms and policies of applying the SMF guidelines in tabular format as done in this piece of paper should be inculcated in thesis/dissertation presentations as a modification in curriculum design by educationalist and policy makers in area of research expertise as a quality initiative

Table 2: The SMF-O2 is to highlight the role of HDAC is in oral cancer and epigenetic changes that occur during carcinogenesis. The framework involves rows and columns. Each row represents Source information (SI) element time centred (Year of Publication), Role Centred (Author, Source/Citation) and Outcome of Each Paper. The column represents the Argument Matrix (AM) element

ARGUMENT MATRIX ELEMENT (AM)	"SMF O2 FRAMEWORK"		
	SOURCE INFORMATION ELEMENT (SI)		
Treatment modalities (as monotherapy or combination therapy) with HDACis (Inhibitors) results in anti-tumorigenic effect in OSCC but distinct variability is found in the mechanism of action of different types of HDAC is and significant adverse effects This variability signifies the knowledge gap that needs to be explored	Year	References	Study Outcome
	2006	Sato T et al.[34]	The crucial timing for drug delivery of HDAC is along with cisplatin in OSCC signified its importance by concluding that the apoptotic response induction by this combination therapy was sequence dependent.
	2007	Rikiishi H et al. [35]	The impact of SAHA's on OSCC was evaluated, concluding that there was increased apoptosis by activating caspases.
	2009	Nagumo T et al.[36]	The effects of SAHA's on OSCC showed cell cycle arrest at G 1 phase with elevated expression of p21 and hyperacetylation of p53.
	2011	Bai LY et al. [37]	The introduction of (S)-HDAC42 showed strong antiproliferative effects which inhibited the growth of the malignant cells by down-regulation of expression proteins.
	2011	Takahashi et al. [38]	The apoptotic effect of HDAC inhibitor Ky-2 as a new novel therapy was demonstrated.
	2013	Schrenk C et al. [39]	The effectiveness of combination of class IIa HDAC inhibitors and proteasome inhibitors as combination therapy was evaluated.
	2013	Chikamatsu K et al. [40]	SAHA and trichostatin A (TSA) in malignant cells showed cell cycle arrest and apoptosis.
	2017	Ahn MY et al. [41]	HDAC8 suppression by HDAC8 siRNAs caused OSCC cells to undergo autophagy and apoptosis.
	2017	Zagni C et al. [42]	New HDAC inhibitors 1a and 1d demonstrated antiproliferative effects by interfering with the PI3K/Akt/mTOR pathway.
	2017	Kakiuchi A et al. [43]	The effects of TSA on HNSCC inferred complete cessation of growth with changed protein expression, thereby arresting cell cycle.

Table 3: SMF- O3 is to implement rubric framework as an objective assessment process (OSP) by applying three category rubrics of literature review (coverage, synthesis & significance) uncovering the normal function of Histone Deacetylases, classification, molecular mechanism The framework involves rows and columns. Each row represents time centred (Year of Publication), Role Centred (Author, Source/Citation) & Outcome of Each Paper.

SMF O3 FRAMEWORK – RUBRICS FOR ASSESSMENT				
Categories	A1	A2	EE1	EE2
Coverage	GOOD	GOOD	GOOD	GOOD
Synthesis	GOOD	GOOD	GOOD	GOOD
Significance	GOOD	GOOD	GOOD	GOOD

measure for better outcomes. This can be a step forward for quality enhancement protocols in the field of scientific writing. Research protocols / proposals guidelines should also try to incorporate this framework as individual separate section, emphasizing more on argument matrix.

Future Directions and Challenges in applications in Clinical Practice:

Personalized treatment plans using combination therapy with HDAC's inhibitors along with traditional therapies such as chemotherapy and radiotherapy have opened new arenas in the field of medical research. Precision medicine targeting specific genomic alterations in oral cancer cases by creating isoform specific HDAC is provide a minimally invasive and highly specific approach for treatment stratification with best outcome approaches and long-term efficiency can be guaranteed by the clinicians. The future holds true for personalised treatment modalities by individual molecular profiling of cancer patients for early diagnosis, prognosis and prediction outcomes. However, every new discovery faces new challenges and, in this case, patient accessibility and biomarker validation process need future concerns.

One major limitation and challenge faced during conduction of this framework was the delay and prolonged timeline in assessing the rubrics by each categorical element and finding the experts for assessment as mentioned in the SMF O 3 objective. This can lead to burnout and fatigue to the authors which needs to be addressed by finding new strategies or policies.

In depth understanding of the structure and pharmokinetic dynamics will be helpful for designing new novel drugs with less toxicity. A ground breaking scaffold using HDACis especially for OSCC as crucial requirement needs to be discovered so as to amend the disease at the earliest phase to improve the survival index.

Conclusion

This comprehensive review with SMF framework can help for greater understanding where the readers can draw significant comparisons between different studies where the concept of synthesising rather than summarizing the literature review aids in providing clues in knowledge gaps and future research.

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