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Corresponding Author
Karthik Shunmugavelu,
Department of Dentistry/Oral and Maxillofacial Pathology, PSP medical college hospital and research institute Tambaram Kanchipuram main road Oragadam Panruti Kanchipuram district Tamilnadu 631604

Author Designation
[1,2]Assistant Professor
[3]Senior Resident

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Vital Role of P63 in the Field of Pathology and Oncology Pertaining to Adult and Paediatric Population A Systematic Review

[1]Teena Eugene, [2]Vinutha Gali and [3]Karthik Shunmugavelu

[1]Department of Pathology, SRM Medical College Hospital and Research Centre, SRM Institute of Science and Technology SRMIST, Potheri, Kattankulathur, Chennai, Tamilnadu,India

[2]Department of Pathology, Sree Balaji Medical College and Hospital, 7, CLC Works Rd, Shankar Nagar, Chromepet, Chennai, Tamil Nadu 600044, India

[3]Department of Dentistry/Oral and Maxillofacial Pathology, PSP medical college hospital and research institute Tambaram Kanchipuram main road Oragadam Panruti Kanchipuram district Tamilnadu 631604

ABSTRACT

Anything that indicates information about a cancer, such as its aggressiveness, potential response to treatment, or state of response to treatment, that is either present in or produced by cancer cells, other cells of the body, or both in response to cancer or certain benign (noncancerous) conditions is called a tumor marker. Major databases such as Medline were explored detailed literature search in resulting in a systematic review pertaining to p63. Three research scientific articles dated between 2020-2024 pertaining to p63 were highlighted. Tumor markers have generally been proteins or other chemicals that are generated at larger concentrations by cancer cells than normal ones. Some cancer patient' blood, urine, faeces, tumors and other tissues and body fluids may include these. Detailed information regarding p63 and its vital role in the field of pathology and oncology is discussed in this systematic review.

INTRODUCTION

Certain markers may be associated with multiple types of cancer, others exhibit specificity to a particular type[1]. Tumor markers offer a diverse array of crucial insights vital for cancer care, including: facilitating cancer diagnosis. Nevertheless, an elevated tumor marker level doesn't conclusively indicate cancer presence. Nonmalignant conditions can also elevate tumor marker levels, while not all individuals with a specific cancer type exhibit heightened level of the associated tumor marker. Hence, tumor marker assessments typically accompany other diagnostic tests like biopsies or imaging studies for accurate cancer diagnosis. Revealing the cancer type, its stage and prognosis, as well as suggesting effective treatment options. Tumor markers indicating suitability for specific targeted therapies are occasionally termed as biomarkers for cancer treatment. Typically, biomarkers are gauged in tumor tissue samples. However, tumors can discharge cells or fragments of biological material into the bloodstream, detectable through liquid biopsy tests. Assessing treatment efficacy. Serial monitoring of tumor marker levels during treatment can provide insights into tumor response. Detecting cancer recurrence. Periodic post-treatment measurements of tumor markers serve as a tool for recurrence surveillance[1].

MATERIALS AND METHODS:

"p63" AND "pathology" AND "oncology'' were the words used in MEDLINE database using advance search strategy targeting different article categories between 2020 to 2024. The result was 37 articles, out of which we selected 3 articles based in the inclusion criteria. Inclusion criteria was of scientific literature between 2020-2024. Exclusion criteria was of scientific literature devoid of scientific literature irrelevant to the specific search. This systematic review was conducted to determine importance of bite marks following the guidelines of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). PubMed, Lilacs, Embase, Scopus and Web of Science were the source of electronic databases. The search strategy used Boolean operators (AND and OR): [ALL ("p63") AND (pathology OR oncology OR cancer OR tumour OR marker OR neoplasm) AND (immunohistochemical)]. The following data were collected: first author, year, country of study, type of study and outcome. The quality of studies was assessed using the STROBE (Strengthening the Reporting of Observational Studies) checklist.

