Dysregulation of LYN Gene Expression in Melanoma Patients: A Statistically Significant Association with Clinical Outcomes

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ABSTRACT

Skin cancer accounts for one-third of all diagnosed cancers, with 132,000 new cases of melanoma detected each year (1). By 2040, the melanoma burden is projected to reach 510,000 new cases (a 50% increase) and 96,000 deaths (a 68% increase) if 2020 incidence rates persist (2). Even though it only accounts for 2% of all occurrences of skin cancer, invasive melanoma is the cause of 80% of skin cancer deaths (3). Skin cancer is more common in the white population compared to the Asian population (2). The risk factors for melanoma include UV exposure, tanning, moles, skin type, gender, age, family history, and immunosuppression (4,5,6). In addition to these environmental and demographic risk factors, mutations in specific genes and dysregulation in signaling pathways significantly contribute to melanoma pathogenesis. Gene mutations associated with skin cancer primarily involve those linked to DNA repair, metabolism, and oxidative stress. Among these, the SRC signaling pathway is crucial for cell survival, migration, and proliferation, with alterations in this pathway significantly impacting skin malignancies. The Lyn gene, a member of the SRC family, is instrumental in signal transduction and is expressed across various tissues. Previous research has indicated that Lyn overexpression enhances cell proliferation, migration, and invasion in several cancers, including cervical, breast, oral, and gastric cancers. However, there is a scarcity of studies focusing on the role of Lyn in skin cancer. This study aimed to investigate the relationship between Lyn gene expression levels and the development and progression of skin cancer. We analyzed 170 skin cancer samples alongside adjacent control tissues using quantitative real-time polymerase chain reaction (qPCR), with β-actin serving as an endogenous control. Statistical analysis was performed using ANOVA and t-tests. Our findings revealed a significant up-regulation of the Lyn gene (P=0.0017) in skin cancer patients compared to adjacent controls, indicating that Lyn overexpression is significantly associated with skin cancer. This study contributes to the understanding of the molecular mechanisms underlying skin cancer and highlights the potential role of Lyn as a biomarker for disease progression.

INTRODUCTION

Skin cancer, comprising melanoma, basal cell carcinoma (BCC), and cutaneous squamous cell carcinoma (SCC), displays one of the highest global occurrences of all cancer types (1).

The etiology of this malignancy lies within abnormal skin cell proliferation due to unrepaired DNA damage from mutation or genetic defects, primarily affecting the epidermis which is the top layer of the skin composed of epithelial cells and melanocytes and thus leading to non-melanoma skin cancer (NMSC), the most common type worldwide, while mutations in melanocytes can cause the formation of malignant melanoma (2). And despite representing about 2% of all skin cancer incidences, aggressive melanoma accounts for 80% of skin cancer fatalities (3).

Individuals with increased susceptibility to melanoma often exhibit a combination of risk factors, including excessive exposure to ultraviolet radiation (especially during childhood and from artificial sources like tanning beds), phenotypic traits associated with reduced melanin production (fair skin, light-colored eyes and hair), a family history of melanoma, the presence of numerous or atypical nevi, advanced age, and compromised immune system function due to various medical conditions or treatments (4).

Lyn, a member of the Src family kinases (SFKs) located on chromosome 20 at locus 8q13 in humans, plays a crucial role in various cellular processes like proliferation, differentiation, and apoptosis, and is overexpressed in many diseases such as solid tumors and autoimmune diseases; however, despite its potential value in analyzing the developmental mechanism of melanoma, the role of Lyn in melanoma remains poorly understood (5).

And although Lyn is rarely a primary driver of oncogenesis, its frequent overexpression and participation in critical oncogenic signaling cascades in diverse hematopoietic malignancies (including AML, CML, and B-cell leukemias) and solid tumors (such as prostate, colon, and basal breast cancers) underscore its significant role in sustaining the malignant phenotype, thus establishing Lyn as a promising therapeutic target (6).

Given the established role of Lyn in various cancers, this study aims to specifically investigate its involvement in skin cancer. By analyzing Lyn gene expression in 170 tumor and adjacent control tissue samples using quantitative real-time polymerase chain reaction (qPCR), this research will elucidate the clinical significance of Lyn dysregulation in disease progression and its potential as a therapeutic target. Ultimately, this study seeks to provide novel insights into the molecular underpinnings of skin malignancies and pave the way for future studies exploring targeted interventions.

