Cutaneous Squamous Cell Carcinoma (CSCC)

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Contributor: Natalia García

Cutaneous squamous cell carcinoma (CSCC) is the second most frequent cancer in humans and its incidence continues to rise. Although CSCC usually display a benign clinical behavior, it can be both locally invasive and metastatic. The signaling pathways involved in CSCC development have given rise to targetable molecules in recent decades. In addition, the high mutational burden and increased risk of CSCC in patients under immunosuppression were part of the rationale for developing the immunotherapy for CSCC that has changed the therapeutic landscape. Several drugs have been developed for CSCC treatment, but the disease may actually be induced by drugs as well. Molecular mechanisms underlie pharmacologically-induced CSCC, and a sound knowledge of them could help physicians better tackle this tumor.

Keywords: cutaneous squamous cell carcinoma ; azathioprine ; cyclosporine ; voriconazole ; Sonic-Hedgehog inhibitors ; BRAF inhibitors ; mTOR inhibitors

1. Immunosuppressive Drugs and CSCC

The immunosuppressive therapy used in organ transplant recipients (OTRs) to prevent allograft rejection promotes cutaneous infection and skin neoplasms [1][2]. The classic immunosuppressant drugs used for organ transplantation are glucocorticosteroids (prednisone and prednisolone), calcineurin inhibitors (cyclosporine and tacrolimus), and anti-proliferative agents (azathioprine and mycophenolic acid). Here we focus on cyclosporine and azathioprine.

1.1. Cyclosporine and CSCC

Cyclosporine is a calcineurin inhibitor that increases the risk of CSCC, especially under UVR [3][4][5]. Cyclosporine A reduces UVB-induced DNA damage repair and inhibits apoptosis in human keratinocytes by inhibiting the nuclear factor of activated T-cells (NFAT) [6]. Calcineurin inhibition is known to selectively induce the expression of activating transcription factor 3 (ATF3), which downregulated p53 expression and increased CSCC formation in a mouse model and in human CSCCs [7]. In vitro studies demonstrated that chronic treatment of human HaCaT keratinocytes with cyclosporine enhances AKT activation by suppressing PTEN, and promotes tumor growth of the CSCC A431 cell line in immune-deficient nude mice [8][9]. Furthermore, cyclosporine enhances epithelial-to-mesenchymal transition involving the upregulation of TGFβ signaling [10].

The increased risk of CSCC in patients under cyclosporine has led physicians to search for different options. Some studies of tacrolimus, a calcineurin inhibitor introduced to replace cyclosporine, demonstrated no difference in a comparison of overall cancer rates of the two drugs [11]; however, more recent data from a clinical trial and from in vivo studies indicate a lower skin cancer risk associated with tacrolimus [12][13]. Nevertheless, the most important drugs for preventing cyclosporine-induced CSCC development are the mTOR inhibitors.

The newest immunosuppressants used for OTRs are sirolimus (rapamycin) and everolimus. Both inhibit interleukin (IL)-2 and IL-15 via mTOR. It is not known whether these inhibitors have anticarcinogenic effects [14]. Preliminary data suggest that conversion from calcineurin inhibitors to sirolimus reduces the incidence of skin cancer in renal graft recipients [15][16], possibly because sirolimus reduces vascularization and the thickness of post-transplant CSCCs [17]. The change of therapy from calcineurin inhibitors to sirolimus in patients with one CSCC lowered the risk of a new CSCC, and metastasis events only occurred in patients who received calcineurin inhibitors [18], the effect being maintained over five years of follow-up [19]. In vivo studies of hairless mice show that sirolimus significantly increases the latency of large tumors and reduces their multiplicity. Tumors from the rapamycin group have a lower UV-signature p53 mutation rate [20]. Case reports of conversion to everolimus show a reduced likelihood of CSCC development [21].

Recent studies have shown that cyclosporine exposure upregulates IL-22R1 [22] and causes increased JAK1, STAT1, and STAT3 expression. Using ruxolitinib, an FDA-approved JAK1/2 inhibitor, in human CSCC cells and xenografts reduces proliferation and growth. This could be a feasible option for preventing CSCC in OTRs who face long-term immunosuppression [23].