RESULTS AND DISCUSSIONS

Three articles were included in this systematic review based on the selection criteria and PRISMA flow chart. We analyzed and mentioned in the three articles

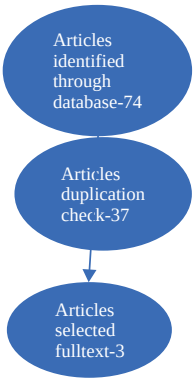

Fig. 1: PRISMA flowchart

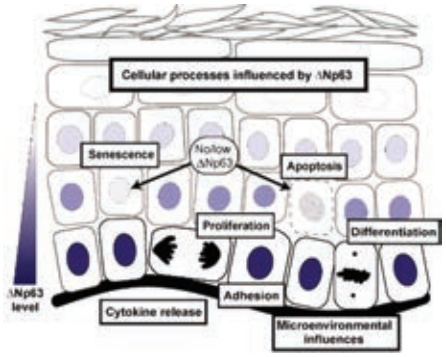

Fig. 2: ΔNp63α regulates cell intrinsic and extrinsic biological processes involved in normal epidermal morphogenesis and homostasis. In cancer, amplification of p63 leads to the hijacking of these processes to support conversion to and progression of the malignant state.

reviewed. This included only relevant research articles and excluded articles pertaining to non specific search terms (Fig 1 and 2).

The significance of p53 in maintaining genomic integrity is emphasized by the frequent occurrence of mutation or inactivation of p53 in human cancers[2]. Nearly two decades following the characterization of the p53 gene, the identification of two additional family members, p63 and p73, further elucidated this importance. These discoveries were based on structural resemblances in key p53 functional domains: the transactivation (TAD), DNA binding (DBD) and oligomerization (OD) domains[3]. Unlike the conventional understanding of p53, these newly identified family members were found to comprise multiple protein isoforms resulting from alternative promoter usage and C-terminal splicing.

Both p63 and p73 encompass two subclasses of proteins, distinguished by the presence of either TA or

Table 1: An overview.

Author	Title	Journal	Outcome
Steurer S, Riemann C, Büscheck F, Luebke AM, Kluth M, Hube-Magg C, *et al*.	p63 expression in human tumors and normal tissues: a tissue microarray study on 10,200 tumors.	Biomark Res. 2021 Jan 25;9(1):7.	Aggressiveness - loss of p63
Yuichiro Hatano.	The Pathology according to p53 Pathway.	Pathobiology. 14 Nov 2023.1-14. https://doi.org/10.1159/000535203	Potential biomarker Collaboration between pathologist and data scientist
Lépine C, Klein P, Voron T, Mandavit M, Berrebi D, Outh-Gauer S, Péré H, Tournier L, Pagès F, Tartour E, Le Meur T, Berlemont S, Teissier N, Le Meur T, Berlemont S, Teissier N, Carlevan M, Leboulanger N, Galmiche L, Badoual C.	Histological Severity Risk Factors Identification in Juvenile-Onset Recurrent Respiratory Papillomatosis: How Immunohistochemistry and AI Algorithms Can Help?	Front Oncol. 2021 Mar 8;11:596499. doi: 10.3389/fonc.2021.596499. PMID: 33763347; PMCID: PMC7982831.	

N domains at the amino terminus. The TAp63 isoforms feature a transactivation domain resembling that of p53, capable of mimicking its functionality. In contrast, the N isoforms lack this domain and act as dominant negatives to TAp63/73 and p53. Despite lacking a TA domain, the N isoforms of p63 can positively regulate gene transcription through additional transactivation domains. Shortly after the identification of p63 and p73 isoforms, similarly transcribed p53 isoforms were also reported, co-expressed with canonical p53, thereby introducing further biological complexity that can influence functional outcomes[4]. Within the p63 subclasses, a total of ten p63 isoforms stemming from C-terminal alternative splicing have been documented thus far: TA- and N- p63α, ß, γ, δ and e. Structurally, the C-terminus of Np63a encompasses additional functional protein domains, including a Sterile Alpha Motif (SAM) protein–protein interaction domain, a transactivation inhibitory domain (TID) and two distinct alternate transactivation domains: one termed TA2, encoded by exon11 and 12 and another situated in the N terminus[2].

