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Review Article

Insulin Resistance and Cutaneous Squamous Cell Carcinoma: A Narrative Review of Molecular Mechanisms

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What's Known

- Insulin resistance (IR) increases the risk of various cancers through mechanisms of metabolic dysfunction.
- Cutaneous squamous cell carcinoma (cSCC) is a common skin cancer with a rising global incidence.
- Ultraviolet (UV) radiation remains the primary environmental risk factor for cSCC.
- Metabolic disorders are implicated in the pathogenesis of cSCC.
- The specific molecular connections between IR and cSCC are poorly understood.

What's New

- This narrative review delineated the molecular nexus between insulin resistance (IR) and cutaneous squamous cell carcinoma (cSCC).
- It established that hyperinsulinemia and hyperglycemia drive cSCC pathogenesis through the activation of the IGF-1R/MAPK/PI3K pathway, AGE-RAGE-induced DNA damage, and an NF-κB-mediated inflammatory cascade involving IL-6, TNF-α, and matrix metalloproteinases.

Abstract

Although the association between diabetes and cutaneous squamous cell carcinoma (cSCC) is well recognized, the specific role of insulin resistance (IR) as an independent driver of cSCC pathogenesis remains underexplored. This review synthesized emerging evidence on the ultraviolet (UV)-independent molecular mechanisms by which IR promotes cSCC initiation and progression. Hyperinsulinemia activates the insulin-like growth factor-1 receptor (IGF-1R), which triggers both the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) and phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) pathways, stimulating keratinocyte proliferation and suppressing apoptosis. In parallel, hyperglycemia-driven formation of advanced glycation end products (AGEs) and oxidative stress cause deoxyribonucleic acid (DNA) damage and impair tumor suppressor functions, notably that of tumor protein p53 (TP53). The resulting reactive oxygen species (ROS) activate nuclear factor-kappa B (NF-κB), establishing a chronic inflammatory milieu that remodels the tumor microenvironment through cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), and by upregulating matrix metalloproteinases (MMPs). These processes collectively facilitate the malignant transformation of actinic keratosis (AK) to invasive cSCC. The analysis in the present study identified novel therapeutic targets and reaffirmed the importance of further studies on microbiome interactions and lifestyle interventions for IR-associated cSCC.

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Introduction

The clinical burden of cutaneous squamous cell carcinoma (cSCC) represents a substantial global public health challenge. The cSCC accounts for approximately 20% of all keratinocyte carcinomas, and its global incidence has increased dramatically, rising by an estimated 345% since 1990.[1] Although often perceived as less aggressive than melanoma, cSCC is responsible for most deaths among keratinocyte carcinomas and can cause significant morbidity.[2] The 5-year survival rate is 99% with early detection. Nonetheless, it falls to less than 50% once metastasis occurs.[3] This potential for metastasis, coupled with

a high recurrence rate that necessitates lifelong surveillance, imposes a formidable public health burden.[4] This impact is further amplified by a considerable strain on healthcare systems, as reflected in high hospitalization costs.[5]

Metabolic dysregulation is a fundamental hallmark of cancer and contributes to tumor initiation, progression, and therapeutic resistance. First described by Otto Warburg in the 1920s as aerobic glycolysis (the "Warburg effect"),[6] altered tumor metabolism is now recognized as a key driver of oncogenesis.[7, 8]

Insulin resistance (IR) refers to a diminished biological response to insulin in target tissues, manifested by impaired glucose uptake in skeletal muscle and adipose tissue, inadequate suppression of hepatic glucose production, and dysregulated lipid metabolism.[9, 10] Mechanistically, IR involves defective insulin receptor (INSR) activation, impaired insulin receptor substrate 1 (IRS-1) phosphorylation, and downstream signaling anomalies, often exacerbated by obesity-related adipokine dysregulation and pro-inflammatory cytokine release from visceral adipose tissue.[10]

Compensatory hyperinsulinemia—a hallmark of IR—exerts oncogenic effects through multiple mechanisms. Elevated insulin levels promote tumorigenesis by binding to insulin receptor A (IR-A) and hybrid INSR/ insulin-like growth factor-1 receptor (IGF-1R) complexes, activating the mitogen-activated protein kinase/ extracellular signal-regulated kinase (MAPK/ ERK) and phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) signaling pathways that drive cellular proliferation and inhibit apoptosis.[11]

