Systematic Review

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Integral Nuclear Proteins in Cell Signaling in Relation to Oral Cancer and its Treatment Modalities; A Systematic Review

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Author`s Contribution

[1,2,3,7]Substantial contributions to the conception or design of the work or the acquisition, Final approval of the version to be published. [4,5,6]methodology, analysis,

Funding Source: None
Conflict of Interest: None

Received: May 20, 2024
Accepted: June 06, 2024

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ABSTRACT

Objective: To advance our understanding of the integral nuclear protein's role in cell interaction and their capacity as diagnostic and therapeutic targets in oral cancer treatment.

Methodology: This review was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. The data of our systematic review were collected from six search engines i.e HEC Digital Library, PubMed/Medline, Elsevier, Wiley Online Library, Google Scholar and Wolter Kluwer, from the year 2014 to 2024. In order to conduct this review, studies selection was done based on the following criteria which includes Articles with Abstract containing integral nuclear proteins Cell signaling and Oral cancer, Top fifty most cited articles based on their citation count and articles containing role of Integral nuclear proteins in cancer treatment.

Results: In order to carry out this study, forty studies were searched and assessed which discussed the role of integral nuclear proteins in cell signaling and recent advancements describing the application of these proteins as a diagnostic tool in oral cancer detection and prevention.

Conclusion: This systematic review describes the application of role of integral nuclear protein plays in pathophysiology of Oral cancer and that it can be used as a diagnostic parameter as well as treatment for oral cancer. However, this review did not discuss regarding the individual proteins role in cancer treatment and their use as a diagnostic and preventive tool such as role of YAP (Yes-associated protein) and p53.This research may have missed some studies written in language other than English..

Keywords: Integral Nuclear Proteins, Transcription factors, Cell signaling, Oral Cancer, DNA repair proteins, Diagnostic aids

Cite this article as: Humayoun S, Sajid M, Yaqoob B, Abbasi N, Qazi SH, Mumtaz R, Noor N. Integral Nuclear Proteins in Cell Signaling in Relation to Oral Cancer and its Treatment Modalities; A Systematic Review. Ann Pak Inst Med Sci. SUPPL-1 (2024): *401-409. doi. 10.48036/apims.v20iSUPPL-1.1062*

Introduction

Cell signaling is a characteristic prerequisite for cellular actions and reactions. The epicenter of activity in a cell is nucleus, which contains integral nuclear proteins (INPs) which acts as a mediator and controls the signaling pathways present in cells. Various INPs have been studied and their mechanism of action has been explained as to how they affect cell signaling. This whole mechanism is complex and intricate known as cell signaling which is in charge of many activities such as interaction of cell with environmental triggers as well as growth and development. [1] Many studies have been done in the past to assess the role of cytoplasmic signaling molecules

however, recent research has highlighted the significance of INPs in managing cell signaling processes.[2] These proteins constitute a major portion in the nucleus and actively take part in various signaling pathways. The multifaceted role of INPs and their effect on cell signaling are discussed in this article, along with their regulatory mechanisms, consequences of cellular homeostasis and illness and use in treatment. [3]

There is a broad group of molecules that live in close contact with each other inside the nuclear compartment are known as integral nuclear proteins (INPs), also called nuclear signaling proteins. They can greatly affect the cellular processes by precisely controlling DNA, chromatin remodeling, repair gene expression and epigenetic alterations.[4] This review is being conducted to have an understanding of the integral nuclear protein's role in cell interaction and their capacity as diagnostic and therapeutic targets in oral cancer treatment. [4]

Transcription Factors; Masters of Gene Expression: The core of cellular signaling is gene expression and its control. INPs work by interacting with response elements, which are particular DNA sequences. They recruits coactivators or corepressors and act as transcription factors, regulating the activity of target genes. These interactions act and play a pivotal role in cellular activities, such as cell development, differentiation, as well as reactions towards environmental cues, by assessing if the genes are active or repressed.[5] Transcription factors are activated by various signaling routes such as cytokine signaling, hormone signaling and tyrosine kinase (RTK) signaling. [6]

