Cutaneous Squamous Cell Carcinoma Arising in Immunosuppressed Patients: A Systematic Review of Tumor Profiling Studies

Elliot D. Blue1,5, S. Caleb Freeman2,5, Marissa B. Lobl3, Dillon D. Clarey1, Rose L. Fredrick4, Ashley Wysong1 and Melodi Javid Whitley1

As solid organ transplantation becomes more prevalent, more individuals are living as members of the immunosuppressed population with an elevated risk for cutaneous squamous cell carcinoma (cSCC). Although great progress has been made in understanding the pathogenesis of cSCC in general, little is known about the drivers of tumorigenesis in immunosuppressed patients and organ-transplant recipients, specifically. This systematic review sought to synthesize information regarding the genetic and epigenetic alterations as well as changes in protein and mRNA expression that place this growing population at risk for cSCC, influence treatment response, and promote tumor aggressiveness. This review will provide investigators with a framework to identify future areas of investigation and clinicians with additional insight into how to best manage these patients.

JID Innovations (2022) 2:100126 doi:10.1016/j.sjid.2022.100126

INTRODUCTION
Over 5 million cases of nonmelanoma skin cancer (NMSC) are diagnosed each year in the United States, which is more than all other cancers combined (American Cancer Society, 2019; Garrett et al., 2017; Madan et al., 2010). Cutaneous squamous cell carcinoma (cSCC) accounts for 20–30% of all NMSC and leads to local recurrence and metastasis at rates of 10% and 3–5%, respectively (Garrett et al., 2017). cSCC is estimated to be responsible for up to 9,000 deaths annually in the United States (Karia et al., 2013).

cSCC is the most common post-transplant malignancy in organ-transplant recipients (OTRs) (Garrett et al., 2017). The number of organ transplants performed in the United States has tripled in the last 30 years, with over 36,000 transplants performed in 2018 compared with 12,623 performed in 1988 (United States Department of Health & Human Services, 2021). Owing to advances in immunosuppressive drug regimens and medical care, patients are now living longer lives post-transplant. Kidney transplant recipients live an average of 8–20 years after their transplant, and 50% of liver transplant recipients are alive after 20 years (Beth Israel Deaconess Medical Center Transplant Institute, 2018; Petrowsky et al., 2013). Transplant patients are 65–108 times more likely to develop cSCC than the general population, and the morbidity ratio in OTRs with cSCC increases by 60–250 times compared with immunocompetent patients (ICPs) (Euvrard et al., 2003; Jensen et al., 1999; Lindelöf et al., 2000; Moloney et al., 2006; Tessari et al., 2010). These differences have been attributed to a more aggressive phenotype, a higher risk of metastasis (approximately 7%), and an increased recurrence rate (7–45%) (Berg and Otley, 2002; Lanz et al., 2019; Sheil et al., 1993).

Genetic and epigenetic alterations between cSCC arising in OTRs and ICPs may contribute to the differences in the behavior of cSCC in these groups. In cSCC in ICPs, classic mutational signatures exist, such as mutations in NOTCH1/2, CDKN2A, and P53 (Li et al., 2015; Lobl et al., 2021). These mutations may also be present in the OTR population, but the prevalence of these mutations in the OTR population remains to be elucidated. In addition, gene mutations may be influenced by immunosuppressive therapies used to prevent transplant rejection, which may lead to varying mutational signatures even among OTRs (Harwood et al., 2017). cSCC occurring in patients on azathioprine (AZA), for example, are more likely to have the classic mutational signature of NOTCH1/2, CDKN2A, and P53, as described above, than patients on other immunosuppressants (Inman et al., 2018). Few reports exist in the literature that compare differences in cSCC between the OTR and ICP populations, and a complete systematic review has yet to be performed. This review aims to provide a complete summary and analysis of reports in the literature regarding the genetic and epigenetic alterations, polymorphisms (germline mutations found in every cell of the
body), and changes in protein and mRNA expression in cSCC arising in immunosuppressed patients (ISPs) compared with ICPs and ISPs with and without cSCC. A better understanding of the differences in cSCC between these two populations may further facilitate meaningful research investigation and improve patient management.

**RESULTS**

**Search results**

Databases were queried for all articles indexed before 1 November 2021 with no start date, and a total of 2,594 articles were retrieved from MEDLINE, Cinahl, and Scopus (Figure 1). An additional six articles were identified during the review and were also included. After removing duplicates, 2,138 articles remained. A total of 1,979 articles were excluded after reviewing title and abstract. A full-text assessment of the remaining 159 articles was completed and a further 81 articles were excluded for not meeting the inclusion and exclusion criteria, resulting in 78 articles for the qualitative synthesis (Figure 1). The characteristics of original articles included are provided in the Tables 1–8.

**Study populations**

The majority of the compiled articles focused on renal transplant recipients (RTRs) (30 of 78 studies) and the general organ-transplant population (26 of 78 studies). A slightly smaller number of studies focused on cell and mouse models (17 of 78 studies), and even less on nonspecified immunosuppression (7 of 78 studies) and other specified organ transplants including the heart, liver, and lung (3 of 79 studies) (Tables 1–8).

**Protein and mRNA expression**

There were 30 studies (38% of all articles) that examined protein and mRNA expression and a total of 63 unique proteins/genes of interest (Tables 1 and 2). Of these, 21 studies (27% of all articles) directly compared primary cSCC tumors in ICPs and their immunosuppressed counterparts, with a total of 50 unique proteins/genes of interest being identified (Table 1). Genes with significantly higher expression in cSCC from ISPs than in ICPs included markers of growth and proliferation FOXO1 and MKI67 (P = 0.007 and P < 0.05, respectively) (Feldmeyer et al., 2016; Zhang et al., 2013). Conversely, levels of the activated oncogene

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**Figure 1. PRISMA 2009 flow diagram.** PRISMA flowchart depicting steps taken during systematic review of the literature for the genetic alterations in ISPs and OTRs. From: Moher et al. (2009). cSCC, cutaneous squamous cell carcinoma; ISP, immunosuppressed patient; OTR, organ transplant recipient; PRISMA, preferred reporting items for systematic reviews and meta-analyses.
Ki-67 Zhang et al. 2013 SCC from 12 OTRs and 20 ICPs Ki-67 expression increased nearly two-fold in OTRs when compared with ICPs (1.4 vs. 2.1, respectively; P = 0.013).

IL-17A Kosmidis et al. 2010 SCC from 42 OTRs and 43 ICPs GATA-3 expression did not differ with immunosuppression (P > 0.05). Four-fold higher expression of FOXO1 in OTRs than in ICPs (1.05 mean ± 0.27 SD in ICPs and 8-fold in OTRs compared with normal skin (OTR mean 5.03 ± 1.56 SD vs. ICP mean 2.44 ± 0.45 SD, respectively; P = 0.013).

Mcl-1 Burke et al. 2015 SCC from 21 RTRs and 10 ICPs No difference existed between groups in Mcl-1 expression intensity (P = 0.277) or percentage of cells with Mcl-1 expression (P = 1.00).

Table 1. Gene Expression Differences in cSCC between ISPs and ICPs

| Proteins/Genes of interest | Author | Year | Study Population | Findings |
|---------------------------|--------|------|------------------|----------|
| B7-H3                     | Varki et al. 2018 | SCC from 42 ICPs and 24 ISPs (13 OTRs, 8 HIV, and 3 others) | 60% of ICP tumors expressed B7-H3 in comparison to 28% of ISP tumors (P = 0.025). |
| Bax                       | Seçkin et al. 2002 | SCC from 10 RTRs and 14 ICPs | No difference in Bax expression (P > 0.05). |
| Bcl-2                     | Seçkin et al. 2002 | SCC from 10 RTRs and 14 ICPs | No difference in Bcl-2 expression (P > 0.05). |
| Bcl-xl                    | Burke et al. 2015 | SCC from 21 RTRs and 10 ICPs | Decreased Bcl-xl expression staining intensity was found in RTRs when compared with ICPs (1+ [48%], 2+ [52%], and 3+ [0%] vs. 1+ [10%], 2+ [80%], and 3+ [10%], respectively; P = 0.042). |
| CD4                       | Zhang et al. 2013 | SCC from 12 OTRs and 20 ICPs | OTRs had decreased numbers of CD4+ Th1 T cells compared with ICPs (15.1% ± 2.3% vs. 25.1% ± 3.2%, respectively; P = 0.05). |
| CD8                       | Carroll et al. 2010 | SCC from 25 RTRs and 25 ICPs | Ratio of CD8-to-FOX3 expression was significantly lower in SCC excised from RTRs than in matched SCC from ICPs (1.4 vs. 2.1, respectively; P = 0.013). |
| hBD2                      | Muehleisen et al. 2016 | SCC from 10 OTRs and 7 ICPs | Four-fold higher expression of FOXO1 in OTRs than in ICPs (P = 0.007). |
| FOXO3                     | Zhang et al. 2013 | SCC from 12 OTRs and 20 ICPs | Proportion of FOXP3+ cells to CD8+ cells was increased in OTRs compared with ICPs by nearly two-fold (0.97 ± 0.22 vs. 0.45 ± 0.05, respectively; P < 0.05). |
| IFN-γ                     | Kosmidis et al. 2010 | SCC from 42 OTRs and 43 ICPs | FOXO3 mRNA and protein expression was diminished in OTRs compared with ICPs (by qPCR: P = 0.045; OTR mean 6.89 ± 10^−4 e, interquartile range 1.35 to 10^−4 e to 1.2 ± 10^−3 e; ICP mean 2.44 ± 10^−3 e, interquartile range 4.6 ± 10^−4 e to 1.74 ± 10^−3 e, and by IHC: P = 0.04). |
| FOXP3                     | Kosmidis et al. 2010 | SCC from 42 OTRs and 43 ICPs | GATA-3 expression did not differ with immunosuppression (P = 0.08; OTR mean 1.89 ± 10^−2 e, SD ± 0.10 ± 10^−2 e, interquartile range 1.03 ± 10^−2 e to 2.75 ± 10^−2 e; ICP mean 1.15 ± 10^−2 e, SD ± 1.02 ± 10^−2 e, interquartile range 3.08 ± 10^−3 e to 1.74 ± 10^−2 e). |
| hBD1                      | Muehleisen et al. 2012 | SCC from 11 OTRs and 17 ICPs | SCC in OTRs, in contrast to ICPs, did not overexpress hBD1 in tumors compared with normal skin (ICP difference: P < 0.05; OTR difference P > 0.05). |
| hBD2                      | Muehleisen et al. 2012 | SCC from 11 OTRs and 17 ICPs | hBD2 showed increased expression in both OTRs and ICPs compared with normal skin (OTR difference: P < 0.01; ICP difference: P < 0.01). |
| hTERT                     | Perem et al. 2007 | 66 RTRs and 66 ICPs (44 SCC and 22 BD in each) | Larger percentage of SCC RTR tumors (18 of 39; 46.2%) had higher hTERT expression than ICP tumors (12 of 42; 28.5%) but not statistically significant (P = 0.1738). |
| IL-17A                    | Kosmidis et al. 2010 | SCC from 42 OTRs and 43 ICPs | IFN-γ mRNA expression was decreased in OTRs compared with ICPs (P = 0.02; OTR mean 1.56 ± 10^−4 e, SD ± 2.87 ± 10^−4 e, interquartile range 2.1 ± 10^−4 e to 1.52 ± 10^−2 e; ICP mean 5.65 ± 10^−3 e, SD ± 8.3 ± 10^−3 e, interquartile range 8.63 ± 10^−3 e to 8.2 ± 10^−3 e). |
| IL-22                     | Zhang et al. 2013 | SCC from 12 OTRs and 20 ICPs | Mean IL-22 mRNA expression was increased approximately 30-fold in ICPs and 8-fold in OTRs compared with normal skin (P < 0.05). IL-22 mRNA was increased 111-fold in ICP and 97-fold in OTR peritumoral skin. |
| IL-22                     | Zhang et al. 2013 | SCC from 12 OTRs and 20 ICPs | Ki-67 expression increased nearly two-fold in OTRs when compared with ICPs (55.08 ± 7.4 cells/μm² × 10^7 vs. 30.12 ± 7.1 cells/μm² × 10^7 mean ± SEM, respectively; P < 0.05). Ki-67 expression pattern in OTR tumors was diffused, whereas in ICP tumors expression was mostly present on the periphery of tumor nests. |
| MAGE-A4                   | Muehleisen et al. 2007 | SCC from seven OTRs and nine ICPs | OTRs showed scattered expression of MAGE-A4, whereas ICPs showed focal expression (3 of 4 (75%) vs. 4 of 4 (100%), respectively). |