The epidemiological association between diabetes and cSCC is well documented. However, a review focusing on IR as an independent driver of cSCC pathogenesis is both novel and warranted. Emerging evidence suggests that IR contributes to cSCC development through multifaceted mechanisms, including metabolic dysregulation, chronic inflammation, oxidative stress, and epigenetic modifications, even in the absence of overt diabetes.[12]

This narrative review addressed this gap by synthesizing experimental and clinical evidence to delineate the molecular links between IR and cSCC. By integrating insights into metabolic dysregulation, oxidative stress, chronic inflammation, and tumor microenvironment remodeling, this study provided a comprehensive framework for understanding the systemic impact of IR on cSCC development.

This schematic illustrates the key molecular mechanisms by which IR contributes to the pathogenesis and progression of cSCC (figure 1). Hyperinsulinemia, a key feature of IR, activates IGF-1R. This activation triggers the MAPK/ ERK and PI3K/Akt pathways, enhancing cell proliferation and survival. Concurrently, these pathways contribute to the dysregulation of tumor suppressor genes, including *TP53*, Harvey rat sarcoma viral oncogene homolog (*HRAS),* and cyclin-dependent kinase inhibitor 2A *(CDKN2A)*. These molecular events facilitate the transformation of keratinocytes, the development of actinic keratosis, and progression to cSCC *in situ*, ultimately leading to invasive cSCC. In parallel, hyperglycemia—another metabolic consequence of IR—induces the production of reactive oxygen species (ROS), which cause DNA damage and promote genomic instability, key drivers of carcinogenesis. Hyperglycemia also stimulates the formation of advanced glycation end products (AGEs), which activate the receptor for advanced glycation end products (RAGE), further amplifying oxidative stress and inflammatory signaling. This cascade activates the NF-κB pathway, a critical mediator of tumor-associated inflammation. NF-κB induces the expression of pro-inflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). IL-6 stimulates matrix metalloproteinases (MMPs) and promotes extracellular matrix (ECM) degradation, facilitating tumor invasion. TNF-α upregulates vascular endothelial growth factor (VEGF) expression, promotes angiogenesis, and enhances the tumor microenvironment (TME). Arrows indicate activation, stimulation, or facilitation of molecular events. The diagram emphasizes the intricate interplay between metabolic dysregulation, oncogenic signaling, oxidative stress, inflammatory responses, and tumor microenvironment remodeling, highlighting potential molecular targets for therapeutic intervention in cSCC.

The relationship between IR and cancer progression is an emerging focus of study, with increasing evidence linking metabolic dysregulation to the pathogenesis of cSCC. As illustrated in figure 1, IR initiates a cascade of molecular and cellular events that culminate in invasive cSCC.

IR promotes cSCC through three interrelated mechanisms. First, hyperinsulinemia activates IGF-1R signaling, perpetuating tumorigenesis via the MAPK/ERK and PI3K/Akt pathways. Second, sustained hyperglycemia induces the accumulation of AGEs and oxidative stress, thereby impairing DNA repair. Third, chronic activation of nuclear factor κB (NF-κB) drives persistent inflammation, creating a tumor-permissive microenvironment.