Cytokine signaling can activate transcriptional regulators. Interferons and interleukins are cytokines which can activate the STAT pathway, that acts as transcription activator and signal transducer. After the activation of STAT proteins, dimerization will occur and they will go for binding to response element in target genes in the nucleus and start their production. [7] Hormonal signaling can cause transcription factor activation. Hormones such as estrogen and testosterone can also activate nuclear receptors. Nuclear receptors increase target genes expression is increased when nuclear receptors bind in the promoter region. [8]

Nuclear Receptors: These proteins are transcription factors that enable and control gene expression while interacting with diverse ligands, such as vitamins, hormones and metabolites. They play a crucial role in cell signaling. The majority of time, These proteins are mainly found in the nucleus of cells either activating or suppressing the transcription of target genes after binding to particular DNA sequences.[9] They can be further understood after their identification as they are divided into various subfamilies of nuclear receptor proteins, based on the DNA binding domains and ligands. The retinoid receptors, steroid hormone receptors, peroxisome proliferator-activated receptors (PPARs) and thyroid hormone receptors are some of the most well-known subfamilies.[10] For instance, the control lipid metabolism and inflammation is done by the PPARs, as they form a heterodimer with the retinoid X receptor (RXR) and bind to specific DNA sequences. [11]

DNA Repair Proteins: The maintenance of genetic integrity is directly linked with the survival of cell. INPs are critical for DNA repair pathways as they recognize damages being done to the DNA and in return activate their repair system, coordinate cellular checkpoints to ensure precise DNA replication. Any disruption or dysregulation in these proteins can cause instability in the genomic makeup and helps fostering illnesses like cancer.[12] DNA repair proteins helps in maintaining integrity of the genome and the prevention of mutations thereby keeping in check for diseases such as cancer. They respond to DNA damage and activate signaling pathways that control cell cycle progression, cell death, and other cellular processes, these proteins can also contribute to cell signaling.[13]

A DNA tumor suppressor protein which is being employed in cell signaling is P53. [14] One of the DNA repair protein Poly (ADP-ribose) polymerase (PARP) is involved in cell signaling. In order to mend single-strand DNA breaks, an enzyme called PARP is used. PARP can also activate downstream pathways that control cell cycle progression and cell death, therefore contributing to cell signaling.[15] The significance of comprehending the function of DNA repair proteins in cell signaling is such that it will help to create novel therapeutic strategies for a number of diseases, including cancer. [16]

Chromatin Remodeling and Epigenetic Modification A group of proteins that modify the makeup of nucleosomes and arrangement are known as Chromatin remodeling factors. They control the structure and accessibility of DNA, acting as the fundamental building blocks of chromatin. They can alter the chromatin structure and histone modifications in order to dynamically control DNA access and affect the chromatin landscape. They also play a critical part in cellular development, differentiation, and disease progression by working on gene activation or silencing through epigenetic modifying enzymes and

chromatin remodeling.[17] The two main categories of chromatin remodeling agents include ATP-dependent chromatin remodelers and Histone-modifying enzymes. ATP-dependent chromatin remodelers utilize energy from ATP hydrolysis in order to move nucleosomes along DNA and histone-modifying enzymes covalently modify histones and change their connections with DNA. [18]

ATP-dependent chromatin remodelers contribute to cell signaling by controlling gene expression in response to various environmental cues. For instance, for activation INO80, Notch system and for the activation of SWI/SNF transforming growth factor-beta (TGF-) pathway are involved which are signaling pathways. They further control the expression of target genes significant for cell proliferation, differentiation, and survival.[19]

Histones are responsible for packaging DNA is packaged into chromatin, which are proteins. Chromatin enables DNA to fit inside the nucleus of a cell. Histones help in structural function along with gene expression during cell signaling. [20] Histone-modifying enzymes influence cell signaling by altering the composition and operation of chromatin. Histone modification involves the process by which various chemical groups, such as methyl, acetyl and phosphate groups, can alter histones. [20] The histone acetyltransferases (HATs) can acetylate histones and upsurge gene expression whereas histone deacetylases (HDACs) can deacetylate histones and suppress gene expression. [21]