(continued)
### Table 1. Continued

| Proteins/Genes of interest | Author                        | Year   | Study Population                                      | Findings                                                                 |
|----------------------------|-------------------------------|--------|-------------------------------------------------------|--------------------------------------------------------------------------|
| miR-135b                   | Olasz et al.                  | 2015   | 11 SCCs from OTRs, 32 SCCs from ICPs, and 15 normal skin samples | Examined 88 cancer-related miRNA and found that miR-135b was the most upregulated in OTRs (21.5-fold in OTRs and 13.3-fold in ICPs; \( P = 0.0001 \)). Upregulation resulted in concomitant decreased expression of LZTS1, as well as increased tumor growth, motility, and invasiveness. |
| MMP-1                      | Kuivanen et al.               | 2009   | SCC from 20 ISPs and 20 ICPs                           | No difference in MMP-1 expression (\( P > 0.05 \)).                      |
| MMP-2                      | Chebassier et al.             | 2002   | SCC from 30 RTRs and 30 ICPs (15 in situ and 15 invasive in each) | Overexpression of MMP-2 was identified in the epidermis surrounding tumor cells in RTRs compared with ICPs with invasive SCC (10 of 15 vs. 6 of 15). |
| MMP-7                      | Kuivanen et al.               | 2009   | SCC from 20 ISPs and 20 ICPs                           | No difference in MMP-7 expression (\( P > 0.05 \)).                      |
| MMP-8                      | Kuivanen et al.               | 2009   | SCC from 20 ISPs and 20 ICPs                           | No difference in MMP-8 expression (\( P > 0.05 \)).                      |
| MMP-9                      | Kuivanen et al.               | 2009   | SCC from 20 ISPs and 20 ICPs                           | MMP-9 expression was less abundant in stromal macrophages surrounding SCCs of ICPs (\( P = 0.02 \)). |
|                            | Chebassier et al.             | 2002   | SCC from 30 RTRs and 30 ICPs (15 in situ and 15 invasive in each) | Overexpression of MMP-9 was identified in the epidermis surrounding tumor cells in RTRs compared with ICPs with invasive SCC (7 of 15 vs. 4 of 15). |
| MMP-10                     | Boyd et al.                   | 2009   | SCC from 25 RTRs and 25 ICPs                           | Stromal expression of MMP-10 occurred in 12% of RTR tumors and 40% of ICP tumors (\( P = 0.009 \)). |
| MMP-12                     | Boyd et al.                   | 2009   | SCC from 25 RTRs and 25 ICPs                           | No difference in MMP-12 expression (\( P > 0.05 \)).                      |
| MMP-13                     | Kuivanen et al.               | 2009   | SCC from 20 ISP and 20 ICP                            | No difference in MMP-13 expression (\( P > 0.05 \)).                      |
| MMP-21                     | Boyd et al.                   | 2009   | SCC from 25 RTRs and 25 ICPs                           | No difference in MMP-21 expression (\( P > 0.05 \)).                      |
| MMP-26                     | Kuivanen et al.               | 2009   | SCC from 20 ISPs and 20 ICPs                           | MMP-26 expression was significantly more intense in tumor cells of ICPs than in tumor cells of ICPs (\( P = 0.01 \)). |
| OX40                       | Feldmeyer et al.              | 2016   | SCC from 10 OTRs and 7 ICPs                           | A 5.3-fold higher expression of OX40 in OTRs than in ICPs (\( P = 0.03 \)). |
| p-mTOR (Ser2448)           | Gutierrez-Dalmau et al.       | 2010   | SCC from 37 RTRs and 51 ICPs                           | p-mTOR was reduced in RTRs when compared with ICPs (28.3 vs. 18.7 vs. 55.0 + 22.1, respectively; \( P < 0.001 \)). |
| p-p70S6K (Thr421Ser424)    | Gutierrez-Dalmau et al.       | 2010   | SCC from 37 RTRs and 51 ICPs                           | p-p70S6K was reduced in RTRs when compared with ICPs (30.0 vs. 23.0 vs. 45.4 + 22.5, respectively; \( P = 0.026 \)). |
| p-Smad1                    | Harradine et al.              | 2009   | 200 SCC lesions from 87 OTRs and 184 lesions from 184 ICPs | No difference in p-Smad1 expression (\( P > 0.05 \)).                     |
| p-Smad2                    | Harradine et al.              | 2009   | 200 SCC lesions from 87 OTRs and 184 lesions from 184 ICPs | Increased p-Smad2 staining intensity in OTRs compared with ICPs (\( P < 0.001 \)). |
| p-Smad5                    | Harradine et al.              | 2009   | 200 SCC lesions from 87 OTRs and 184 lesions from 184 ICPs | No difference in p-Smad5 expression (\( P > 0.05 \)).                      |
| p-Smad8                    | Harradine et al.              | 2009   | 200 SCC lesions from 87 OTRs and 184 lesions from 184 ICPs | No difference in p-Smad8 expression (\( P > 0.05 \)).                      |
| p14                        | Küsters-Vandevelde et al.     | 2009   | SCC from 18 RTRs and 16 ICPs                           | p14 expression was independent of immune status (ICP 8 of 16 [50%] vs. RTR 9 of 18 [50%]; \( P > 0.05 \)). |
| p16                        | Küsters-Vandevelde et al.     | 2009   | SCC from 18 RTRs and 16 ICPs                           | p16 expression was independent of immune status (ICP 9 of 16 [56%] vs. RTR 12 of 18 [67%]; \( P > 0.05 \)). |
| p53                        | Gutierrez-Dalmau et al.       | 2010   | SCC from 37 RTRs and 51 ICPs                           | p53 staining intensity was greater in SCC from RTRs than in SCC from ICPs (42.1 vs. 28.4 vs. 21.8 vs. 28.5, respectively; \( P = 0.007 \)). |
|                            | Küsters-Vandevelde et al.     | 2009   | SCC from 18 RTRs and 16 ICPs                           | p53 expression was independent of immune status (ICP 16 of 16 [100%] vs. RTR 12 of 18 [67%]; \( P > 0.05 \)). |
|                            | de Graaf et al.               | 2008   | SCC from 19 RTRs and 13 ICPs                           | p53 patches were more prevalent in RTRs than in ICPs in normal skin adjacent to SCC (\( P = 0.02 \)). |
|                            | Bloxx et al.                  | 2003   | SCC from 44 RTRs and 42 ICPs                           | SCC tumors in RTRs were more likely to be p53-negative than that in ICPs (30% vs. 0%, respectively; \( P = 0.02 \)). |
|                            | Seckin et al.                 | 2002   | SCC from 10 RTRs and 14 ICPs                           | No difference in p53 expression (\( P > 0.05 \)).                       |
| PD-L1                      | Varki et al.                  | 2018   | SCC from 42 ICPs and 24 ICPs (13 OTRs, 8 HIV, and 3 others) | No difference in PD-L1 expression (\( P = 0.05 \)).                      |
| Psoriasis (S100A7)         | Muehelesen et al.             | 2012   | SCC from 11 OTRs and 17 ICPs                           | Psoriasis levels in the tumor center of OTRs were significantly lower than in ICPs (71.9 vs. 49.1 vs. 133.4 + 690; \( P < 0.01 \)). |
| RAGE                       | Iotzova-Weiss et al.          | 2015   | SCC from 13 OTRs and 19 ICPs                           | No significant difference in RAGE expression (\( P > 0.05 \)).           |
| S100A8                     | Iotzova-Weiss et al.          | 2015   | SCC from 13 OTRs and 19 ICPs                           | S100A8 expression was significantly higher in OTRs with invasive SCC than in ICPs with invasive SCC (\( P < 0.01 \)). |
| S100A9                     |                                |        |                                                        |                                                                         |

(continued)
MTOR and its downstream target P70-S6 kinase 1 were lower in RTRs than in ICPs (P < 0.001 and P = 0.026, respectively) (Gutierrez-Dalmau et al., 2010). OX40, which activates NF-κ to suppress apoptosis, was expressed more highly in tumors from OTRs (P = 0.03) (Feldmeyer et al., 2016). Expression of the anti-apoptotic protein Bcl-XL was decreased in RTRs compared with that in ICPs, whereas no difference was observed in the expression of the pro-apoptotic proteins Bax and Bcl-2 (P = 0.042, P > 0.05, and P > 0.05, respectively) (Burke et al., 2015; Seckin et al., 2002). Expression of the DNA damage repair protein XPC was lost at higher rates in tumors from OTRs than in ICPs (P = 0.08) (de Feraudy et al., 2010). Of the examined microRNAs (miRNAs) in OTRs, miR-135b was the most upregulated, by 21.5-fold in OTRs and 13.3-fold in ICPs (P = 0.0001) (Olasz et al., 2015).