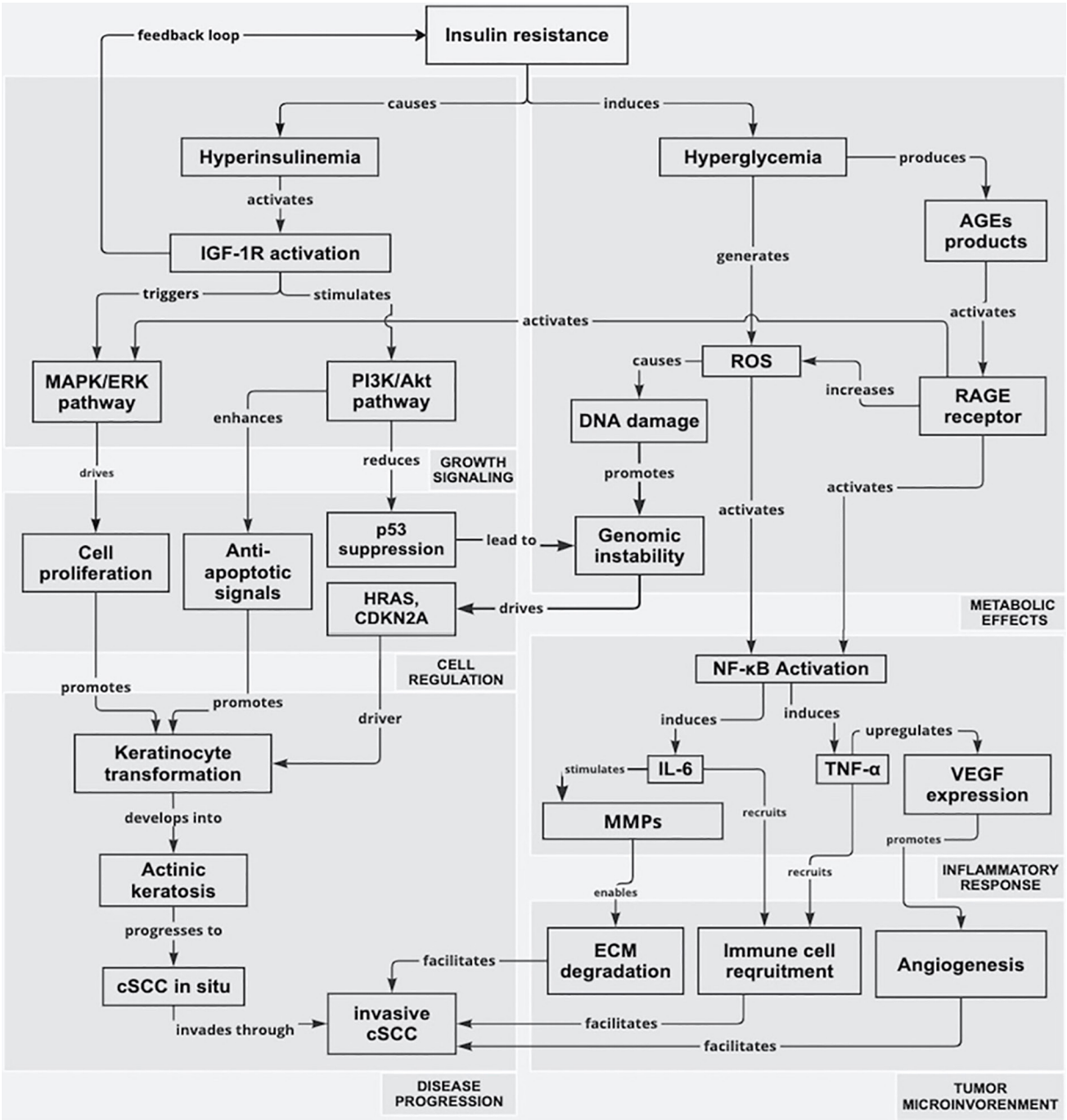

Figure 1: Molecular pathways link insulin resistance to cutaneous squamous cell carcinoma progression. AGEs: Advanced glycation end products; AK: Actinic keratosis; CDKN2A: Cyclin-dependent kinase inhibitor 2A; cSCC: Cutaneous squamous cell carcinoma; ECM: Extracellular matrix; HRAS: Harvey rat sarcoma viral oncogene homolog; IGF-1R: Insulin-like growth factor-1 receptor; IL-6: Interleukin-6; IR: Insulin resistance; MAPK/ERK: Mitogen-activated protein kinase/extracellular signal-regulated kinase; MMPs: Matrix metalloproteinases; NF-κB: Nuclear factor-kappa B; PI3K/Akt: Phosphoinositide 3-kinase/protein kinase B; RAGE: Receptor for advanced glycation end products; ROS: Reactive oxygen species; TME: Tumor microenvironment; TNF-α: Tumor necrosis factor-alpha; VEGF: Vascular endothelial growth factor.

Growth Signaling Pathways: Hyperinsulinemia and Oncogenic Activation

IR disrupts glucose homeostasis, leading to compensatory hyperinsulinemia. The metabolic dysregulation is a hallmark of both metabolic syndrome (MetS) and type 2 diabetes mellitus (T2DM).[13] IR triggers a complex signaling cascade via IGF-1R, establishing a self-reinforcing cycle that promotes tumorigenesis. The resulting compensatory hyperinsulinemia directly activates the IGF-1R, a tyrosine kinase receptor crucial for cellular transformation.[14, 15] This relationship is bidirectional: IGF-1R activation not only results from elevated insulin levels but also exacerbates IR, creating a feed-forward loop that perpetuates both metabolic dysregulation and oncogenic signaling.[16, 17] This bidirectionality is particularly relevant to tumor development, as sustained IGF-1R activation maintains a protumorigenic environment while worsening the underlying metabolic perturbations.