The histone acetyltransferases (HATs) can be activated by the MAPK pathway. PI3K pathway activates Histone deacetylases (HDACs), which remove acetyl groups from histones and suppress gene expression.[20] Histones are involved in more than just histone modification in cell signalling pathways. For example, histones can act as a scaffolding protein to attract other proteins that are involved in signalling cascades. Another class of damage-associated molecular pattern (DAMP) that can break free from cells and trigger an inflammatory response is histones, which can also activate immune cells. [21] Chromatin remodeling factors have the potential to be highly significant in cell signalling since they regulate gene expression and have an impact on numerous cellular processes. If we are to develop new treatment modalities for diseases like cancer, we must understand how chromatin remodeling factors affect cell signaling. [17]

Signaling Adapter Proteins: The nuclear envelope is a double-membrane structure in eukaryotic cell, separates the nucleus from the cytoplasm. It comprises of an outer and inner nuclear membrane, separated by the perinuclear gap, which is a small area. The movement of molecules between the nucleus and the cytoplasm is tightly controlled by the nuclear envelope. A broad set of proteins known as nuclear envelope proteins is connected to or contained inside the nuclear envelope. These proteins perform a variety of tasks, including as supporting the nuclear envelope structurally, controlling nuclear pore complex (NPC) construction and operation, and taking part in nuclear signaling pathways. [22]

These significant nuclear envelope proteins and their functions in nuclear signaling are listed.

Lamin proteins; Laminin proteins are intermediate filament proteins that weave together below the inner nuclear membrane to support the structural integrity of the nuclear envelope. They also affect nuclear location, gene expression, and DNA replication. Laminopathies and particular forms of muscular dystrophy have both been linked to mutations in Lamin proteins, which are involved in many different disorders. [23]

Emerin: Emerin is a protein found in the inner nuclear membrane that communicates with Lamins and other proteins found in the nuclear envelope, and controls the gene expression, DNA repair and nuclear signalling. [24]

SUN proteins: A group of inner nuclear membrane proteins interacts with Lamins and nucleoporins. They interact with nucleoplasmic proteins KASH, as well as Lamins and other nuclear envelope proteins. They affect nuclear signaling pathways by interacting with signaling molecules including kinases and transcription factors. [25]

The nuclear pore complex (NPC) The nuclear pore complex (nucleoporins) is enclosed in the nuclear envelope and associated with nuclear signaling. For instance, it has been demonstrated that nucleoporins like Nup153 and Nup98 interact with transcription factors to control gene. [26]

Role of adapter proteins in mediating signaling crosstalk

By enabling communication between several signaling pathways and coordinating their responses, Adapter proteins play a critical role in orchestrating signaling crosstalk. By connecting several signaling components and enabling the transfer of signals from one pathway to another, they serve as molecular bridges. [27]

Interplay with Cytoplasmic Signaling Pathways: The cytoplasmic signaling pathways interact with integral nuclear proteins when they are located inside the nucleus. Nuclear shuttling of signaling molecules, the creation of signaling complexes at the nuclear periphery and translocation of activated receptors, all contribute to the facilitation of this communication. Nuclear and cytoplasmic signaling pathways integration coordinates the cellular responses to environmental stimuli.[1]

Nucleocytoplasmic shuttling protein also known as Nuclear cytosolic proteins, are crucial for controlling the movement of signaling molecules between the nucleus and the cytoplasm. These proteins take part in a number of biological functions, such as gene expression, apoptosis and cell cycle regulation. Nucleocytoplasmic shuttling proteins such as importins and exportins control the moving of proteins and RNAs between the nucleus and cytoplasm. Importins bind to nuclear localization signals (NLSs) on cargo proteins and transport them into the nucleus and Exportins bind to nuclear export signals (NESs) and transport cargo proteins out of the nucleus. A family of nuclear cytosolic proteins that participate in cell signaling are nuclear receptors. [28] The receptor controls the expression of the target genes once it has entered the nucleus by binding to particular DNA sequences. [29]

Methodology

In order to carry out this systematic review, Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were taken into consideration. Our aim was to scrutinize suitable studies by searching the following online databases: HEC Digital Library, Wolter Kluwer, Wiley Online Library, Google Scholar and Elsevier. Articles with Abstract containing integral nuclear proteins Cell signaling and Oral cancer, Top fifty most cited articles based on their citation count and articles containing role of Integral nuclear proteins in cancer treatment were included in the study. Whereas Articles which did not include Integral nuclear proteins, Cell signaling and Oral cancer in their abstract, Articles which were not published in the journals falling in the category of dentistry, Oral surgery, medicine were excluded from the study.