In addition to p63, there are twenty-nine p73 mRNA transcripts, some of which may not undergo translation and twelve p53 protein isoforms (4,5). These family members function as tetramers via their oligomerization domains, with p63 and p73 showing a preference for interaction over p53, favouring hetero-tetramer formation (6). Interactions between p63/p73 and p53 occur primarily through the DNA binding domain (DBD). Wild type (WT) p53 targets Np63a for degradation via this domain, while mutant p53 also hinders the transactivation capacities of p63 and p73 through this interaction[7-9]. Therefore, the structural resemblances within the p53/p63/p73 family enable diverse interaction mechanisms among them. Consequently, the balance and expression levels of these isoforms in a specific context can significantly influence biological outcomes[2]. Canonical p53 is universally expressed and activated during cellular stress, while p63 and p73 isoforms display tissue-specific expression patterns crucial for normal development and homeostasis[10,11]. ΔNp63α predominates in adult human epidermis, particularly in the proliferative skin compartment[10]. In vivo studies underscore p63's indispensability for normal epidermal development and homeostasis[12], with mutations in p63 associated with ectodermal dysplasia syndromes featuring skin phenotypes in humans[13]. Similarly, the loss of p73 has been implicated in tissue-specific roles[14,15]. Initially, there was an expectation that mutations in p63 might contribute to the development of cancers where p53 remains unaltered. However, rather than mutation, the focus shifted towards the overexpression of p63, particularly the Np63 isoforms, which has been linked to malignant conditions, notably squamous carcinomas like those affecting the head and neck and skin[16]. This systematic review offers an in-depth exploration of the pivotal role of p63, particularly Np63a, in normal epidermal development and homeostasis, shedding light on the diverse pathways influenced by Np63a dysregulation, which are implicated in the pathogenesis of squamous cancers[2].

p63 modulates gene expression profiles locally and globally through various mechanisms, including direct binding to gene promoters, “bookmarking” of enhancers and influencing the chromatin landscape in a context-dependent manner. Additionally, it regulates non-coding RNAs. The balance of isoforms is crucial in DNA binding due to shared homology within the DNA binding domain. ΔNp63 isoforms, particularly ΔNp63α, can bind to canonical p53 DNA binding sites, competing with p53 and TAp63/73. However, discrete p63 consensus binding sites have also been identified. ΔNp63a can both activate and repress gene transcription. In a genome-wide mapping approach, p63 and p73 were found to share genomic targets in a cervical carcinoma cell line, suggesting a biological outcome influenced by the relative expression levels of isoforms. Context-dependent co-factors also affect direct gene regulation, with ΔNp63a interacting with transcription factors such as SOX2, c-Rel and Y-box binding protein-1[17]. Moreover, p63 influences global gene expression through chromatin remodeling. It acts as a “bookmark” for genomic loci, maintaining an open chromatin landscape required for transcriptional activity during differentiation. Non-coding RNAs, like micro RNAs (mi RNAs) and long non-coding RNAs (lncRNAs), provide alternate mechanisms for gene