Table 1: Summary of key studies on molecular pathways linking insulin resistance to cutaneous squamous cell carcinoma progression

Authors	Object of Investigation	Intervention/Model	Variables Studied	Key Findings/Outcomes
Hu et al., 2016[20]	MAPK/ERK pathway activation (contextual evidence for keratinocyte growth signaling)	Mechanistic studies in cancer cell lines (non-cSCC)	ERK phosphorylation; proliferation markers	Mortalin activates MAPK/ERK to promote proliferation; supports the IR→IGF-1R→MAPK axis relevance to keratinocytes.
Scheiblecker et al., 2020[21]	CDK4/6–MAPK crosstalk in oncogenic signaling	Review/preclinical synthesis	CDK4/6 and MAPK pathway interactions	CDK4/6–MAPK crosstalk highlights targetable nodes converging with IGF-1R/MAPK in keratinocyte proliferation.
Campos et al., 2020[40]	Expression in cSCC	Immunohistochemistry of clinical samples	TP53 overexpression rate	TP53 overexpression is observed in ~82% of cSCC and is associated with prognosis.
Yilmaz et al.,2017[41]	TP53 mutations in primary vs metastatic cSCC	Genomic analysis of patient tumors	TP53 mutation frequency	Detected TP53 mutations in ~54% of primary cSCC; mutation patterns differ with progression.
Shukla et al.,2017[50]	FOXO/BCL2L11 (BIM) axis in apoptosis/ chemosensitivity	Review of chemotherapy mechanisms	BIM (BCL2L11)	BIM is a pro-apoptotic effector; suppression contributes to therapy resistance.
Sun et al.,2023[51]	AKT-mediated FOXO3a export and BIM-mediated apoptosis	Cancer cell line experiments	FOXO3a localization; BIM expression	Blocking AKT-FOXO3a export restores BIM-driven intrinsic apoptosis.
Mallardo et al., 2023[67]	Baseline IL-6 and outcomes in advanced cSCC on cemiplimab	Clinical cohort study	Serum IL-6; OS; PFS	IL-6>5.6 pg/mL predicts shorter OS and PFS.
Madani et al.,2021[71]	Risk of cSCC among patients with AK	10-year longitudinal follow-up	AK diagnosis; cSCC incidence	17.1% cumulative cSCC incidence; AK increases annual risk by ~1.92%.
Hei et al.,2025[76]	MMPs as biomarkers in skin SCC and melanoma	TCGA RNA-seq analysis	MMP7; MMP11; MMP14 expression; survival	High MMP expression associates with poorer survival.
Georgescu et al., 2024[77]	MMP9 in progression from AK to cSCC	Clinical/biomarker analysis (AK vs. cSCC)	MMP9 expression	Higher MMP9 in cSCC vs. in AK; linked to tumor progression.
Riihilä et al.,2021[78]	MMP9 in keratinocyte carcinomas	Review with experimental evidence	MMP9 functional role	MMP9 contributes to tumor invasion; supports AK→cSCC transition relevance.
Siljamäki et al., 2020[87]	TGF-β signaling and fibroblast-induced invasion	*In vitro* CAF–keratinocyte models	TGF-β pathway; laminin-332; HRAS	Fibroblast-derived TGF-β via HRAS increases laminin-332 and invasion in cSCC.
Gallego-Rentero et al.,2021[88]	CAF-derived TGF-β1 and therapy resistance	*In vitro* photodynamic therapy resistance models	TGF-β1; invasion/ therapy-resistance markers	CAF-secreted TGF-β1 induces resistance and promotes invasion.
Zhu et al.,2021[82]	VEGF pathway and immune infiltration (HNSCC; relevance to cSCC)	RNA-seq cohort (n=522)	VEGF; immune gene signatures; OS	Higher VEGF correlates with increased immune infiltration and improved OS in HNSCC.