Reports on the comparative expression of matrix metalloproteinases (MMPs) (Zou et al., 2021), a family of proteins reported to be associated with tumor progression, showed mixed results. Chebassier et al. (2002) found higher levels of MMP-2 and MMP-9 in the peritumoral skin of RTRs than that in the peritumoral skin of ICPs (10 of 15 vs. 6 of 15 and 7 of 15 vs. 4 of 15, respectively), and Kuivanen et al. (2009) found that intratumoral expression of MMP26 was increased among tumors from ICPs compared with that among tumors from OTRs (P = 0.01). Conversely, the same study showed that MMP-9 was less abundant in tumor-associated macrophages of ISPs (P = 0.02) (Kuivanen et al., 2009), and Boyd et al. (2009) showed that squamous cell carcinoma (SCC) from RTRs was less likely to express MMP10 than tumors from ICPs (P = 0.009).

Several studies examined the expression of p53, and two groups found increased staining intensity of p53 within OTRs (P = 0.007 and P = 0.02, respectively) (de Graaf et al., 2008; Gutierrez-Dalmau et al., 2010). On the contrary, Kusters-Vandevelde et al. (2009) found that levels of both mRNA and protein for the tumor suppressor genes P14, P16, and P53 were independent of immune status (P > 0.05). Another study by Seckin et al. (2002) also found no difference in p53 expression (P > 0.05). In contrast, Blokx et al. (2003) showed a higher prevalence of p53-negative tumors in cSCC from RTRs than in ICPs (30% vs. 0%, respectively; P = 0.02). Together, the results from different studies are entirely inconsistent.

Data on TGFβ expression was also equivocal. TGFβ signaling is often dysregulated in human cancer, with tumor suppressive function in premalignant and early-stage lesions and oncogenic effects in more advanced lesions (Zhang et al., 2021). One study found TGFβ mRNA levels to be decreased in tumors from OTRs (P = 0.036) (Kosmidis et al., 2010), whereas another showed TGFβ staining to be more intense among the RTR population (P = 0.049) (Gutierrez-Dalmau et al., 2010). A third study by Harradine et al. (2009) found no difference in TGFβ expression (P > 0.05) but did show that tumors from ISPs had increased staining for phosphorylated Smad (p-Smad) 2 (P < 0.001), which is downstream of TGFβ to promote growth and differentiation. Levels of p-Smad1, p-Smad5, and p-Smad8 were not different between the two groups (P > 0.05) (Harradine et al., 2009). The same study also showed decreased expression of the type II TGFβ receptor in cSCCs from OTRs (P = 0.03) (Harradine et al., 2009).
The expression of the S100 family of calcium sensing proteins was also probed. One study found that S100A7 levels were lower in cSCC from OTRs than from ICPs (P < 0.01) (Muehleisen et al., 2012). Another study looking at the expression of S100A8 and S100A9, showed higher expression in invasive cSCC from OTRs than from ICPs (P < 0.01 and P < 0.05, respectively) (Iotzova-Weiss et al., 2015). In other tumor types, S100A7 has been associated with decreased proliferation and metastases, whereas S100A8 and S100A9 are associated with increased growth and immune evasion (Bresnick et al., 2015). Human β-defensin (hBD) levels were measured by Muehleisen et al. (2012), showing that hBD-1 and hBD-2 expression was increased in tumors from ICPs compared with normal skin (P < 0.05 and P < 0.01, respectively). However, this overexpression was only seen with hBD-2 among ISPs and not hBD-1 (P < 0.02 and P > 0.05, respectively) (Muehleisen et al., 2012). hBDs are important components of the innate immune system in the skin but have controversial roles in oncogenesis.

Some studies focused on the expression of immune cell markers. The expression of T-Bet, which promotes the T helper type 1 phenotype, was decreased in OTRs compared with that in ICPs in one study (P = 0.0056) (Kosmidis et al., 2010), and CD4+ cells were decreased in tumors from OTRs (P < 0.05) (Zhang et al., 2013). Consistently, the CD8+ T cells were decreased and the expression of FOXP3 was higher, whereas absolute FOXP3 expression was diminished in OTRs compared with that in ICPs (P = 0.013, P < 0.05, and P = 0.45, respectively) (Carroll et al., 2010; Frazzette et al., 2020; Kosmidis et al., 2010; Zhang et al., 2013). B7-H3, a known oncogene and immune checkpoint molecule was shown to be widely expressed in tumors from ICPs (P = 0.025) (Varki et al., 2018), and IFN-γ, a key regulator of innate and adaptive immunity, was expressed more highly among tumors from ICPs (P = 0.02) (Kosmidis et al., 2010). Other key immune responses, IL-17A and IL-22R, had lower expression in tumors from ISPs (P = 0.016 and P < 0.05, respectively) (Table 1) (Kosmidis et al., 2010; Zhang et al., 2013).

### Table 2. Gene Expression Associated with cSCC in ISPs

| Genes of interest | Author | Year | Study Population | Findings |
|-------------------|--------|------|------------------|----------|
| CD57              | Bottomley et al. | 2015 | 110 RTRs (57 with SCC and 53 without) | RTRs exhibiting a population of >50% of CD8+ T cells expressing CD57 were at significantly greater risk of developing a future SCC (HR = 5, 95% CI = 1.11–22.3, P = 0.04). |
| CGRP              | Frauenfelder et al. | 2017 | SCC from 34 OTRs (18 pain-associated tumors, 16 without) | No difference in CGRP expression levels in SCC with pain compared with SCC without pain in OTRs. |
| FOXP3             | Shenton et al. | 2014 | 57 RTRs with SCC and 49 RTRs without SCC | Proportion of CD4+ FOXP3+ cells was higher in RTRs with SCC than in RTRs without SCC. (P = 0.017). |
| HLA-A11           | Bouwes Bavinck et al. | 1997 | 1,098 RTRs of whom 271 developed SCC | Expression of HLA antigen HLA-A11 was associated with increased risk of skin cancer in RTRs (RR = 1.7, 95% CI = 1.1–2.4, P = 0.009). |
| HLA-DRB1*13       | Kim et al. | 2020 | 46 RTRs who developed cSCC after transplant | HLA-DRB1*13 was associated with SCC risk in RTRs after transplant (HR = 2.24, 95% CI = 1.12–4.49, P = 0.023). |
| HLA-G             | Aractingi et al. | 2003 | 37 SCC from RTRs and 24 benign lesions from RTRs | HLA-G expression was higher in SCC (P < 0.02, Fischer's exact test) and in Bowen's disease (P < 0.004, Fischer's exact test) than in benign lesions. The level of positivity was not different when comparing SCC and Bowen's disease (P = 0.25). |
| IL-1β             | Frauenfelder et al. | 2017 | SCC from 34 OTRs (18 pain-associated tumors and 16 without) | No difference in IL-1β expression levels in SCC with pain compared with SCC without pain in OTRs. |
| mir-1246          | Geusau et al. | 2020 | Eight OTRs with cSCC and eight OTRs without cSCC | mir-1246 was significantly upregulated in both tumor tissue and serum in OTRs with cSCC compared to those without (p = 0.013). |
| mir-1290          | Geusau et al. | 2020 | 8 OTRs with cSCC and 8 OTRs without cSCC | mir-1290 was significantly upregulated in both tumor tissue and serum in OTRs with cSCC compared with those without (P = 0.037). |
| NGF               | Frauenfelder et al. | 2017 | SCC from 34 OTRs (18 pain-associated tumors, 16 without) | No difference in NGF expression levels in SCC with pain compared with SCC without pain in OTRs. |
| p53               | Maurer et al. | 1997 | SCC and normal skin from 33 patients with HIV excised from both UV-exposed and UV-protected areas | 92% (22 of 24) of SCC specimens and 93% (17 of 20) of tissue specimens adjacent to SCCs stained for p53, whereas control specimens from UV-protected skin did not stain for p53. |
| PGE2              | Frauenfelder et al. | 2017 | SCC from 34 OTRs (18 pain-associated tumors and 16 without) | SCC with pain is associated with increased levels of PGE2 (OR = 1.9, 95% CI = 1.1–3.4, P = 0.002), adjusted for age and sex. |
| POMC              | Frauenfelder et al. | 2017 | SCC from 34 OTRs (18 pain-associated tumors, 16 without) | SCC with pain was associated with increased levels of POMC compared with SCC without pain (OR = 1.5, 95% CI = 0.99–2.0, P = 0.05), adjusted for age and sex. |
| TNF-α             | Frauenfelder et al. | 2017 | SCC from 34 OTRs (18 pain-associated tumors and 16 without) | SCC with pain was associated with increased levels of TNF-α compared with SCC without pain (adjusted OR = 1.4, 95% CI = 0.99–2.0, P = 0.05). |

Abbreviations: CI, confidence interval; cSCC, cutaneous squamous cell carcinoma; HR, hazard ratio; ICP, immunocompetent patient; ISP, immunosuppressed patient; NGF, nerve GF; OTR, organ-transplant recipient; PGE2, prostaglandin E2; POMC, pro-opiomelanocortin; RR, relative risk; RTR, renal transplant recipient; SCC, squamous cell carcinoma.