regulation by p63[7,18,19]. miRNAs targeted by p63 impact expression of epigenetic regulatory factors and transcriptional regulators, affecting keratinocyte growth regulation and chemotherapeutic response. Dysregulated lncRNAs, targeted by ΔNp63α, are associated with cancer, including head and neck squamous cell carcinomas (HNSCCs). Additionally, mechanisms regulating ΔNp63α, such as stabilization, degradation, cellular localization, interactions with other proteins and differential methylation status, play pivotal roles in modulating its activity[16]. Early investigations in p63-/- mice revealed a profound absence of stratified squamous epithelium, suggesting pivotal roles for p63 in lineage commitment and/or stem cell maintenance. Subsequent studies employed various models to investigate the effects of gain or loss of individual p63 isoforms, utilizing strategies like basal cell-targeted overexpression, tissue-specific knock-in (on a p63-null background) and isoform-specific knock-out transgenic lines. For instance, TAp63a overexpression driven by the keratin 14 promoter in WT mice resulted in epidermal hyperplasia and loss of terminal differentiation, implying a role for TAp63a in driving epithelial stratification. However, knock-in studies on a p63-null background failed to replicate these effects, suggesting that TAp63a reconstitution in keratin 5-expressing keratinocytes was insufficient for complete epidermal formation. Conversely, keratin 5-driven expression of Np63a in p63-/- mice partially restored the epidermal basal layer and expression of specific keratins but failed to fully re-establish upper epidermal layer markers. Similarly, induction of Np63a or Np63ß in a p63-null background partially restored epithelial integrity, stratification and differentiation marker expression, indicating a role for Np63a or Np63ß in initiating stratification. Specific knockout of Np63a isoforms largely recapitulated the phenotype of original p63-null mice, emphasizing the significance of Np63a in regulating epidermal development and commitment. These findings highlight the necessity for a finely balanced expression of p63 isoforms for complete epidermal stratification. Moreover, co-expression of TAp63a and Np63a in mice resulted in enhanced structured epidermal formation and differentiation, indicating synergistic effects compared to single isoform reconstitution[2]. Increasing evidence supports a role for p63 in stem cell maintenance. Studies in p63-deficient mice suggested progenitor cell exhaustion and non-regenerative differentiation, supporting the hypothesis that p63 is involved in maintaining epithelial stemness and regenerative capacity. Within the epidermis, Np63a is highly expressed in stem cells and basal keratinocytes, suggesting its role in stem cell maintenance. Premature aging observed in p63+/- mice was attributed to diminished progenitor cell self-renewing capacity. Furthermore, epidermal-specific conditional knockout of TAp63 in transgenic mice led to premature senescence and depleted precursor cell populations, indicating the involvement of p63 in maintaining stemness and tissue renewal. Collectively, these findings suggest that p63 isoform activity promotes stem cell maintenance and tissue renewal.(2) Additionally, p63 plays a broader role as a regulator of epidermal cell fate via epigenetic regulatory mechanisms. TFAP2C, a transcription factor, interacts with p63 in epidermal development, priming keratinocyte maturation. Feedback regulation between p63 and TFAP2C enforces epidermal lineage maturation. Np63a interactions with chromatin modifiers can mediate transcriptional repression. Histone deacetylases (HDACs) regulate gene transcription by affecting chromatin structure. Deletion of HDAC1/2 resulted in a phenotype reminiscent of p63-/- mice, indicating their role in regulating gene targets repressed by Np63 in undifferentiated cells[20]. Establishing and maintaining epidermal homeostasis necessitates a delicate equilibrium between positive and negative growth signals, encompassing altered proliferation signaling, differentiation induction, senescence and apoptosis. Np63a orchestrates these processes by modulating downstream targets, including but not limited to bone morphogenetic protein (BMP) 7, Notch1, Dlx3, sonic hedgehog (SHH), keratin 14, fibroblast growth factor receptor 2 (FGFR2) and transforming growth factor ß (TGF-ß). Recent findings highlight Np63a's role in supporting epidermal differentiation by enhancing ZNF185 expression, crucial for epithelial stratification. Moreover, studies elucidating the regulation of the epidermal differentiation complex (EDC) underscore the involvement of p63 in modulating chromatin and nuclear assembly factors such as Satb1 and Brg1. Disruption of p63 or Satb1 alters chromatin conformation within the EDC domain, impacting genes essential for epidermal barrier function. Additionally, Brg1 facilitates the relocation of the EDC to the nuclear interior. Furthermore, the interaction between p63 and histone methyltransferase KMT2D at target enhancers maintains adhesion and proliferation capacity in normal epidermal homeostasis[2]. The significance of p63 and its downstream target genes in both developmental processes and the maintenance of epidermal equilibrium is highlighted by the correlation between human germline mutations in p63 and developmental anomalies typified by ectodermal dysplasias. These disorders encompass a spectrum of manifestations such as limb truncations, craniofacial abnormalities and disruptions in the maturation of the epidermis during development. These ectodermal dysplasia syndromes are attributed to specific domains within the p63 gene and exhibit diverse degrees of