AK: Actinic keratosis; BCL2L11: B-cell lymphoma 2-like 11; CAF: Cancer-associated fibroblast; CDK4/6: Cyclin-dependent kinase 4 and 6; cSCC: Cutaneous squamous cell carcinoma; ERK: Extracellular signal-regulated kinase; FOXO: Forkhead box O; HNSCC: Head and neck squamous cell carcinoma; HRAS: Harvey Rat Sarcoma viral oncogene homolog; IGF-1R: Insulin-like growth factor 1 receptor; IL-6: Interleukin-6; IR: Insulin receptor; MAPK: Mitogen-activated protein kinase; MMP: Matrix metalloproteinase; OS: Overall survival; PFS: Progression-free survival; TCGA: The Cancer Genome Atlas; TGF-β: Transforming growth factor beta; TP53: Tumor protein p53; VEGF: Vascular endothelial growth factor.

The activation of IGF-1R triggers two major signaling cascades, the MAPK/ERK and PI3K/Akt pathways—both critical regulators of cell proliferation and survival.[18, 19] The MAPK/ERK pathway promotes cell proliferation by phosphorylating transcription factors, such as c-Fos and c-Jun. These factors stimulate the expression of cyclin D1 and cyclin-dependent kinases 4 and 6 (*CDK4/6*), which drive cell-cycle progression[20, 21] (table 1). Concurrently, the PI3K/Akt pathway inhibits apoptosis by suppressing pro-apoptotic proteins, such as BCL2-associated agonist of cell death (BAD) and caspase-9.[22, 23] Together, these pathways foster uncontrolled cell growth, a hallmark of early neoplastic transformation.

In keratinocytes, this dysregulation contributes to sustained proliferation—a defining feature of actinic keratosis, the precursor lesion to cSCC.[24-27] Preclinical studies demonstrated

that IGF-1R inhibition reduces keratinocyte proliferation, emphasizing its pivotal role in tumor initiation.

Metabolic Effects: Hyperglycemia, AGEs, and Oxidative Stress

Chronic hyperglycemia, a hallmark of IR,[10, 28, 29] promotes the nonenzymatic glycation of proteins and lipids, generating AGEs.[30, 31] AGEs bind to their RAGE products, a pattern recognition receptor expressed on keratinocytes and immune cells.[32, 33] RAGE activation triggers ROS production via nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, thereby exacerbating oxidative stress.[34, 35] Persistent ROS accumulation induces DNA damage, including double-strand breaks and base modifications, which can overwhelm endogenous repair mechanisms such as base excision repair.[36, 37]

The resulting genomic instability is compounded by suppression of *TP53*, which orchestrates cell-cycle arrest and apoptosis in response to DNA damage.[38, 39] Numerous studies highlighted the significance of p53 suppression in cSCCs. One study reported *TP53* overexpression in 82.1% of the cases, suggesting a high prevalence of mutations.[40] Yilmaz and others reported *TP53* mutations in 54% of primary cSCCs.[41] Similarly, an analysis of 62 patients with head and neck cSCC reported *TP53* overexpression in 72.58% of cases, underscoring its widespread dysregulation. Notably, diffuse *TP53* overexpression was observed in cSCCs with perineural invasion, and no tumors displayed normal p53 staining.[42]

Hyperglycemia-induced ROS also activates NF-κB, a master regulator of inflammation. This creates a feed-forward loop in which oxidative stress and inflammation mutually reinforce each other, further destabilizing the genome.[43, 44]

Several studies demonstrated the critical role of NF-κB in the progression of cSCC. Prolonged activation of the NF-κB pathway enhances the expression of oncogenic genes, a phenomenon observed in normal cells that persists in cancerous tissues and is associated with a poorer prognosis in cSCC.[45] T-LAK cell-originated protein kinase (TOPK) accelerates cSCC development by upregulating histone deacetylase 1 (HDAC1) and promoting autophagy, both of which activate NF-κB signaling.[46] Additionally, downregulation of microRNA-27a (miR-27a) contributes to the activation of the epidermal growth factor receptor (EGFR) and its downstream NF-κB pathway, thereby facilitating proliferation and metastasis in cSCC.[47] These findings collectively underscored the multifaceted involvement of NF-κB in the pathogenesis and progression of cSCC.