The search terms included two categories: (1) “integral nuclear proteins,” “cell signalling,” “transcription factor,” and “;” (2) “oral cancer,” and “DNA repair proteins”. The logical relationship was created with “OR” and “AND,” and the search formula was developed afterwards. Some other databases such as lilac were not search due to inability to access the articles. A pre-retrieval process was carried out to improve the search strategy. Literature that did not conform with the inclusion criteria was excluded by preliminary screening which involved reading titles and abstracts independently by two reviewers. Two reviewers performed the initial screening, read titles and abstracts independently to exclude literature that did not meet the inclusion criteria. When two researchers disagree, they consulted and discussed with a third researcher to reach a consensus. Afterwards, full text reading of the literature was done to identify the studies which met the inclusion criteria. During the full-text screening, following information was extracted: authors, date of publication, study type, subject characteristics, sample number, loss to or withdrawal from follow-up, intervention measures, and measuring indicators, etc. In case of repeatedly reported studies, only the latest or the most comprehensive one was included.

Results

One thousand seven hundred and forty-five studies were selected by the preliminary screening. (table I) Only 40 studies were kept after screening titles, abstracts, and full-texts. The Results are shown below in Figure 1.

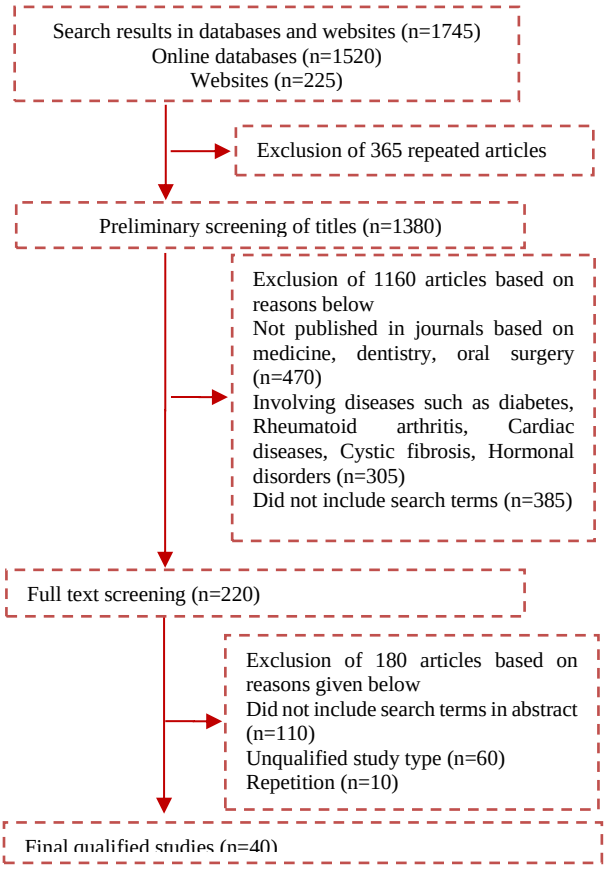

Figure 1: PRISMA flow diagram.

Table I: Brief Summary of included studies.