MATERIAL AND METHODS

Tissue Specimen and Data Collection

This research agreed with past consents from the Ethical Review Board (ERB). Informed consent was taken from the individuals, and a Performa was filled out for every patient with all the required data like age, gender, addiction, and ethnic background. 170 paired Skin cancer tissue samples and adjacent healthy control tissues were collected. The samples were collected from different hospitals of Punjab, Pakistan. The normal tissues or controls were histopathologically confirmed, and their reports were collected from the lab. The average age was determined. Tumor and healthy tissue samples from the immediate surrounding area (about 2 cm) were collected and frozen in RNAlater® (Invitrogen, California). United States of America) Furthermore, kept at 4 degrees Celsius in an ice bucket on the way to the lab. Patients who underwent surgery were surveyed to collect demographic data and clinicopathological features such as tumor grade, nodal involvement, stage, and age.

RNA isolation and quantification

The standard TRIzolTM reagent technique was used for RNA extraction from tissue samples (Qadir et al., 2021). Extracted RNA was measured using a nanodrop (IMPLEN GmbH, Germany). One microliter of RNA was injected into a Nanodrop for each sample. Absorbance was measured at 260 and 280 nm to examine the role of chloride channel dysregulation in the development and progression of bladder cancer. Models with a 260/280 ratio greater than 1.9 were considered high enough RNA quality for further analysis.

cDNA Synthesis

cDNA synthesis was used to analyse *LYN Gene* expression in each sample. The RNA was transcribed into cDNA using a Thermo Scientific cDNA synthesis kit (Cat#K1622) per the manufacturer's instructions. So generated cDNA was verified by electrophoresis in 2% agarose gel.

Quantitative Real-Time Polymerase Chain Reaction

Real-Time PCR, also well-known as quantitative PCR (qPCR), was used to study gene expression at the RNA level. After careful and measured preparation of the reaction mixture, it was transferred into the microcentrifuge tubes. These tubes are designed to fit the PCR rack. The reaction mixture boxes were placed in an RT-PCR frame after properly closing them. The qPCR was carried out using a Step-One Plus RT-PCR system (Applied Biosystems). As an internal control GAPDH was used for *LYN* gene data normalization (Yarotskyy et al., 2022).

Statistical analysis

2 -ΔΔ CT method was used to determine the relative mRNA expression of the gene/reference gene. Graph Pad Prism software was applied to statistically analyze the data obtained from experimentation in this study. The relative expression of genes was determined using ANOVA and Student t-tests and correlated with the proliferation marker's relative expression. The data was considered to be statistically significant at a p-value of 0.05.

RESULTS

This study was designed to analyze Lyn gene mRNA expression using quantitative real-time polymerase chain reaction (qRT-PCR). The relative expression of Lyn was compared between skin cancer patients and control samples. The study included a total of 170 skin cancer samples alongside adjacent normal controls, analyzed with qRT-PCR. The cohort was composed of 54% males and 46% females, with an average age of 48 years. Among participants, 57% were aged 48 years or younger, while 43% were older. The tumor grades were classified as 48% Poor-Moderate and 52% Well-differentiated. The frequency distribution of clinical and demographic factors is summarized in Table 3.1. Real-time PCR analysis revealed that Lyn gene expression was significantly higher in skin cancer patients compared to controls (P=0.0017), as shown in Figure1. A student t-test indicated upregulation of Lyn in males. However, the overall expression difference between genders was not significant (p=0.0949), as depicted in Figure2. Patients over 48 years exhibited higher Lyn expression levels compared to those under 48, although the variation was non-significant (p=0.3232), illustrated in Figure 3. Comparative analysis of Lyn expression between early (I-II) and advanced (III-IV) stages showed non-significant upregulation in stage I-II (p=0.45), as shown in Figure4. The correlation of Lyn expression with T stages revealed non-significant upregulation (p=0.6764) in advanced T stages (T1-T2) compared to early stages (T3-T4), as depicted in Figure 5. The analysis showed non-significant upregulation of Lyn in N0 stage (P=0.136) compared to N1-N3 stages, as illustrated in Figure 6. Lyn gene expression showed non-significant upregulation (p=0.47) in early M stages (M0) compared to advanced M1 stages, as shown in Figure 7.

Table: 1

Parameters	**Patients**	**Controls**
Gender		
Female	(46%)	(46%)
Male	(54%)	(54%)
Age		
Mean	48±0.5	48±0.5
≥48	(44%)	(44%)
≤48	(56%)	(56%)
Clinical Stages		
I-II n (%)	(73%)	-
III-IV n (%)	(27%)	-
TNM Stage Classification		
T Stage		
T1-T2 n (%)	(70%)	-
T3-T4 n (%)	(30%)	-
N Stage		
N0 n(%)	(65%)	-
N1-N2 n (%)	(35%)	-
M Stage		
M0 n (%)	(94%)	-
M1 n (%)	(6%)	-