Dysregulated Cell Cycle and Anti-Apoptotic Signaling

The convergence of IR-driven pathways in cell cycle regulation is pivotal for cSCC development. The PI3K/Akt pathway phosphorylates and inhibits forkhead box O (FOXO) transcription factors (FOXO1, FOXO3, and FOXO4), which normally promote the expression of pro-apoptotic genes such as *BCL2L11* (*BIM*) and BCL2 binding component 3 (*BBC3*, also known as *PUMA*).[48, 49]

FOXO3 directly binds to the *BCL2L11* promoter, and PI3K/Akt inhibition increases *BCL2L11* expression, correlating with apoptosis. Similarly, FOXO-mediated induction of *BBC3* contributes to apoptosis. High *BCL2L11* expression in cSCC is associated with better prognosis, whereas PI3K/Akt-driven *BCL2L11* suppression correlates with chemoresistance,[50,51] (table 1). The PI3K/Akt pathway's suppression of FOXO transcription factors, which reduces expression of pro-apoptotic targets, such as BIM and PUMA, promotes cSCC survival. Targeting this axis offers a promising strategy for restoring apoptosis in therapy-resistant tumors. Simultaneously, hyperactivation of MAPK/ERK signaling downregulates p53 through post-translational modifications, including phosphorylation at Ser15 and ubiquitination.[52, 53]

This phenomenon is particularly evident in actinic keratosis (AK) lesions, where *TP53* mutations are prevalent. Additionally, genomic instability arising from oxidative stress facilitates the accumulation of driver mutations in oncogenes (e.g., *HRAS*) and tumor-suppressor genes (e.g., *CDKN2A*), both of which are frequently altered in cSCC. Activating mutations in *HRAS* have been detected in approximately 9% of cSCC cases, primarily in codons 12, 13, and 61.[54] Mutations in *CDKN2A*, reported in nearly 50% of cSCC cases, hinder the activation of $p16^{INK4a}$ and $p14^{ARF}$, both of which are vital for controlling cellular growth. These mutations are often clonal, suggesting an early contribution to oncogenesis.[55] Thus, the synergy between anti-apoptotic signaling and mutagenesis establishes fertile ground for malignant transformation.

Inflammatory Response: NF-κB and Cytokine-Driven Tumor Promotion

Chronic inflammation is a hallmark of cancer progression, and IR exacerbates this process through NF-κB activation. ROS and AGEs serve as potent NF-κB inducers,[56, 57] prompting the transcription of pro-inflammatory cytokines, including IL-6 and TNF-α.[58, 59] These cytokines

recruit immune cells, such as macrophages and neutrophils, which further amplify inflammation via additional cytokine release.[60]

IL-6 and TNF-α enhance keratinocyte proliferation and survival through signal transducer and activator of transcription 3 (STAT3) signaling.[61,62] IL-6 induces MMPs, which degrade the ECM to facilitate tumor invasion,[63,64] while TNF-α upregulates vascular endothelial growth factor (*VEGF*), promoting angiogenesis and tumor growth.[65,66]

Clinical studies reported elevated serum IL-6 and TNF-α levels in patients with cSCC, correlating with poorer outcomes. High baseline IL-6 levels (>5.6 pg/mL) in patients with advanced cSCC treated with immunotherapy (cemiplimab) were linked to reduced overall survival (OS) (16.1 vs. 20.8 months) and shorter progression-free survival (PFS) (10.3 vs. 18.9 months).[67] IL-6 levels increase with tumor bulk and metastasis. In advanced cSCC, IL-6 promotes immune evasion and epithelial-mesenchymal transition (EMT), thereby facilitating metastasis.[68]

In animal models, TNF-α contributes to tumor invasion and metastasis by upregulating MMPs, such as *MMP1* and *MMP13*, which degrade ECM components.[69] A clinical cohort study found that TNF-α levels were significantly higher in patients with cSCC experiencing pain (adjusted OR=1.4, 95% CI=0.99-2.0, P=0.05) than pain-free patients, suggesting a link to symptomatic progression.[70] Moreover, NF-κB inhibitors were shown to reduce tumor burden in preclinical cSCC models, highlighting their therapeutic potential in targeting inflammation.

Disease Progression: From Premalignant Lesions to Invasive cSCC

The risk of developing cSCC increases significantly over a 10-year follow-up period. Patients diagnosed with AK show a cumulative cSCC incidence of 17.1%, compared to 5.7% in matched controls. The annual risk increase was 1.92% for patients with AK vs. 0.83% for controls, indicating a strong association between AK and subsequent cSCC development[71] (table 1).