A summary of gene expression associated with cSCC in ISPs.
Table 3. Gene Polymorphisms and Haplotypes

| Gene of interest | Author | Year | Study population | Polymorphism | Findings |
|------------------|--------|------|------------------|--------------|----------|
| 3’UTR of PTGS2   | Gomez-Lira et al. | 2011 | 138 OTRs with SCC and 124 OTRs without SCC | +8473T>C, +8293G>C, +10259T>G, +10267G>A, +10335G>A | No allele frequency differences were observed between cases and controls for any of the identified polymorphisms, suggesting that polymorphisms in the 3’UTR of the PTGS2 gene are rare and unlikely to represent risk factor for NMSC after transplantation. |
|                  | Lira et al. | 2007 | 107 OTRs with SCC and 133 OTRs without SCC | +8473T>C | Variant +8473T>C, located in the 3’UTR region of the gene, showed no association with NMSC risk after transplantation. |
| 9p21-22 (p16INK4 and p14ARF) | Mühleisen et al. | 2012 | 42 OTRs with SCC and 43 ICPs with SCC | rs4911414 rs1015362 | Allelic balance at D9S162 was reduced for SCC in OTRs compared with SCC in ICPs (OR = 0.04). |
| ASIP haplotype | Andresen et al. | 2013 | 80 RTRs with SCC and 137 RTRs without SCC | rs3774611 A allele rs893365 T allele | Two SNVs at the CACNA1D gene had a significant association with the development of NMSC in OTRs (OR = 2.67, 95% CI = 1.73–4.10, P = 8.01 × 10⁻⁶; OR = 2.67, 95% CI = 1.73–4.10, P = 8.01 × 10⁻⁶, respectively). |
| CACNA1D | Sanders et al. | 2015 | 88 OTRs with SCC and 300 OTRs without SCC | rs12210050 T allele | An SNV at the CDK10 gene had a significant association with the development of NMSC in OTRs (OR = 2.07, 95% CI = 1.14–3.74, P = 0.02). |
| CDK10 | Sanders et al. | 2015 | 88 OTRs with SCC and 300 OTRs without SCC | rs258322 A allele | Statistical analysis showed no difference between the genotypic distribution of RTRs presenting with skin cancer and those without a history of skin cancer. |
| COX2 gene promoter | Aubin et al. | 2010 | 11 OTRs with SCC and 592 OTRs without SCC | −76hl5 | Three SNVs at the CSMD1 gene had a significant association with the development of NMSC in OTRs (OR = 1.90–5.20, P = 8.78 × 10⁻⁶; OR = 3.14, 95% CI = 1.90–5.20, P = 8.78 × 10⁻⁶; OR = 3.15, 95% CI = 1.90–5.25, P = 9.64 × 10⁻⁶, respectively). |
| CSMD1 | Sanders et al. | 2015 | 88 OTRs with SCC and 300 OTRs without SCC | rs13270945 A allele rs9644363 G allele rs34851282 T allele | RTRs carrying the GSTM1 AB allele had a reduced risk of developing NMSC when compared with other alleles at the same locus (RR = 0.90–3.20; P = 0.032). |
| DLEU7 | Sanders et al. | 2015 | 88 OTRs with SCC and 300 OTRs without SCC | rs1239947 T allele | An SNV at the DLEU7 gene had a significant association with NMSC development in OTRs (OR = 1.58, 95% CI = 1.02–2.47, P = 0.04). |
| EGF | Tartaglia et al. | 2007 | 95 OTRs with SCC and 106 OTRs without SCC | rs4444903 G allele | Genotype and the allele frequencies were not significantly different between the control group and the transplanted patients with and without skin tumors. |
| EXOC2 | Sanders et al. | 2015 | 88 OTRs with SCC and 300 OTRs without SCC | rs12210050 T allele | An SNV at the EXOC2 gene had a significant association with the development of NMSC in OTRs (OR = 1.95, 95% CI = 1.15–3.20, P = 0.049). |
| GSTM1 | Fryer et al. | 2005 | 361 RTRs with SCC and without | GSTM1 AB allele | A significant association was found in RTRs carrying the GSTM1 AB allele null and the development of NMSC (OR = 8.4, P = 0.012). |
|                  | Ramsay et al. | 2001 | 183 RTRs with SCC and without | GSTM1 null | No significant association of the GSTM1 genotype between groups. |
|                  | Marshall et al. | 2000 | 222 RTRs with SCC and without | GSTM1 A/B/AB/null | No significant association of the GSTM1 genotype between groups. |
| GSTM1 and CYP1A1 haplotype | Lira et al. | 2006 | 107 OTRs with SCC and 132 OTRs without SCC | GSTM1 null & CYP1A1 Val⁶² | A haplotype including the GSTM1 and CYP1A1 genes was identified with a significant association with the development of NMSC in OTRs (OR = 0.5, 95% CI = 1.4–34.4, P = 0.01). |
| GSTM3 | Fryer et al. | 2005 | 361 RTRs with SCC and without | GSTM3 AA allele | RTRs with the GSTM3 AA allele had a reduced risk of SCC (RR = 0.50, 95% CI = 0.28–0.87, P = 0.015). |
|                  | Ramsay et al. | 2001 | 183 RTRs with SCC and without | GSTM3 AA/AB/BB | No significant association of the GSTM3 genotype between groups. |
| GSTP1 | Lira et al. | 2006 | 107 OTRs with SCC and 132 OTRs without SCC | Val⁶⁵ | OTRs with the Val⁶⁵ polymorphism in the GSTP1 gene showed a significantly decreased risk of developing NMSC (OR = 0.1, 95% CI = 0.0–0.7, P = 0.012). |
|                  | Ramsay et al. | 2001 | 183 RTRs with SCC and without | GSTP1*1le/le | A significant association was found in RTRs carrying the GSTP1*1le allele and the development of NMSC (OR = 7.6, P = 0.002). |
|                  | Marshall et al. | 2000 | 222 RTRs with SCC and without | GSTP1*C allele | GSTP1*C allele was associated with the development of SCC (P = 0.01). |

(continued)
| Gene of interest | Author                  | Year | Study population                  | Polymorphism | Findings                                                                                                                                                                                                 |
|------------------|-------------------------|------|-----------------------------------|--------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| GSTP1A haplotype | Lira et al.             | 2006 | 107 OTRs with SCC and 132 OTRs without SCC | Ile<sup>105</sup> & Ala<sup>114</sup> | A GSTP1A haplotype was identified with a significant association with the development of NMSC in OTRs (OR = 1.7, 95% CI = 1.1–2.5, P = 0.017).              |
| GSTT1            | Ramsay et al.           | 2001 | 183 RTRs with SCC and without SCC  | GSTT1 null/A | No significant association of the GSTT1 genotype between groups.                                                                                                                                           |
|                  | Marshall et al.         | 2000 | 222 RTRs with SCC and without SCC  | GSTT1 null   | No significant association of the GSTT1 genotype between groups.                                                                                                                                           |
| HERC2            | Wei et al.              | 2017 | 386 OTRs with SCC and without SCC  | rs916977     | OTRs homozygous for brown eye alleles rs916977 (GG) and rs12913832 (AA) had significant delays of time to first cSCC after transplant compared with individuals homozygous for blue eye alleles (HR = 0.34, P < 0.001; HR = 0.54, P = 0.012, respectively). |
| HLA-DQA1         | Asgari et al.           | 2016 | 61,457 SCC (ICPs and ISPs)         | rs4455710     | An intronic polymorphism at the HLA locus at 6p21 in the HLA-DQA1 gene was strongly associated with increased risk of SCC in ISPs (HR = 1.17, 1.86 × 10<sup>6</sup>). |
| Hp               | Speeckaert et al.       | 2012 | 300 RTRs                           | H<sub>p</sub> polymorphism | Significant association of the Hp 1-1 phenotype with a higher risk of SCC/Bowen's disease (P = 0.035) and multiple primary SCCs (P = 0.002). No significant difference between the Hp phenotypes was found in the first 10 years after transplantation. However, after a follow-up of >10 y, significant association between Hp 1-1 phenotype and the occurrence of Bowen's disease and SCC (P = 0.002 and P = 0.001, respectively). |
| IL10 gene promoter haplotypes | Alamartine et al. | 2003 | 40 RTRs with SCC, 70 RTRs without SCC, and 70 ICPS | A<sub>-1082</sub>T<sub>-819</sub>A<sub>-592</sub> (IL-10 low) G<sub>-1082</sub>T<sub>-819</sub>A<sub>-592</sub> (IL-10 high) | Two haplotypes in the IL10 gene promoter were identified in RTRs which resulted in different levels of IL-10 expression. IL-10 low had a protective effect on the development of NMSC (OR = 0.16, 95% CI = 0.06–0.42, P = 0.05), whereas IL-10 high had a significant association with the development of NMSC (OR = 2.58, 95% CI = 1.05–7.04, P = 0.05). |
| Intergenic (CHR 5) | Sanders et al.          | 2015 | 88 OTRs with SCC and 300 OTRs without SCC | rs4460176 T allele | An SNV, rs4460276 T allele, at an intergenic location on CHR 5 had a significant association with NMSC development in OTRs (OR = 1.62, 95% CI = 1.08–2.43, P = 0.02). |
| Intergenic (CHR 6) | Sanders et al.          | 2015 | 88 OTRs with SCC and 300 OTRs without SCC | Intergenic rs1540771 T allele | An SNV, rs1540771, on CHR 6 had a significant association with the development of NMSC in OTRs (OR = 1.89, 95% CI = 1.26–2.82, P = 0.002). |
| Intergenic (CHR 11) | Sanders et al.          | 2015 | 88 OTRs with SCC and 300 OTRs without SCC | rs11820512 A allele | An SNV, rs11820512 A allele, at an intergenic location on CHR 11 had a significant association with the development of NMSC in OTRs (OR = 6.66, 95% CI = 2.91–15.22, P = 7.10 × 10<sup>6</sup>). |
| Intergenic (CHR 18) | Sanders et al.          | 2015 | 88 OTRs with SCC and 300 OTRs without SCC | rs4799088 A allele | An SNV, rs4799088 A allele, at an intergenic location on CHR 18 had a significant association with NMSC development in OTRs (OR = 1.66, 95% CI = 1.03–2.67, P = 0.04). |
| IRF4             | Asgari et al.           | 2017 | 388 OTRs with SCC and without SCC  | rs12203592 T allele | In univariate analysis, the IRF4 rs12203592 T allele was associated with a significantly increased hazard for time to first cSCC (HR = 1.36, P = 0.02); this association was maintained when adjusted for sex, age, organ transplanted, and Fitzpatrick skin type (HR = 1.34, P = 0.04). |
|                  | Sanders et al.          | 2015 | 88 OTRs with SCC and 300 OTRs without SCC | rs12203592 T allele | An SNV at the IRF4 gene had a significant association with the development of NMSC in OTRs (OR = 2.08, 95% CI = 1.23–3.53, P = 0.007). |
| LINC00882        | Sanders et al.          | 2015 | 88 OTRs with SCC and 300 OTRs without SCC | rs6791146 C allele rs68025055 rs13061320 C allele rs34796852 T allele | Four SNVs at the LINC00882 gene had a significant association with NMSC development in OTRs (OR = 3.79, 95% CI = 2.17–6.60, P = 2.76 × 10<sup>-6</sup>; OR = 3.37, 95% CI = 2.13–6.48, P = 4.01 × 10<sup>-6</sup>; OR = 3.71, 95% CI = 2.12–6.47, P = 4.12 × 10<sup>-6</sup>; OR = 3.71, 95% CI = 2.12–6.47, P = 4.12 × 10<sup>-6</sup>, respectively). |
| MCIR             | Sanders et al.          | 2015 | 88 OTRs with SCC and 300 OTRs without SCC | rs4785763 A allele | An SNV at the MCIR gene had a significant association with the development of NMSC in OTRs (OR = 1.62, 95% CI = 1.07–2.45, P = 0.02). |