1.2. Azathioprine and CSCC

In a cohort study of 361 renal transplant recipients, the immunosuppressant drug azathioprine increased the risk of CSCC 2.4-fold [24]; and in an organ transplantation cohort of 207 patients, post-transplant azathioprine treatment increased the risk of CSCC compared with controls in a dose-dependent manner [25]. A systematic review and meta-analysis of 27 studies confirmed the association of OTRs treated with azathioprine and CSCC [26]. It is clear that azathioprine enhances the effect of UVR on skin cancer risk, and indeed, it strongly induces and promotes CSCC in hairless mice exposed to UVR [27]. Azathioprine photosensitizes the skin to UVR by changing the absorption interval of DNA upon incorporation of 6-thioguanine, the active metabolite of azathioprine. UVR absorption then induces the formation of reactive oxygen species that have been linked to DNA damage and cutaneous malignancies [28][29][30]. Whole-exome sequencing has revealed a novel CSCC mutational signature, which is associated with chronic exposure to azathioprine [31].

To reduce the risk of CSCC associated with this drug, azathioprine can be replaced by mycophenolate, leading to lower levels of DNA 6-thioguanine, skin ultraviolet A (UVA) sensitivity, and DNA damage, and a lower risk of CSCC [12][32][33]. However, another study suggests that the calcineurin inhibitor tacrolimus and mycophenolate mofetil (MMF) inhibit UVB-induced DNA damage repair, demonstrating the tumor-promoting action of these immunosuppressants [34].

1.3. Voriconazole and CSCC

Voriconazole, an antifungal used to prevent and treat invasive fungal infections after lung transplantation, has been associated with an increased risk of developing CSCC [35]. Voriconazole causes photosensitivity [36] in a dose-dependent manner [37]. The mechanism underlying this may arise from a primary metabolite, voriconazole N-oxide, which absorbs UVA and UVB wavelengths [36][38]. Expression arrays of in vitro cultures of primary human keratinocytes exposed to voriconazole also show that this drug inhibits terminal epithelial differentiation pathways, resulting in poor formation of epithelial layers that are important for photoprotection, favoring its phototoxicity [39]. In vitro and in vivo assays demonstrated that voriconazole and its product inhibit catalase, raising intracellular levels of UV-associated oxidative stress and DNA damage in keratinocytes to promote skin carcinogenesis [40]. While photoprotection is fundamental for preventing CSCC, this is especially important in patients under voriconazole.

2. Targeted Therapies and CSCC

2.1. Sonic-Hedgehog Inhibitors and CSCC

Medications to treat other skin cancers, such as melanoma and basal cell carcinoma (BCC), can paradoxically lead to the development of CSCC. Vismodegib is a smoothened inhibitor (Hedgehog pathway inhibitor) that the FDA and EMA have approved for treating locally advanced and metastatic BCC [41]. The association of vismodegib with CSCC was reported in several case reports [42][43][44], and a retrospective cohort study highlighted this increased risk [45]. Some researchers disputed the latter study [46], and a subsequent paper failed to replicate such an association [47]. Furthermore, squamous metaplasia has been found in BCCs treated with vismodegib [48]. Nevertheless, there is some evidence to suggest that hedgehog inhibitors may indeed increase the risk of CSCC. The mechanism of action of vismodegib to promote CSCC is thought to be the activation of the RAS/MAPK pathway, which is responsible for CSCC progression [49].

A CSCC may arise from a BCC because both develop from the same target cell, as some authors have suggested. Two studies revealed new roles for *Ptch1* that lie at the nexus between BCC and CSCC formation [50][51]. *Ptch1* gene is thought to occupy a critical role in determining the basal or squamous cell lineage [51], and its polymorphisms are involved in cell fate decisions. In BCC, loss of *Ptch1* activates the Sonic-Hedgehog pathway, but the overexpression of *Ptch1* promotes an alternative cell-fate decision, leading to increased CSCC susceptibility [50].