The transition from AK to invasive cSCC is mediated by a combination of ECM remodeling, immune evasion, and angiogenesis. MMPs, such as MMP2 and MMP9, degrade collagen and laminin in the basement membrane,[72,73] enabling keratinocyte invasion of the dermis.

Previous studies highlighted the crucial role of MMPs in skin cancer progression. Immunohistochemical analysis of 30 head and neck cSCC and 30 basal cell carcinoma (BCC) samples demonstrated significantly stronger MMP10 expression in cSCC tumor epithelium than in the BCC (P<0.001).[74] Additionally, serum MMP13 has emerged as a biomarker for tumor invasiveness; a 2021 case-control study (n=77) reported elevated serum levels in cSCC patients versus healthy individuals (P<0.01), with increasing concentrations correlating with advanced tumor stage.[75] Further evidence from Hei and others, utilizing RNA sequencing data from The Cancer Genome Atlas (TCGA), identified overexpression of MMP7, MMP11, and MMP14 in melanoma and squamous cell carcinoma tissues. High expression levels of these MMPs were significantly associated with poorer survival outcomes (P<0.05), underscoring their prognostic and pathogenic relevance in skin cancer progression,[76] (table 1).

Emerging evidence suggests that MMP9 plays a critical role in the progression of AK to cSCC, making it a potential biomarker for malignancy. Studies indicated that *MMP9* is expressed at higher levels in cSCC than in AK, reinforcing its association with tumor progression. Georgescu and others found that tumor-associated macrophages (TAMs) expressing CD163 released significant amounts of MMP9, specifically in cSCC but not in keratoacanthoma. This finding suggested that *MMP9* might be more relevant to cSCC pathology than to benign or self-limiting lesions.[77] Similarly, Riihilä and others demonstrated that *MMP9* contributed to the invasive properties of cSCC, further supporting its role in the transition from AK to cSCC[78] (table 1). A study analyzing 178 oral squamous cell carcinoma (OSCC) samples revealed that MMP9 levels increased with tumor invasion. This increase was accompanied by a decrease in phosphorylated β-catenin, suggesting a complex interplay between MMP9 and key signaling pathways in tumor progression.[79]

Angiogenesis and immune cell recruitment play vital roles in the progression of cSCC, shaping the tumor microenvironment (TME) and influencing disease outcomes. A key driver of this process is *VEGF*, which promotes new blood vessel formation, ensuring a steady supply of nutrients that support tumor growth and metastasis. Notably, studies have shown that VEGF expression is significantly higher in cSCC than in normal skin, with elevated levels correlating with more advanced disease and a poorer prognosis.[80] Beyond fueling angiogenesis, VEGF also affects immune regulation within the TME. By altering immune cell dynamics, VEGF helps tumors evade immune surveillance, further facilitating their progression.[81]

Zhu and others analyzed RNA sequencing data from 522 patients with head and neck

squamous cell carcinoma (HNSCC) and found that higher VEGF levels were correlated with increased immune cell infiltration, elevated immune-related gene expression, and, unexpectedly, better overall survival (OS)[82] (table 1). VEGF not only drives angiogenesis but also fosters an immunosuppressive TME by blocking T-cell infiltration, enabling immune evasion. In cSCC, its interaction with regulatory T cells (Tregs) reinforces immunosuppression through a feedback loop.[83, 84] When combined with other immunosuppressive factors, this interaction creates a TME that is resistant to conventional immunotherapies.[85, 86]

The TME of invasive cSCC is also shaped by fibroblast activation and the deposition of pro-fibrotic cytokines such as the transforming growth factor beta (TGF-β). Siljamäki and others found that fibroblast-derived TGF-β enhanced laminin-332 synthesis in cSCC cells via H-Ras-dependent signaling, promoting cancer cell invasion.[87] Similarly, Gallego-Rentero and others reported that cancer-associated fibroblast (CAF)-derived TGF-β1 induces resistance to photodynamic therapy, linking it to both tumor progression and therapy resistance[88] (table 1). Knuutila and others further highlighted CAF activation as a driver of cSCC progression, reinforcing the TGF-β pathway as a promising therapeutic target.[89]

Notably, hyperinsulinemia was shown to upregulate TGF-β signaling in keratinocytes, suggesting a direct link between IR and stromal reprogramming. The culmination of these processes manifests as locally invasive tumors with the potential for metastasis, particularly in immunocompromised individuals.