involvement affecting the epidermis and its associated appendages. This association underscores the critical role of p63 in orchestrating proper embryonic development and epidermal tissue integrity[13]. Stuerer *et al*. findings reveal that p63 expression is predominantly observed in specific normal tissues, notably squamous epithelium, urothelium, thymic epithelial cells and basal/myoepithelial cells of various epithelial organs, as evidenced by our study encompassing 12,620 tissues. Remarkably, p63 expression in these tissues tends to be robust, while being entirely absent in other tissue types. This observation aligns seamlessly with p63's established role in orchestrating embryonic cellular differentiation towards distinct cell lineages. The human tumor protein (TP) 63 locus lies on chromosome 3q27-28, a frequently amplified region in squamous cell carcinoma[3]. p63 expression has been detected in the embryonic ectoderm as early as the seventh to eleventh day of development[21]. This observation suggests that p63 may serve as the initial gene product distinguishing stem cells from their transiently amplified progeny in stratified squamous epithelia. Notably, studies have shown that p63 is specifically expressed by stem cells in the human epidermis and limbus, while transient cells do not exhibit p63 expression[22]. This compelling evidence strongly supports the notion that p63 can be regarded as a marker for stem cells[3]. Strong nuclear staining for p63 has been observed in various tissues including squamous epithelium, peripheric germinative cells of sebaceous glands, urothelium, thymic epithelial cells, myoepithelial cells in breast, parotid, submandibular and sublingual glands, basal cells in prostate, seminal vesicle and respiratory epithelium, as well as cytotrophoblasts in the first trimester and mature placenta. In squamous epithelia and urothelium, staining intensity gradually decreased from basal cells to the surface cell layer. Mild staining was also noted in some lymphocytes and high endothelial venules in lymph nodes. Conversely, p63 staining was notably absent in several tissues including aorta (intima and media), left ventricle of the heart, striated and skeletal muscles, uterus (myometrium), muscular wall of the gastrointestinal tract, renal pelvis, bladder, corpus spongiosum of the penis, ovarian stroma, fat tissue, red and white pulp of the spleen, stomach (antrum and corpus), duodenum, ileum, appendix, colon, rectum, gallbladder, liver, pancreas, bone marrow, Brunner gland of the duodenum, cortex and medulla of the kidney, epididymis, testis, bronchial glands, endocervix, proliferative and secretory endometrium, fallopian tube mucosa, corpus luteum, follicular cyst of the ovary, adrenal gland, parathyroid gland, thyroid gland, cerebellum (stratum molecular and neuronorum), cerebrum (grey and white matter) and anterior and posterior lobes of the pituitary gland[23]. A robust correlation has been observed between HSP70 and DNp63a in head and neck squamous cell carcinoma (HNSCC), indicating a significant relationship. This suggests that ▵Np63α plays an active role in the upregulation of HSP70, akin to the mechanism observed in mutant forms of ▵Np63α[24]. High rate of positivity of p63 immunostaining in cancers is usually seen with squamous cell carcinomas, urothelial cancers as well as tumors derived from the thymus[23]. The positivity of p63 in oral squamous cell carcinomas has been well documented. In oral squamous cell carcinomas the expression of p63 has found to be significantly higher in compared to the buccal mucosa[25]. A significantly higher p63 expression in the epithelium of oral sub mucous fibrosis has been found by researchers[26]. In the realm of salivary gland tumors, utilizing p63 immunohistochemical staining proves valuable in distinguishing between acinic cell carcinoma (ACC) and mucoepidermoid carcinoma (MEC) of the salivary glands. MEC consistently exhibits strong positivity for p63, serving as a reliable marker. Conversely, ACC tends to show negativity for p63, with sporadic instances displaying limited focal staining, typically accounting for less than 10% of cases[27]. The expression of the P63 gene has been detected in the majority of tooth germ cells and dental epithelium during the bud and cap stages, suggesting its involvement in epithelial differentiation throughout tooth development[28]. Furthermore, mutations in the P63 gene are associated with various tooth abnormalities in syndromes[29].

Positive immunoreactivity of P63 in seen in all layers of odontogenic keratocysts (OKC) except for the parakeratinized layer. Additionally, P63 reactivity has been observed predominantly in the basal-parabasal layers of dentigerous cysts (DC) and radicular cysts (RC), with weaker expression in the upper layers. (30)In ameloblastoma, P63 expression is more intense in peripheral cells compared to the stellate reticulum, suggesting higher proliferative activity in peripheral cells within tumor islands[30]. Similar patterns have been observed in other studies, indicating consistency in findings across different investigations[29]. Exploring P63 expression in various odontogenic lesions reveals distinct patterns. For instance, acanthomatous and granular cell types of ameloblastoma exhibit lower P63 expression compared to common ameloblastoma[29]. Adenomatoid odontogenic tumors display nuclear positivity for P63, indicating a basal characterization of tumor cells[31] Similarly, Pindborg tumors and Sclerosing odontogenic carcinomas demonstrate positive staining for P63,[32] while central granular cell odontogenic tumors show P63 expression in odontogenic epithelial islands but not in granular cells,

suggesting a lack of expression in mature differentiated cells[33]. The expression of P63 appears to be limited to immature basal-parabasal layers of epithelium, reflecting the immaturity of epithelial cells in keratinocytes of OKCs and suggesting its involvement in epithelial cell differentiation[34]. While some studies report variations in P63 expression among different odontogenic lesions,[34]. Additionally, investigations comparing P63 expression between ameloblastoma and its malignant counterpart, ameloblastic carcinoma, have shown to have no significant differences, suggesting a consistent pattern of P63 expression across these lesions[35,36,37].

CONCLUSION

Tumor markers have generally been proteins or other chemicals that are generated at larger concentrations by cancer cells than normal ones. Some cancer patient's blood, urine, faeces, tumors and other tissues and body fluids may include these. The utilization of genomic markers as indicators for tumors is steadily expanding. These markers encompass both genetic and non-genetic alterations within tumor DNA, along with the intricate patterns of gene expression within the tumor and mutations present in tumor genes. These indicators are detectable not only within the actual tumor tissue but also in tumor fragments released into bodily fluids. Numerous distinct tumor markers have been identified and are employed in therapeutic settings.

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