No	Author Name	Year	Study Design	Main findings
1	Pawar S et.al	2021	Original article	The role of nuclear envelope and inner nuclear membrane proteins in various cellular functions.
2	Nair et.al	2019	Original article	Crucial parameters involved in cytoplasmic cell signaling
3	Dobrzynska A et.al	2016	Original article	The extensive contact between nuclear lamina with integral nuclear proteins and their actions critical for cellular processes and therapeutic approaches.
4	Ptak C et.al	2017	Review	The inter-relation of nuclear proteins is explained.
5	He H et.al	2023	Review	The role of transcription factors in cellular viability and various metabolic conditions along with their rational applications such as use of biosensors are being discussed.
6	Wang X et.al	2014	Original article	The modular organization of core modular complex is discussed.
7	Lee H et.al	2019	Review	The role of STAT3 in signaling cascades associated with tumor microenvironment and cancer progression.
8	Kraemer WJ et.al	2020	Review	Testosterone, estrogen, insulin signaling pathways are discussed.
9	Weikum ER et.al	2018	Original article	The role of nuclear receptors in various physiological processes as well as their role in acting as a therapeutic targets in conditions such as cancer.
10	Xu HE et.al	2015	Original article	The various nuclear receptor families such as hormone receptors are being discussed alongwith their potential as drug targets.
11	Gou Q et.al	2017	Overview	The regulative mechanism of PPARs on cancer progression is discussed.
12	Antolin A et.al	2014	Original article	Therapeutic targets and agents targeting DNA repair pathways specifically PARP inhibitors and proteins to develop anti-cancer agents.
13	Del Nagro C Et.al	2014	Original article	The depletion of NAD, a central metabolite depletion is discussed in regards with a novel therapeutic target in oncology.
14	Okuda A et.al	2017	Original article	The role of PARP inhibitors in activating the p53 signaling pathway in neural stem cells.
15	Pietrzak et.al	2018	Original article	The role of PARP1 in cell protection by activating expression of proteins, redox signaling pathways and DNA repair machinery.
16	Bantele et.al	2019	Original article	The role of DNA damage checkpoint kinase Mec1-Ddc2 in DNA damage is assessed by analyzing its effect quantitatively on different ssDNA signals.
17	Tyagi et.al	2016	Original article	The role of chromatin remodelers in molecular and cellular function viz nucleosome sliding, eviction, histone exchange, histone post-translational modification, chromatin compaction, accessibility, transcription, replication, DNA repair.
18	Clapier CR et.al	2017	Original article	The mechanisms of action and regulation of ATP-dependent chromatin remodeling complexes are discussed.
19	Sundaramoorthy R et.al	2020	Original article	The role of different classes of chromatin remodeling enzymes is discussed.
20	Marc A et.al	2020	Original article	The role of histone modifying enzymes in transcriptional regulation and their association with chromatin modifications is discussed.
21	Bishop TR et.al	2023	Original article	The implications of histone acetyltransferases (HATs) and the use of acetyl-CoA competitive HAT inhibitors as potential therapeutic agent in cancer treatment is discussed.
22	Gauthier BR et.al	2021	Review	The dynamic nature of nuclear envelope is discussed in relation to its physiological functions and its role as a diagnostic factor for pathologies like cancer.
23	Buchwalter et.al	2023	Review	The dynamic regulation of lamin filaments through their biogenesis, assembly, disassembly, and degradation is discussed
24	Nastaly et.al	2020	Original article	This study suggested that emerin is an important determinant of nuclear polarity and front-rear cell polarity is transmitted to the nucleus.
25	Sun Z et.al	2019	Review	Protein homeostasis in eukaryotes is discussed.
26	Ibarra A et.al	2015	Review	The genome-related functions of nuclear pore complex and their impact on essential DNA metabolism processes such as transcription, chromosome duplication, and segregation is discussed.
27	Borowicz P et.al	2020	Original article	The role of adaptor proteins for normal immune cell operation as well as in pathogenesis of cancer is discussed.
28	Qin Y at.al	2023	Original article	The isolation of nuclear proteins, critical for nuclear proteome profiling was performed for the evaluation of nuclear proteins.