(continued)
| Gene of interest | Author | Year | Study population | Polymorphism | Findings |
|------------------|--------|------|------------------|--------------|----------|
| **MC1R haplotype** | Andresen et al. | 2013 | 80 RTRs with SCC and 137 RTRs without SCC | rs1805007 (red hair) Any two of the following in combination: rs1805006 rs1805007 rs1805008 rs1805009 rs1805005 rs2228479 rs885479 | Significant associations with SCC risk in RTRs were indicated in carriers of the red hair color associated MC1R variant p.Arg151Cys (OR = 1.99, 95% CI = 1.05 –3.75), and in carriers of two of any of the MC1R variants included to the left (OR = 2.36, 95% CI = 1.08 –5.15). |
| **MTHFR** | Laing et al. | 2007 | 117 RTRs with SCC and 250 RTRs without SCC | rs1801133 T allele | Individuals carrying the MTHFR 677T allele had a marked increase in risk of SCC (adjusted OR = 2.54, P = 0.002), after adjustment for age, gender, skin type, sun exposure score, and immunosuppression duration. |
| **MYPN** | Sanders et al. | 2015 | 88 OTRs with SCC and 300 OTRs without SCC | rs6480314 G allele | An SNV at the MYPN gene had a significant association with NMSC development in OTRs (OR = 1.66, 95% CI = 1.02–2.71, P = 0.04). |
| **OCA2** | Wei et al. | 2017 | 386 OTRs with SCC and without | rs916977 brown eye allele compared with blue eye allele and rs12913832 brown eye allele compared with blue eye allele | OTRs homozygous for the brown eye alleles of rs916977 (GG) and rs12913832 (AA) had significant delays of time to first cSCC after transplant than those individuals homozygous for the blue eye alleles (HR = 0.34, P < 0.001; HR = 0.54, P = 0.012, respectively). |
| **Promoter of PTGS2** | Lira et al. | 2007 | 107 OTRs with SCC and 133 OTRs without SCC | −765C>G, −1195A>G | Variant −1195G was over-represented in patients with SCC undergoing transplantation after 50 y of age, but this difference did not reach significance (P = 0.09). |
| **PTGS2 Haplotype** | Lira et al. | 2007 | 107 OTRs with SCC and 133 OTRs without SCC | G_{1195}.G>T_{-765}.T_{-8473} | A significant association between a PTGS2 haplotype and development of NMSC in OTRs was identified (OR = 4.77, 95% CI = 1.47–16.41, P = 0.01). |
| **RNF5P1** | Sanders et al. | 2015 | 88 OTR with SCC and 300 OTR without SCC | rs7832232 A allele | An SNV at the RNF5P1 gene had a significant association with NMSC development in OTRs (OR = 1.50, 95% CI = 1.02–2.21, P = 0.04). |
| **SLC45A2** | Asgari et al. | 2017 | 388 OTRs with SCC and and without | rs16891982 C allele | The SLC45A2 rs16891982 C allele was associated with a decreased hazard for cSCC in univariate analysis (HR = 0.58, P = 0.04), and the effect was similar but not significant in the multivariate model (HR = 0.74, P = 0.06). |
| **TLR4** | Laing et al. | 2009 | 168 RTRs with SCC and 286 RTRs without SCC | rs4986790 rs179008 rs3764880 | No significant association of the TLR4 genotype between groups. |
| **TLR7** | Laing et al. | 2009 | 168 RTRs with SCC and 286 RTRs without SCC | rs4986790 rs179008 rs3764880 | No significant association of the TLR7 genotype between groups. |
| **TLR8** | Laing et al. | 2009 | 168 RTRs with SCC and 286 RTRs without SCC | rs4986790 rs179008 rs3764880 | No significant association of the TLR8 genotype between groups. |
| **TMC6/EVER1** | Burger et al. | 2015 | 16 RTRs with SCC and 25 RTRs without SCC | 26 SNVs within both TMC and EVER genes | No significant association was found between any SNP genotype within TMC6/EVER1 and risk of SCC development in RTRs. |
| **TMC6/EVER2** | Burger et al. | 2015 | 16 RTRs with SCC and 25 RTRs without SCC | 26 SNVs within both TMC and EVER genes | No significant association was found between any SNP genotype within TMC6/EVER2 and risk of SCC development in RTRs. |
| **TP53** | Cairey-Remonnay et al. | 2002 | 53 RTRs with SCC, 50 RTRs with benign lesions, 41 ICPS with SCC, and 29 blood samples from ICPS without SCC | Codon 72 of exon 4 | Rate of arginine homozygosity in SCC from RTRs was significantly higher (83%) than in ICPS with or without SCC (60% and 59%, respectively). |
| **TYR** | Andresen et al. | 2013 | 80 RTRs with SCC and 137 RTRs without SCC | rs1126809 | No significant association of the TYR genotype between groups. |
| **TYRP1** | Andresen et al. | 2013 | 80 RTRs with SCC and 137 RTRs without SCC | rs1408799 | No significant association of the TYRP1 genotype between groups. |
Table 3. Continued

| Gene of interest | Author | Year | Study population | Polymorphism | Findings |
|------------------|--------|------|------------------|--------------|----------|
| Upstream of RP116365.6, FBXO25, and ORF2 | Kuzmanov et al. | 2019 | 61 OTRs with cSCC and 908 OTRs without cSCC | rs34567942 | GWAS identified one SNV, rs34567942, to be significantly associated with cSCC in OTRs at the P-value threshold of 5 × 10⁻⁵. |

Abbreviations: CHR, chromosome; CI, confidence interval; cSCC, cutaneous squamous cell carcinoma; HR, hazard ratio; ICP, immunocompetent patient; ISP, immunosuppressed patient; NMSC, nonmelanoma skin cancer; OTR, organ-transplant recipient; RR, relative risk; RTR, renal transplant recipient; SCC, squamous cell carcinoma; UTR, untransplanted region.

A summary of polymorphisms identified in the ISP population with an associated risk of SCC.

The other nine studies (12% of all articles) assessed differences in protein and mRNA expression in ISPs with and without cSCC, with a total of 16 unique proteins/gene of interest being identified (Table 2). Some studies reported the circulating host immune phenotype. One study found that the population of circulating regulatory T cells was higher in ISPs than in those without (P = 0.017) (Sherston et al., 2014). Patients with higher levels of CD8⁺ T cells expressing the senescence marker CD57 were at higher risk for developing cSCC (hazard ratio [HR] expressing the senescence marker CD57 were at higher risk for developing cSCC (hazard ratio [HR] = 2.13–6.48, P = 4.01 × 10⁻⁶; OR = 3.71, 95% CI = 2.12–6.47, P = 4.12 × 10⁻⁶; and OR = 3.71, 95% CI = 2.12–6.47, P = 4.12 × 10⁻⁶) (Sanders et al., 2015). Haplotypes with the greatest risk for cSCC included the combination of GSTM1 null and the cytochrome P450 allele CYP1A1 Val¹⁶² (OR = 6.5, 95% CI = 1.4–34.4, P = 0.01) (Lira et al., 2006), as well as the COX-2 encoding gene PTGS2 haplotype G-1195-G-765-T-8473 (OR = 4.77, 95% CI = 1.47–16.41, P = 0.01) (Lira et al., 2007). A protective role was found for several alleles located within genes influencing pigmentation, including the brown eye allele at OCA1/HCR2 and the C allele for SLC45A2 (Asgari et al., 2017; Wei et al., 2017). OTRs homozygous for the brown eye alleles rs916977 (GG) and rs12913832 (AA) had significant delays of time to first cSCC post-transplant compared with individuals homozygous for the blue eye alleles (HR = 0.34, P < 0.001 and HR = 0.54, P = 0.012, respectively) (Wei et al., 2017), whereas the SLC45A2 rs16891982 C allele was associated with a decreased HR for cSCC in univariate analysis (HR = 0.58, P = 0.04) (Asgari et al., 2017). In contrast to the increased risk shown by GSTM1 null, a protective effect was found for the GSTM1 AB allele (RR = 0.23, 95% CI = 0.05–0.99, P = 0.049) (Fryer et al., 2005). Greatly reduced risk of developing cSCC was also found in those ISPs who possessed the A¹⁰⁸₂,T¹⁹⁵₉,A₅₉₂ (IL-10 low) haplotype (OR = 0.16, 95% CI = 0.06–0.42, P = 0.05) (Table 3) (Alamartine et al., 2003).