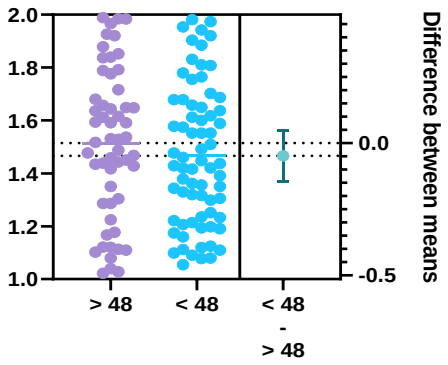

Fig 1 Age based relative expression of Lyn gene at mRNA level in skin cancer patients
***(p<0.05), ** (p<0.01), *** (p<0.001)**

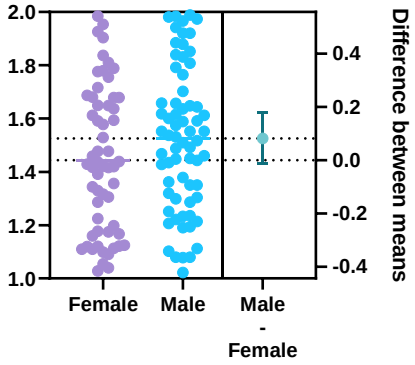

Fig 2 Gender based relative expression of *Lyn* gene at mRNA level in skin cancer patients
***(p<0.05), ** (p<0.01), *** (p<0.001)**

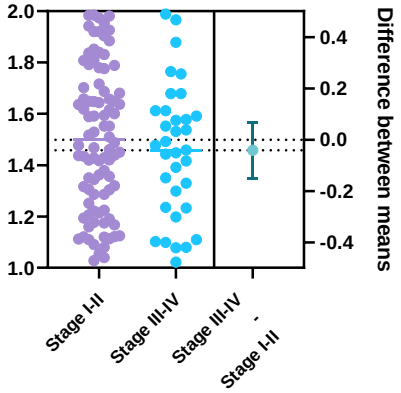

Fig 3 Relative expression of *Lyn* gene at mRNA level in clinical stages I-II and III-IV in skin cancer patients.
***(p<0.05), ** (p<0.01), *** (p<0.001)**

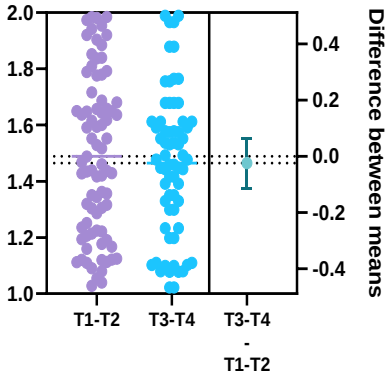

Fig 4 Relative *Lyn* mRNA expression in T stages in skin cancer patients.
***(p<0.05), ** (p<0.01), *** (p<0.001)**

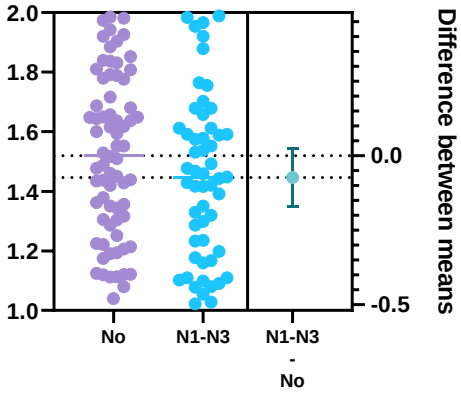

Fig 5 Relative *Lyn* mRNA expression in N stages (N0 and N1-N3) in skin cancer patients.
***(p<0.05), ** (p<0.01), *** (p<0.001)**

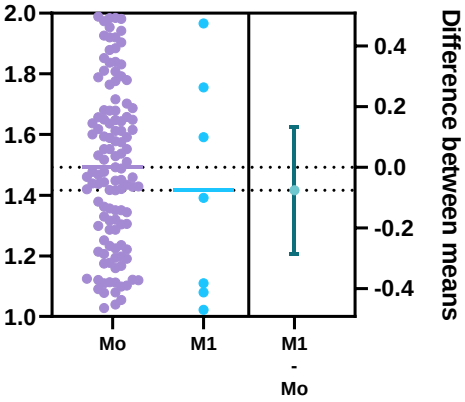

Fig 6 Relative *Lyn* mRNA expression in M stages (M0 and M1) in skin cancer patients.
***(p<0.05), ** (p<0.01), *** (p<0.001)**