Clinical and Therapeutic Implications

The clinical and therapeutic implications of understanding IR's role in cSCC development open promising avenues for targeted interventions (table 1). Metformin has emerged as a particularly intriguing therapeutic option because of its dual mechanism of action. By suppressing IGF-1R signaling, metformin reduces hyperinsulinemia-driven cellular proliferation,[90] while simultaneously attenuating NF-κB-mediated inflammatory responses.[91] This mechanistic understanding suggests potential benefits beyond glycemic control in high-risk patients.

The identification of AGE-induced genomic instability suggested therapeutic strategies that incorporate ROS-scavengers to protect DNA integrity,[92] In addition, the strong correlation between IL-6 levels and survival outcomes in patients receiving immunotherapy highlighted the potential value of anti-IL-6 therapies as part of a combined treatment approach. This approach becomes especially relevant given the immunosuppressive nature of the TME influenced by TGF-β signaling.[93]

Understanding these molecular pathways would enable more precise therapeutic timing and selection. The development of biomarker-driven treatment algorithms that incorporate AGE levels and inflammatory markers could help optimize intervention strategies. Particular attention should be paid to patients showing early signs of metabolic dysregulation, as the cumulative incidence data from AK progression underscore the importance of early intervention in metabolically compromised individuals.

These insights suggested moving toward combined approaches that simultaneously target both metabolic and inflammatory pathways. Such strategies could prove particularly effective given the complex interplay between IR and tumor progression. The role of the TGF-β-mediated immunosuppressive microenvironment in treatment resistance further emphasizes the need for comprehensive therapeutic approaches that address multiple aspects of disease pathogenesis.

Limitations and Future Directions

Although this review provided comprehensive insights into the relationship between IR and cSCC, several knowledge gaps remained. An important gap is the temporal sequence of events; whether hyperinsulinemia precedes inflammation or vice versa remains unresolved. Longitudinal studies in prediabetic cohorts might help clarify this relationship.

Recent studies suggested that gut microbial dysbiosis influenced systemic inflammation and IR, potentially affecting skin carcinogenesis. Future research should explore whether microbial metabolites modulate inflammatory or oxidative pathways in cSCC. This understanding would particularly benefit immunocompromised individuals, who have an increased susceptibility to cSCC. Additionally, the impact of lifestyle interventions, such as dietary modifications and exercise, on molecular pathways in insulin-resistant individuals remains underexplored.

Future research should integrate multi-omics approaches to better understand disease progression dynamics. Investigating extracellular vesicles that mediate communication between metabolically dysregulated tissues and the TME could reveal new therapeutic targets. Advanced three-dimensional models and organoid systems might provide more physiologically relevant insights than current two-dimensional

cell culture methods. These comprehensive approaches are essential for developing effective personalized treatment strategies and improving patient outcomes.

Conclusion

This review highlighted the complex relationship between IR and cSCC through the interconnected pathways of metabolic dysregulation, inflammation, and genomic instability. Hyperinsulinemia creates a protumorigenic environment by activating IGF-1R signaling, while AGEs from sustained hyperglycemia impair DNA repair mechanisms. The inflammatory cascade, mediated by NF-κB, serves as a critical link between metabolic disruption and tumor progression.

However, significant knowledge gaps remained regarding the temporal relationship between hyperinsulinemia and inflammation, as well as the role of the microbiome in these processes. Additionally, the effects of lifestyle interventions on molecular pathways in insulin-resistant individuals remain unclear. These limitations emphasize the need for longitudinal studies and sophisticated experimental models.

Future research should integrate multi-omics approaches and advanced three-dimensional models to better understand disease progression. Investigations of extracellular vesicles and microbiome interactions might reveal novel therapeutic targets. Such advances could lead to more personalized treatment strategies, ultimately improving outcomes for patients with both metabolic dysregulation and cSCC.

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Authors' Contribution

TI.A: Study conception and design, data acquisition, analysis, interpretation and reviewing the manuscript, D.A: Conception and design of the study, data acquisition, analysis, interpretation, and drafting the manuscript; A.Y: Study conception and design, data acquisition, analysis, interpretation and reviewing the manuscript; MA.P: Conception and design of the work, data acquisition, analysis, interpretation, and reviewing the manuscript; All authors approved the submission of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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