29	Hopkins MM et.al	2016	Original article	The proliferation of prostate cancer cells in relation with receptor tyrosine kinase. Lysophosphatidic acid (LPA) and Epidermal growth factor (EGF) is discussed.
30	Hadzic S et.al	2017	Original article	The Toluidine blue test can be auxiliary in clinical diagnosis but does not replace the pathohistological analysis in detection of oral cancer.
31	Parakh MK et.al	2017	Original article	The sensitivity of toluidine blue was found to be statistically significant for identifying biopsy site in potentially malignant lesions.
32	Parakh et.al	2020	Narrative review	The use of toluidine blue stain, methylene blue, Lugol's iodine, and chemiluminescence for identifying a site for biopsy in early premalignant states.
33	Nigam P et.al	2014	Review	The use of Optical coherence tomography (OCT),Fluorescence diagnostic imaging and Optical spectroscopy in early and accurate diagnosis of oral cancer is discussed.
34	Kokubun K et.al	2023	Original article	Histological and cytological examinations should be performed if tumor-like lesions in oral cavity are suspected clinically because cytological diagnosis of superficial-differentiated oral squamous cell carcinoma is occasionally inconsistent .
35	Vibhute NA et.al	2021	Original article	Autofluorescence Examination by VELscope can be used as a potential complementary diagnostic aid in early detection of oral cancer.
36	Ganga RS et.al	2017	Original article	The VELscope examination alone cannot provide a definitive diagnosis as to the presence of dysplastic tissue change due to the high number of false-positive results limits its efficiency as an adjunct.
37	Contaldo M et.al	2019	Original article	In vivo, reflectance confocal microscopy (RCM) is recommended to avoid the need for biopsy of lesions suspected of tumoral changes.
38	Goldoni R et.al	2021	Review	All molecules and nano biochemical substances, or materials present in saliva and potentially suitable as biomarkers of local/systemic diseases or conditions are discussed.
39	Venkata et.al	2023	Original article	The assessment of p53 in oral cancer will be able to predict adverse features.
40	Sujir N et.al	2019	Case series	The recent trend of changing demographics and etiology associated with oral cancer adding to the diagnostic challenges is discussed.

Discussion

Through a number of several mechanisms, including post-translational changes, protein-protein interactions, and subcellular localization, the function of integral nuclear proteins is closely regulated. These regulatory systems can become dysregulated or mutated, which can interfere with cellular signaling and contribute to the pathogenesis of a variety of illnesses, including as cancer, neurodegenerative diseases, and cardiovascular ailments.[3] This review provides a comprehensive examination of many integral nuclear proteins and their diverse functions in cellular signaling. Its diverse functions in chromatin remodeling, DNA repair, epigenetic alterations, and transcriptional regulation highlight its impact on cellular behavior and pathological processes.

Our review findings were aligned regarding the cellular interactions of integral nuclear proteins such as MAPK pathway, role of histones with a study done by Bahar et.al in 2023. [30]. However, certain studies in our review lack proper methodology such as study done by Goldoni et. al in 2021. [39]

We are set to further understand the intricacies of nuclear signaling as technology develops. Innovative technologies such as cutting-edge imaging methods, genome-wide studies, and computer modelling, will make it possible to better comprehend the dynamic interactions between integral nuclear proteins and the wider signaling environment. With certainty, this information will present new therapeutic targets and approaches for treating a variety of disorders such as amyotrophic lateral sclerosis, frontotemporal dementia, Alzheimer's disease, and Huntington's disease.[31] Few of the cutting-edge imaging methods used for detection of potentially malignant disorders and oral cancers are mentioned below:

A dye named as Toluidine blue (TB) has strong affinity for precancerous lesions, as it binds to them aiding in their detection. It is combined with Lugol's iodine, to help in effective diagnosis with oral malignancies and other abnormalities. It is a metachromatic dye that is used to stain DNA and RNA. A cell's mitochondrial DNA is stained, and cells with an extreme or lacking measure of DNA might be seen in tissues that have dysplastic changes. A brown-black stain is obtained when glycogen and Lugol's solution iodine interact, allowing a clear definition

of the malignant alteration.[32] TB is an effective, quick, affordable, and additional diagnostic method for finding a few PMLs. It has been demonstrated that TB aids in the selection of biopsy sites and the definition of lesion borders. LOH at 9p has been linked to loss of heterozygosity, LOH at 3p and 17p is associated with dysplasia, as demonstrated by latest research on lesions stained with TB.[33] The methylene blue staining technique uses a dye made of glycerol, dimethyl sulfoxide, 1% malachite, 1% methylene blue, and 0.5 percent eosin.[34]