Gene polymorphisms and haplotypes

Of the reviewed articles, 21 studies (27% of all articles) discussed gene polymorphisms (germline mutations) or associated haplotypes and the associated risk of cSCC in ISPs and OTRs (Table 3). A total of 44 specific genes of interest and associated polymorphisms or haplotypes were delineated. One study evaluated chromosomal inactivation at 9p21-22 and found broadly reduced allelic balance at 9p21-22 in both OTRs and ICPs; however, a unique microsatellite location, D9S162, was identified in OTRs that showed reduced allelic balance when compared with ICPs (P = 0.04) (Mühleisen et al., 2012). Alleles identified with the greatest associated risk included genes coding for the glutathione S-transferase supergene family including GSTM1 null (OR = 8.4, P = 0.012) and GSTP1*Ile/Ile (OR = 7.6, P = 0.002) (Ramsay et al., 2001). The nonfunctional intergenic variant

Drug-induced alterations

This review found 15 articles (19% of all articles) that examined the effects of calcineurin inhibitors (CNIs), such as cyclosporine (CsA) and tacrolimus (Table 4). Treatment with CsA was shown to hasten tumor growth, upregulate IL-22R expression, and cause increased Jak1, signal transducer and activator of transcription (STAT) 1, and STAT3 expression (P < 0.05) (Abikhair et al., 2016; Abikhair Burgo et al., 2018). CsA was also shown to enhance production of proinflammatory cytokines by decreasing expression of tristetraprolin (P < 0.05) (Wu et al., 2018). In addition, ATF3 was shown to be selectively induced by CNIs and an additive effect was found between CsA and UVA (Dzjuncz et al., 2014; Wu et al., 2010). In a mouse model, Goldstein et al. (2015) revealed increased signaling of Nfatc1 in CsA-
treated mice, with associated increased spontaneous SCC formation (Goldstein et al., 2015). Other murine studies found that tacrolimus-treated mice showed higher numbers of chromosomal aberrations than CsA, sirolimus, and mycophenolate (Dworkin et al., 2009), and that IFN-γ-neutralization in tacrolimus-treated mice abrogated SCC regression, significantly reducing CD8+ T-cell infiltration into SCC, and significantly impairing the secretion of CXCL9, CXCL10, and CCL5 within the tumor microenvironment (Zeng et al., 2021). Other notable findings included reduced expression intensity of Mcl-1 in tacrolimus-treated RTRs compared with sirolimus-treated RTRs and ICPs (Burke et al., 2015), augmented tumor growth in CsA-treated human cells lines through activation of TGFB-activated kinase 1 (TAK1) (Xu et al., 2011), and greater abundance of MMP-26 expression in cancer cells (P = 0.04), and MMP-9 in neutrophils (P = 0.005) in SCCs of patients taking CsA (Table 4) (Kuivanen et al., 2009).

Six articles (8% of all articles) discussed genetic alterations owing to AZA (Table 5). AZA was shown to lead to the accumulation of 6-thioguanine (6-TG) in cellular DNA (0.02% substitution of DNA guanine vs. 0% in those not treated with AZA), which has a greater absorption potential for UVA than normal DNA, and thus increased development of cutaneous malignancies (O’Donovan et al., 2005) while also reducing DNA repair activity (Brem et al., 2010). In addition, a previously unknown mutational signature in cSCC of OTRs, termed signature 32, was discovered during whole exome sequencing and mutational signature analysis of OTRs (Inman et al., 2018). Analysis of treatment times revealed a strong positive correlation with the estimated time of AZA exposure and the prevalence of signature 32 (Spearman’s rank order correlation r_s (26) = 0.679, P < 0.0001) (Inman et al., 2018). In a mouse model, Kalra et al. (2012, 2011) revealed that genetic upregulation of Keap1/Nrf2/ARE reduces incorporation of 6-TG in DNA after treatment with AZA and that a robust systemic induction of the Keap1/Nrf2/ARE pathway protects cells with 6-TG incorporations against oxidative stress caused by UVA radiation (Table 5) (Kalra et al., 2012, 2011).

One article (1% of all articles) described cSCC risk associated with the antifungal medication voriconazole (Table 6). Voriconazole was associated with a 73% increased risk for cSCC development in lung transplant recipients. Allelic variant *17 of CYP2C19 had a 74% increased hazard for SCC (95% CI = 1.06–2.84, P = 0.03) (Table 6) (Williams and Arron, 2016).

Four articles (5% of all articles) reported on gene expression changes associated with mTOR inhibitors (Table 7). Sirolimus was reported to downregulate the ATF3 expression caused by CNIs and UVA and was found to significantly inhibit GRO-α expression in keratinocytes and tumor cell lines (Schaper-Gerhardt et al., 2021, 2018). In addition, Yu et al. (2018) revealed that CCND1 gene overexpression was most closely related to mTOR inhibitor resistance (Table 7) (Yu et al., 2018).

Epigenetic alterations (DNA methylation)

There were five articles (6% of all articles) that discussed epigenetics in cSCC among OTRs (Table 8). A comparison of RTRs who developed cSCC and those who did not identified 16 differentially methylated regions. Notable genes included ZNF577 and FLOT1 (Peters et al., 2018). In addition, a study by Peters et al. (2019) revealed higher DNA methylation of SERPINB9 in RTRs who developed cSCC than those that did not. Median DNA methylation of SERPINB9 was 58.7% (range 32.5-81.3%) for region 1 and 54.4% (30.0-78.5%) for region 2 in patients with cSCC, and 50.2% (21.8–77.5%) for region 1 and 46.4% (22.1–74.0%) for region 2 in the non-cSCC patients (region 1: P = 0.004; region 2: P = 0.008) (Table 8) (Peters et al., 2019).

DISCUSSION

This study generated a comprehensive list of 44 genes of interest and associated polymorphisms or haplotypes presently identified in the literature as having a possible association with risk of cSCC in ISPs (Table 3). Alleles identified with the greatest associated risk included genes coding for the glutathione S-transferase supergene family, which are involved in the detoxification of reactive and mutagenic compounds such as the products of UV-induced oxidative damage. We hypothesize that this increased risk is a result of decreased ability of cells to break down products of metabolic stress, in conjunction with systemic immunosuppression, providing an opportunity for neoplastic change and subsequent growth outside of immune surveillance. The nonfunctional intergenic variant polymorphism rs11820512 A allele on chromosome 11 was also highly associated with cSCC development, as well as a group of polymorphisms in the LINC00882 gene, a nonprotein coding RNA that, when overexpressed, has been associated with a poor prognosis in hepatocellular carcinoma (Zhu et al., 2018). Haplotypes with the greatest risk for cSCC included the combination of GSTM1 null and the cytochrome P450 allele CYP1A1 Val462, as well as the COX-2 encoding gene PTGS2 haplotype G_1195,G-765,T_8473, or rs689466, rs20417, rs5275, respectively. A protective role was found for several alleles located within genes influencing pigmentation, including the brown eye allele at OCA1/HERC2 and the C allele for SLC45A2, a transporter protein that mediates melanin synthesis and plays a role in skin pigmentation. OTRs homozygous for the brown eye alleles rs916977 (GG) and rs12913832 (AA) had significant delays of time to first cSCC post-transplant compared with individuals homozygous for the blue eye alleles, whereas the SLC45A2 rs16891982 C allele was associated with a decreased HR for cSCC in univariate analysis. In contrast to the increased risk shown by GSTM1 null, a protective effect was found for the GSTM1 AB allele. Greatly reduced risk of developing cSCC was also found in those ISPs who possessed the A1082,T819,A592 (IL-10 low) haplotype.

A 2016 study by Williams and Arron (2016) investigated an association between CYP2C19 genotypes and cSCC risk in lung transplant recipients taking voriconazole, an agent commonly used to treat invasive aspergillosis in OTRs (Table 4). Although the exact mechanism of voriconazole-associated cutaneous neoplasms is unknown, this study hypothesized that a greater accumulation of voriconazole-N-oxide (VNO), a chromophore for UVB and a breakdown product of voriconazole, could lead to increased...
### Table 4. CNI

| Study Drug | Author                  | Year | Study Population | Findings                                                                                                                                 |
|------------|-------------------------|------|------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| CsA        | Abikhair Burgo et al.   | 2018 | Five Cell lines: | CsA exposure hastened tumor growth, upregulated IL-22R, upregulated oncogenes such as AP-1, and caused increased Jak1, STAT1, and STAT3 expression (P < 0.05). |
|            |                         |      | A4321: nonmetastasizing SCC from ICPs |                                                                                                                                          |
|            |                         |      | T1: nonmetastasizing SCC from OTRs |                                                                                                                                          |
|            |                         |      | T8: metastatic SCC from OTRs |                                                                                                                                          |
|            |                         |      | MET1: metastatic SCC from OTRs |                                                                                                                                          |
|            |                         |      | MET4: derived from metastasized cells of MET1 |                                                                                                                                          |
| CsA        | Abikhair et al.         | 2016 | 114 OTRs with SCC, 7 SCC from OTRs and 9 SCC from ICPs, Human epidermoid carcinoma cell line A431 | CsA was associated with significant risk for catastrophic SCC. SCC in OTRs treated with CsA showed increased expression of IL-22R than in ICPs. Cell lines treated with CsA showed a similar increase in IL-22R. SCC cells treated with IL-22 and CsA showed increased migratory and invasive capacity. |
| CsA        | Arumugam et al.         | 2012 | Human epidermoid carcinoma cell line A431 | Blockade of Akt and p38 kinase-dependent signaling pathways in CsA-treated tumors abrogated growth by >90% with a decrease in proliferation and increase in apoptosis. |
| CsA        | Dziunycz et al.         | 2014 | SCC from 12 OTRs (treated for at least 5 y with CsA) and 19 ICPs | SCC from OTRs treated with CsA showed upregulation of ATF3 expression. CsA-treated cells showed increased ATF3 mRNA and protein expression. Skin pretreated with CsA and then exposed to UVA irradiation strongly induced ATF3 expression at both the mRNA and protein level. |
| CsA        | Goldstein et al.        | 2015 | Mice | CsA resulted in increased signaling through Nfatc1. Nfatc1 expression was associated with increased spontaneous SCC formation. |
| CsA        | Iotzova-Weiss et al.    | 2015 | 13 OTRs and 19 ICPs with invasive SCC, 1 OTR, and 5 ICPs with in situ SCC | CsA and prednisolone can induce S100A8/A9 expression in keratinocytes and activate NF-κB downstream. |
| CsA        | Kuivanen et al.         | 2009 | SCC from 20 ISPs and 20 ICPs | MMP-26 expression in cancer cells (P = 0.04) and that of MMP-9 in neutrophils (P = 0.005) were more abundant in SCCs of patients using CsA. |
| CsA        | Sommerer et al.         | 2008 | 55 RTRs treated with CsA | Of the 55 RTRs treated with CsA, 14 developed NMSCs. NFAT-regulated gene expression (IL-2, GM-CSF, and IFN-γ) was significantly lower in patients with NMSCs. |
| CsA        | Walsh et al.            | 2011 | Human epidermoid carcinoma cell line A431 | CsA treatment increases tumor size of xenograft human SCC. CsA treatment increased expression of the cell cycle regulatory proteins cyclin D1/3, CDK4/6, as well as VEGF. Pro-apoptotic protein Bax was decreased in CsA-treated mice, whereas Bcl-2 was increased. |
| CsA        | Wu et al.               | 2010 | Mice, xenografts, and cell lines | Genetic and pharmacologic suppression of calcineurin/nuclear factor of activated T cells (NFAT) promotes tumor formation. Calcineurin/NFAT inhibition counteracts p53-dependent cancer cell senescence, thereby increasing tumorigenic potential. ATF3, a member of the AP-1 family, is selectively induced by calcineurin/NFAT inhibition. Increased ATF3 expression accounts for suppression of p53-dependent senescence and enhances tumorigenic potential. Intact calcineurin/NFAT signaling is critical for p53-associated mechanisims that protect against cSCC development. |
| CsA        | Wu et al.               | 2018 | Mouse keratinocytes, human keratinocytes, SCC lines SCC12, 13, 15, 25, and SCC and normal skin from ISPs and ICPs | Treatment with CNI resulted in enhanced production of pro-inflammatory cytokines such as TNF-α, IL-8, and CXCL1. Treatment with CNI resulted in decreased expression of TTP, a zinc-finger protein which mediates decay of cytokine mRNA and has a tumor suppressing role (P < 0.05). |
| CsA        | Xu et al.               | 2011 | Human epidermoid carcinoma cell line A431 | CsA was shown to augment tumor growth by activating TAK1, which ultimately activates NF-κB and p38 MAP kinase. |
| CsA and tacrolimus | Dworkin et al.    | 2009 | Mouse models to mimic OTRs | Tacrolimus-treated mice showed a higher number of chromosomal aberrations than CsA, sirolimus, and mycophenolate. Tacrolimus and CsA showed a variation in alterations in the genome suggesting a potential for different methods of inducing SCC. |