DISCUSSION

Cancer typically arises when DNA is damaged, leading to uncontrolled growth and division of these damaged cells. Such alterations can result in skin cancer, characterized by the development of tumors as damaged cells proliferate uncontrollably. Skin cancer is generally diagnosed within the epidermis, the skin's outermost layer, facilitating its early detection (Qadir, 2016). Skin cancers are predominantly classified into two categories: melanoma and non-melanoma skin cancers (NMSCs). The latter includes basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), with melanoma representing the more aggressive form of skin cancer (Penta et al., 2018; Qadir, 2016). The incidence of melanoma has surged globally over the past four decades, particularly in Australia, where the occurrence rates can reach up to 40 cases per 100,000 individuals annually (Madan et al., 2010a). Studies indicate that men have a higher likelihood of developing melanoma compared to women (Khazaei, Ghorat, et al., 2019). Among NMSCs, BCC accounts for approximately 80% of cases, while SCC constitutes about 20% (Eisemann et al., 2014). A comparative analysis highlights an

increase in NMSC cases—53% in women versus 26% in men, with a more rapid rise in incidence for males (Waldman & Grant-kels, 2019). Furthermore, nearly 80% of individuals over 70 years of age are affected by NMSCs, with a threefold increase in incidence for males in this age group compared to females (Apalla et al., 2017). Geographical location and skin pigmentation significantly influence skin cancer incidence rates. Approximately 20-40% of Caucasians, 2-4% of Asians, and 1-2% of African Americans will develop skin cancer (Gloster & Neal, 2006). In Pakistan, the incidence rate appears lower at 0.47% compared to the global average of 3.1% (GLOBOCAN, 2018). Several endogenous and exogenous risk factors are associated with an increased susceptibility to skin cancer. These include genetic predisposition, fair skin, prior skin dysplasia, family history of cancer, and exposure to ultraviolet (UV) light—both intermittent and cumulative. Melanoma is primarily linked to sun exposure in early life, whereas NMSCs relate to both early and later life UV exposure (Wu et al., 2014). The human Lyn gene has been extensively characterized, predominantly expressed in hematopoietic cells. Lyn, a member of the SRC kinase family, plays a pivotal role in regulating growth factors, cytokines, and antigen-stimulating factors (Iqbal et al., 2010). Various cancer types have been linked to signal transduction pathways influenced by Lyn, which has been shown to regulate epithelial-mesenchymal transition (EMT) in breast cancer (Choi et al., 2010) and enhance the growth and motility of tumor cells in head and neck cancers (Wheeler et al., 2012). Additionally, activation of epidermal growth factor receptors (EGFRs) by Lyn promotes lung cancer cell proliferation (Sutton et al., 2013), and facilitates androgen receptor expression and activity in castrate-resistant prostate cancer (Zardan et al., 2014). Previous studies confirm that Lyn overexpression correlates with enhanced cell invasion, proliferation, and migration (Lin et al., 2019). In our study, Lyn expression was quantitatively assessed at the mRNA level in 170 skin cancer patients alongside their adjacent control samples using qPCR. The analysis considered various histopathological parameters, including gender (97 males, 73 females), age (≤48 and ≥48 years), clinical stages, TNM stages, and survival status. Our results demonstrated a significant upregulation of the Lyn gene ($p=0.0017$) in skin cancer patients compared to adjacent controls. This finding is consistent with previous studies reporting Lyn overexpression in cervical cancer (Lin et al., 2019), breast cancer (Choi et al., 2010), oral cancer, and gastric cancer (Su & Zhang, 2020).

Furthermore, we observed significant upregulation of the Lyn gene in early T stages (T1-T2) compared to advanced T stages (T3-T4). This aligns with earlier findings indicating that Lyn overexpression enhances cell invasion and migration across various cancer types (Lin et al., 2019).

Moreover, prior research demonstrated that Lyn knockdown significantly inhibits cell migration, proliferation, and invasiveness, indicative of its critical role in apoptosis and autophagy (Lin et al., 2019). Additionally, Lyn has been positioned as an invasion mediator and could represent a potential therapeutic target in the treatment of skin cancer (Choi et al., 2010).

CONCLUSION

The expression of the Lyn gene is vital in the formation and advancement of skin cancer, exhibiting notably elevated levels in cancerous tissues when compared to normal tissues. This positions Lyn as a potentially valuable biomarker for both diagnosis and monitoring, as well as a therapeutic target. In conclusion, the findings from our study underscore the regulatory role of the Lyn gene in skin cancer and its potential as a biomarker and therapeutic target for future clinical applications.

Limitations

This study has several limitations, including a restricted range of skin cancer types and a primary focus on gene expression without functional assessments of Lyn. Additionally, it did not differentiate

between various skin cancer forms, relied on lab-based models that may not fully represent human biology, and overlooked patient variability and treatment applicability, highlighting the need for further research to clarify Lyn's role in skin cancer.

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