Utilizing a single-handled, chemiluminescent light stick that can emit light at wavelength of 430, 540, and 580 nm, it enhances conventional visual assessments, according to research. Dysplastic or hyperkeratinized lesions reflect light, seeming white, while typical epithelium retains light, seeming dark.[35] Practitioners can use a chemiluminescent light like Vizilite and a rinse of diluted acetic acid for early detection of oral cancer. Latest research on high-risk individuals have corroborated that when Vizilite is used in combination with TB, it can precisely distinguish lesions with visible signs of dysplasia or any malignant growth in situ. The strategy is preventive, non-invasive, and has the potential to save lives. [36]

Another technique can be used which is affordable, painless, and safe alternative named as Brush Cytology. A Utilizing a non-lacerating cytobrush collect cells from the oral epithelium, which are transferred on a glass slide stained with a modified Papanicolaou test and examined. A major controversy around Brush cytology is that it has given false-negative results in detecting oral epithelial dysplasia in tumors. This cannot be used as the definitive diagnostic tool for the detection of oral cancer and additional cutting-edge diagnostic tools are required for early detection and prevention.[37]

VELscope is a portable optical device which is designed to detect abnormality via autofluorescence in the oral cavity. This tool has been proven to be very helpful amongst medical professionals as it aids in early detection of oral diseases. It has been used as a screening tool for various types of cancers such as lung, cervical, skin and oral cavity thereby aiding in preventing and early detection of malignancies.[35] VELscope utilizes tissue autofluorescence to identify dysplastic lesions in the oral cavity, which can otherwise go undetected in normal light. The normal mucosa fluoresces bluish-green color so it helps in detection if there is any change in color. [38]

This imaging technique has many benefits such as high resolution imaging and optical sectioning. It helps in identifying oral cancer from normal oral mucosa by identifying markers like nuclear abnormalities. However, this tool needs further refinement. Confocal images have shown the presence of characteristic features of oral cancer, such as nuclear irregularities. A more advanced iteration of this device is needed so that it can be deemed a dependable noninvasive tool used for early diagnosis of oral cancer. [39]

One of the recent developments for detecting oral cancer is the use of saliva. This method is preferred because it is easily accessible, minimally invasive, and highly efficient as a diagnostic medium. Another way of detecting oral cancer is by analyzing a patient's saliva transcriptome. As this is a latest technique, studies are under going to identify genetic pattern in saliva that can be linked with oral cancer.[40]

They can be found in various cell types: plasma, cytoplasm, cell membranes and body fluids. Amongst the most reliable indicators of oral squamous cell carcinoma progression are inherited mutations in the tumor suppressor gene p53, chromosomal polysomy (DNA ploidy), and abnormalities (known as loss of heterozygosity, LOH) in chromosomes 3p or 9p, due to changes in another tumor suppressor gene, p16.[41]

Few of the analytical tests that could be used to examine and characterize are cancer silencer activity, oncogene expression, cell proliferation markers, angiogenic factors, and cell adhesion molecules can provide insight into the prognosis of individuals with Oral cancer. Molecular analysis of exfoliated cells reveals similar alterations to those observed in tumor biopsy specimens.[42]

Conclusion

This review offers a thorough examination of many integral nuclear proteins and their varied functions in cell signaling. Their various functions in chromatin remodeling, DNA repair, epigenetic alterations, and transcriptional regulation highlight their impact on cellular behavior and disease processes. Our review contains the role of integral nuclear proteins, chromatin complexes and transcription factors and we might have missed analysis of other associated factors such as global protein expression and secretion in OSCC tissues that may provide an unbiased approach to find vital biological pathways, that are responsible for disease development and progression.

Further research into integral nuclear proteins and how they interact with cytoplasmic signaling pathways will enrich our comprehension of cellular communication and open up possibilities for future development of novel treatments that specifically target nuclear signaling. The expertise and training of dentists in diagnosing oral cancer at its pre malignant stage is essential to halt its progress to later stages.

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