(continued)
voriconazole—associated cSCC. Allelic variant *17 (rs12248560) found in rapid metabolizers of voriconazole showed a 74% increased hazard for cSCC in these patients, presumed to be related to the increased accumulation of VNO (Williams and Arron, 2016). Considering this fact, clinicians typically suggest that alternative antifungal agents be used where possible among this population. Overall, the identified polymorphisms and haplotypes confirm a genetic component and predisposition in the development of cSCC among OTRs. Understanding these risks and identifying relevant polymorphisms in OTRs could allow for identification and closer surveillance of high-risk patients and ultimately improve morbidity and mortality among this population.

Thirty-eight percent of articles focused on somatic gene mutations or mRNA/protein expression within cSCC tumors in ISPs (Tables 1 and 2). The CDKN2A gene encodes both p14ARF and p16INK4A and is commonly mutated in cSCC (Lobl et al., 2021). These proteins act as tumor suppressor genes and regulators of the p53 and Rb pathways, respectively. This review included two studies that evaluated chromosomal inactivation at 9p21-22, an area that includes the tumor suppressors p16INK4A and p14ARF (Tables 3 and 8). DNA methylation at this location was shown to be the most common mechanism of inactivation in cSCC, irrespective of immune status. Interestingly, OTRs showed significantly lesser genetic and epigenetic inactivating events at 9p21-22 than ICPs, and according to the authors, the explanation for these findings remains elusive (Table 8) (Brown et al., 2004). A separate study found broadly reduced allelic balance at 9p21-22 in both OTRs and cSCC; however, a unique microsatellite location, D9S162, was identified in OTRs that showed reduced allelic balance when compared with ICPs (Table 3) (Mühleisen et al., 2012). Taken together, considering that OTRs have a greater risk of developing cSCC despite showing fewer genetic and epigenetic inactivating events at 9p21-22, reduced allelic balance at D9S162 could contribute to the increased incidence and more aggressive carcinogenesis of cSCC in OTRs. Although the underlying cause of this reduction remains unknown, it is pertinent to also consider the effect of reduced immune surveillance in ISPs that may allow for tumors with fewer mutations to proliferate.

Although the literature suggests p14 and p16 may contribute to the development of cSCC in OTRs, the role of p53 expression, a commonly upregulated and sometimes mutated tumor suppressor, is more controversial. Although some studies found increased staining intensity of p53 within OTRs, others found that expression of both mRNA and protein for p14, p16, and p53 is independent of immune status (Table 1) (de Graaf et al., 2008; Gutiérrez-Dalmau et al., 2010; Küsters-Vandevelde et al., 2009; Seçkin et al., 2002). Bloxk et al. (2003) showed higher prevalence of p53-negative tumors in cSCC from RTRs than in ICP tumors (30% vs. 0%) (Table 1). One possible explanation was discovered by Maurer et al. (1997), who examined both UV-exposed and UV-protected skin in patients with HIV and found that a significant positive correlation existed between the amount of sun exposure and the amount of p53 staining seen in adjacent epidermal tissue (Table 2) (Maurer et al., 1997). This lack of congruity involving p53 expression is likely multifactorial and could be a result of many factors such as differences in immunosuppressive regimen, smoking status, and UV exposure, among others. Further clarity might be provided by studies with larger sample sizes, assessing both p53 expression and mutational status.

There is a well-known role of altered miRNA expression causing gene dysfunction within tumors. Of the examined miRNAs in OTRs, mir-135b was the most upregulated, by 21.5-fold in OTRs and 13.3-fold in ICPs ($P = 0.0001$) (Table 1) (Olasz et al., 2015). Upregulation of mir-135b ultimately resulted in increased tumor growth, motility, and invasiveness in several types of tumors, including cSCC (Olasz et al., 2015). Identification of mir-135b in OTRs could potentially be used by clinicians during routine surveillance of OTRs. These miRNAs can suppress protein translation and regulate gene expression post-transcriptionally. In addition, miRNA plays a role in modulating the immune response, particularly among OTRs (Sarma et al., 2012).

Table 4. Continued

| Study Drug | Author | Year | Study Population | Findings |
|------------|--------|------|------------------|---------|
| Tacrolimus | Burke et al. | 2015 | 10 RTRs treated with sirolimus, 11 RTRs treated with tacrolimus, and 10 ICPs | Mcl-1 expression intensity was reduced in tacrolimus-treated patients ($1+ \[0\%\], 2+ [36\%], and 3+ [64\%]) than in sirolimus-treated ($1+ \[0\%\], 2+ [0\%], and 3+ [100\%]) and ICPs ($1+ \[0\%\], 2+ [0\%], and 3+ [100\%]) ($P = 0.024$). No difference between groups in percentage of cells with Mcl-1 expression ($P = 1.00$), Bcl-xL expression intensity ($P = 0.134$), or the percentage of cells with Bcl-xL expression ($P = 1.00$). |
| Tacrolimus | Zeng et al. | 2021 | Mice treated with tacrolimus | IFN-γ—neutralization abrogated SCC regression, significantly reduced CD8+ T-cell infiltration into SCC, and significantly impaired the secretion of CXCL9, CXCL10, and CCL5 within the tumor microenvironment. |

Abbreviations: Akt, protein kinase B; CNI, calcineurin inhibitor; CsA, cyclosporin A; ICP, immunocompetent patient; ISP, immunosuppressed patient; MAP, mitogen-activated protein; MMp, matrix metalloproteinase; NMSC, nonmelanoma skin cancer; OTR, organ- transplant recipient; RTR, renal transplant recipient; SCC, squamous cell carcinoma; STAT, signal transducer and activator of transcription; TAK1, TGFβ-activated kinase 1.
**Table 5. AZA**

| Author          | Year | Study Population                   | Findings                                                                                                                                               |
|-----------------|------|-----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|
| Brem et al.     | 2010 | HaCaT keratinocyte cell line      | Interaction between low doses of UVA and AZA causes DNA single-and double-strand breaks. AZA/UVA-induced DNA lesions provoke canonical DNA damage and activate the ATM/Chk2 and ATR/Chk1 pathways. Higher levels of photochemical DNA damage induce a proteasome-mediated degradation of Chk1 and checkpoint abrogation. |
| Inman et al.    | 2018 | 30 SCCs from ISPs and 7 SCCs from ICPs | Signature 32 found to be a mutational signature unique to ISPs receiving AZA. Signature 32 was responsible for 65% of the significantly mutated genes in the SCC samples, including NOTCH1/2, TPS3, and CDKN2A. |
| Kalra et al.    | 2012 | AZA-treated mice                  | A robust systemic induction of the Keap1/Nrf2/ARE pathway protects cells with 6-thioguanine incorporations against oxidative stress caused by UVA radiation. |
| Kalra et al.    | 2011 | AZA-treated mice and non-treated mice | Genetic upregulation of Keap1/Nrf2/ARE reduces incorporation of 6-thioguanine in DNA after treatment with AZA. |
| O’Donovan et al. | 2005 | Normal skin from three AZA-treated patients and three without treatment, normal skin in five patients newly started on AZA than to skin from the same patients before treatment | Skin from AZA-treated patients showed 6-thioguanine representing around 0.02% substitution of DNA guanine, whereas those without treatment had no 6-thioguanine incorporation. AZA treatment caused a significant reduction in the minimal erythema dose for UVA (P = 0.025 by paired t-test compared with the pretreatment value). |
| Perrett et al.  | 2010 | 52 SCCs from OTRs treated with AZA and 34 SCCs from ICPs | MSH2 and MLH1 protein expression was not altered in SCCs from OTRs on AZA and there was no difference in expression levels between SCCs from OTRs and ICPs. |

**Table 6. Voriconazole**

| Author          | Year | Study Population                   | Findings                                                                                                                                         |
|-----------------|------|-----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|
| Williams and Aron | 2016 | A total of 177 lung transplant recipients who developed SCC after taking voriconazole | Voriconazole was associated with a 73% increased risk for SCC development in lung transplant recipients. Allelic variant *17 of CYP2C19 had a 74% increased hazard for SCC (95% CI = 1.06–2.84; P = 0.03). |

**Table 7. mTOR Inhibitors**

| Author          | Year | Study Population                   | Findings                                                                                       |
|-----------------|------|-----------------------------------|------------------------------------------------------------------------------------------------|
| Koletsa et al.  | 2018 | 23 SCCs from OTRs before or after switch to mTOR inhibitor | mTOR inhibition did not significantly change the immunohistochemical expression of molecules upstream of mTOR (p-mTOR, PI3K, p-Akt). |
| Schaper-Gerhardt et al. | 2018 | Human epidermoid carcinoma cell line A431, SCC 12/13 cell lines, and organotypic skin models | Sirolimus downregulated the expression of the oncogene ATF3 that is commonly induced by CsA and UV light. |
| Schaper-Gerhardt et al. | 2021 | Neonatal normal human epidermal keratinocytes, human epidermoid carcinoma cell line A431, SCC 12/13 cell lines, and organotypic skin models | Sirolimus significantly inhibited GRO-α expression in keratinocytes and tumor cell lines and decreased the expression of the corresponding receptor CXCR2. |
| Yu et al.       | 2018 | Everolimus-sensitive (HSC-1) and everolimus-resistant (A431) SCC cell lines | CCND1 gene overexpression was most closely related to mTOR inhibitor resistance. MYC/CCND1/TP73/NUPR1/SBD/ERBB2/CDKN2B genes were all related to mTOR inhibitor resistance. |

**Abbreviations:** AZA, azathioprine; ICP, immunocompetent patient; ISP, immunosuppressed patient; OTR, organ-transplant recipient; SCC, squamous cell carcinoma.