2.2. BRAF Inhibitors and CSCC

BRAF is mutated in around 50% of melanomas, and some years ago, the therapeutic landscape of this tumor broadened through the development of BRAF inhibitors [52], specifically vemurafenib and dabrafenib [53]. These drugs provided greater overall survival and PFS compared with dacarbazine [54][55], but they also increased the risk of CSCC development [56][57][58]. The effectiveness of these drugs stems from their ability to attenuate the MAPK pathway, which is

downstream of constitutive BRAF activation [59]. However, BRAF inhibitors are capable, paradoxically, of activating the MAPK pathway in cells containing non-mutated *BRAF*, and this pathway is essential for CSCC development [60][61][62][63]. The inhibition of MEK proved to be effective in preventing CSCC while on BRAF inhibitors, and thereafter BRAF inhibitors were combined with MEK inhibitors to avoid these side effects. Specifically, vemurafenib is combined with cobimetinib [64], and dabrafenib with trametinib [65]. A meta-analysis of five phase III randomized controlled trials, 17 phase II trials, and two phase IV trials [66] demonstrated that combined BRAF and MEK inhibition (trametinib) reduces the incidence of CSCC relative to BRAF monotherapy, as seen in another study [67]. More recent work demonstrated that BRAF inhibitors induce *RAS* mutations that are essential for MAPK activation. *RAS* mutations were detected in 21%–60% of lesions after BRAF inhibitor treatment in contrast to 3%–30% in normal CSCCs [60][68]. A mutational signature has been noted in squamous proliferative lesions induced by BRAF inhibitors that differs from the mutation pattern seen in spontaneous CSCCs [69]. Additionally, human papillomaviruses (HPVs) are detected more frequently in BRAF inhibitor-induced CSCCs, which means that HPV might accelerate keratinocyte oncogenesis in this subset of patients [70].

Other than MEK inhibitors, the inhibition of cyclooxygenase (COX)-2 has been evaluated as a strategy to prevent BRAF-inhibitor-mediated CSCC development. Experimental investigations that induce CSCC carcinogenesis by UVR have shown that COX-2 inhibitors (celecoxib and diclofenac) decrease prostaglandin production, thereby mitigating CSCC development [71][72]. Moreover, celecoxib delayed the onset of CSCC in a mouse model mediated by DMBA/TPA and of CSCC induced by the BRAF inhibitor PLX7420, reducing the tumor burden by 90% [73]. All the drugs that may contribute to the development of CSCC are listed in **Table 1.**

Table 1. Pharmacologically-induced CSCC.

Drug	Treatment	Mechanisms to Promote CSCC	Options to Reduce CSCC Risk
Cyclosporine	Immunosuppressant	Reduces UVB-induced DNA damage repair and inhibits apoptosis by inhibiting nuclear factor of activated T-cells (NFAT) [6]	Sirolimus and everolimus [15][16][17][19][20][21]
		Induces the expression of ATF3, which downregulates p53 and increases CSCC formation [7]	
		Enhances AKT activation by suppressing PTEN and promotes tumor growth [8][9]	
		Enhances epithelial-to-mesenchymal transition involving the upregulation of TGFβ signaling [10]	
Azathioprine	Immunosuppressant	Photosensitizes the skin to ultraviolet radiation (UVR) by changing the absorption interval of DNA upon incorporation of 6-thioguanine and induces the formation of reactive oxygen species [28][29][30]	Mycophenolate mofetil [12][32][33]
Voriconazole	Antifungal	The primary metabolite, voriconazole N-oxide, absorbs UVA and UVB wavelengths and causes photosensitivity [36][37][38]	Photoprotection
		Inhibits terminal epithelial differentiation pathways resulting in poor formation of epithelial layers that are important for photoprotection [39]	
		Inhibits catalase, raising intracellular levels of UV-associated oxidative stress and DNA damage [40]	
Vismodegib (Sonic-hedgehog inhibitor)	Basal cell carcinoma	Activates RAS-MAPK pathway [49]	Close follow-up
Vemurafenib and dabrafenib (BRAF inhibitors)	Melanoma	Activate, paradoxically, MAPK pathway and induce *RAS* mutations [60][61][62][63][68]	BRAF inhibitors + MEK inhibitors [64][65][66][67] or BRAF inhibitors + cyclooxygenase (COX)-2 inhibitors [71][72][73]

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