A summary of the genetic mutations, polymorphisms, and expression alterations that increase risk of cSCC in patients taking AZA.

A summary of the genetic mutations, polymorphisms, and expression alterations that increase risk of cSCC in patients taking voriconazole.

A summary of the genetic mutations, polymorphisms, and expression alterations that increase risk of cSCC in patients taking mTOR inhibitors.

This review identified many reports of drug-induced genetic alterations associated with immunosuppressive medications in OTRs (Tables 4–7). AZA has been linked to the development of cSCC in ISPs (Table 5). AZA use has been shown to lead to the accumulation of 6-TG in cellular DNA, which has a greater absorption potential for UVA than normal DNA, and thus increased development of cutaneous malignancies, while also reducing DNA repair activity (de Graaf et al., 2008; O’Donovan et al., 2005). Recently, a previously unknown mutational signature in cSCC of OTRs, termed signature 32, was discovered during whole exome sequencing and mutational signature analysis of OTRs. Analysis of treatment times revealed a strong positive correlation with the estimated time of AZA exposure and the prevalence of signature 32 (Table 5) (Inman et al., 2018). These findings indicate that although AZA may prevent...
organ-transplant rejection, it may actively lead to the development of cutaneous malignancy.

Commonly used transplant medications also lead to changes in the transcriptional profile that can influence tumor phenotype. CNIs, in particular, have been linked to multiple potential methods of inducing and promoting cSCC. Several studies examined the relationship between CNIs and proinflammatory cytokines and their downstream pathways in the pathogenesis of cSCC (Table 8). Treatment with CsA, a frequently used CNI, was shown to hasten tumor growth, upregulate IL-22R expression, and cause increased Jak1, STAT1, and STAT3 expression (Abikhair Burgo et al., 2018). Upregulation of IL-22R has a strong association with the development of catastrophic cSCC, which is defined as multiple primary tumors manifesting at the same time in the same patient (Abikhair et al., 2016). CsA was also shown to enhance production of proinflammatory cytokines by decreasing expression of tristetraprolin, a tumor suppressor that negatively controls production of proinflammatory cytokines (Wu et al., 2018).

Another pathway by which CsA induces a proinflammatory response is through phosphorylation of TAK1, which ultimately activates NF-κB, resulting in enhanced proliferation and reduced apoptosis (Xu et al., 2011). The last group of studies involved ATF3, an oncogene and member of the AP-1 family that has been linked with cSCC development (Wang et al., 2007). ATF3 was shown to be selectively induced by CNIs (Wu et al., 2010). In addition, an additive effect was found between CsA and UVA, which together induce ATF3 expression through a direct drug effect and UV-induced ROS formation (Table 4) (Dziunycz et al., 2014).

This review also identified a role for epigenetic alterations, such as DNA methylation alterations, in the development of cSCC among OTRs (Table 8). Both hypomethylation and hypermethylation have previously been associated with the development of skin cancer in ICPs (Sigalotti et al., 2002; Tyler et al., 2003). A comparison of RTRs who developed cSCC and those who did not identified 16 differentially methylated regions. Notable genes included ZNF577, coding for a zinc-finger protein, and FLOT1, coding for a protein involved in T-cell migration (Peters et al., 2018). Because of the important adaptive immune response to neoplastic growth, it follows that alterations in ZNF577 and T-cell migration could predispose patients to cSCC development. Clinicians should be aware of the potential for testing methylation patterns because this could lead to an effective method of stratifying pretransplant patients according to future risk of cSCC development. Overall, very little data exists regarding epigenetic alterations among OTRs with cSCC. Overall, epigenetic changes such as altered DNA methylation patterns indicate additional potential factors contributing to the high incidence and morbidity of cSCC in OTRs while also providing possible avenues of pretransplant risk stratification, post-transplant surveillance, and treatment selection to improve outcomes.

Furthermore, one study focused on a unique area that will require further research. Speeckaert et al. (2012) reported a significant association of the haptoglobin phenotype Hp 1-1 with the risk of cSCC (Table 3) (Speeckaert et al., 2012). Considering this increased long-term risk of cSCC, patients with this phenotype have an increased need of preventive measures including self-skin exams, regular visits to a dermatologist, and thorough UV-protection habits.

A limitation to this review was the exclusion of studies focusing solely on the ICP population. The goal of this review was to gather all studies to date that have focused on tumor profiling in the ISP population. Although it is necessary to understand these same tumor characteristics in the ICP population, the studies included in this review highlighted the direct comparisons between the ICPs and ISPs as well as studies comparing ISPs with and without cSCC. Significant work has been done in ICP populations with notable findings including the significant roles of TP53, NOTCH, TGFβ, and CDKN2A in the development of cSCCs in this population (Al-Rohil et al., 2016; Chitsazzadeh et al., 2016; Ji et al., 2020; Lazo de la Vega et al., 2020; Sarin et al., 2020; Thomson et al., 2021; Zheng et al., 2021). Review of these important studies did not alter the conclusions in this study. However, future studies may more closely examine any differences in these key pathways between the ISP and ICP populations, with a focus on using advanced approaches such as single cell transcriptomics.

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### Table 8. Epigenetic Alterations

| Author       | Year | Study Population | Findings |
|--------------|------|------------------|----------|
| Brown et al. | 2004 | 30 SCCs from ISPs and 10 SCCs from ICPs | SCCs in ISPs showed fewer epigenetic inactivating events at p14 and p16 when compared with ICPs. |
| Laing et al. | 2010 | 47 SCCs and 40 normal skin samples from RTRs | SCC was hypomethylated compared with adjacent non-neoplastic skin. |
| Peters et al. | 2018 | 27 RTRs with SCC and 27 RTRs without SCC | Identified 16 differentially methylated regions in RTRs including ZNF577, a zing-finger protein, and FLOT1, a protein involved in T-cell migration. |
| Peters et al. | 2019 | Cohort 1: 19 RTRs with cSCC and 19 RTRs without cSCC; Cohort 2: 45 RTRs with cSCC and 37 RTRs without cSCC | Higher DNA methylation of SERPINB9 in RTRs who developed cSCC than those that did not. Median DNA methylation of SERPINB9 was 58.7% (range: 32.5–81.3%) for region 1 and 54.4% (30.0–78.5%) for region 2 in patients with cSCC and 50.2% (21.8–77.5%) for region 1 and 46.4% (22.1–74.0%) for region 2 in the non-cSCC patients (region 1: P = 0.004 and region 2: P = 0.008). |
| Sherston et al. | 2014 | 57 RTRs with SCC and 49 RTRs without SCC | TSOD methylation analysis also showed an association between high Treg levels in RTRs with SCC compared with those without. |

Abbreviations: cSCC, cutaneous squamous cell carcinoma; ICP, immunocompetent patient; ISP, immunosuppressed patient; RTR, renal transplant recipient; SCC, squamous cell carcinoma; Treg, regulatory T cell.

A summary of epigenetic alterations discovered in ISPs with an associated risk of SCC development.
CONCLUSION AND FUTURE DIRECTIONS

To our knowledge, this is the first systematic review of the genetic, epigenetic, transcriptional, and translational alterations associated with cSCC arising in ISPs compared with ICPs. ISPs are a growing group with known increased risk of cSCC and limited treatment options, specifically for late-stage disease. Understanding the drivers of cSCC in this population is an important step to reducing morbidity and mortality in this high-risk population.

Dermatologists are faced with the challenge of identifying which patients are at increased risk for SCC to determine appropriate screening intervals and preventive strategies. Understanding a patient’s risk may also inform the approach to pharmacologic immunosuppression for solid OTRs and other patients on chronic immunosuppressive medications. Mutations in the genes coding for the glutathione S-transferase family of proteins (GSTM1, GSTM3, and GSTP1), and the gene coding for IRF4 were shown in this review to modulate the risk for NMSC in OTRs. This may serve as an additional tool for patient risk stratification for dermatologists and physicians prescribing immunosuppression.

Treatment is another important challenge, specifically in patients with advanced disease of the head and neck. Currently available systemic treatments have poor response rates and there are few options, especially for OTRs that are not eligible for checkpoint inhibitor therapy. This review highlights potential therapeutic targets that warrant further exploration such as Bcl-xl.

Recently, techniques such as single cell RNA sequencing and spatial transcriptomics have emerged that allow high-definition profiling of tumors. Proteomic and metabolomic approaches also provide valuable phenotypic information, specifically regarding pathways that may be pharmacologically targeted. Studies using these technologies to compare tumors from ISPs to ICPs should be performed to improve the understanding of cSCC carcinogenesis in these patients, leading to improved targeted therapies.

MATERIALS AND METHODS

This review was conducted according to the 2009 preferred reporting items for systematic reviews and meta-analyses guidelines (Moher et al., 2009). A literature search was conducted on 1 November 2021 in MEDLINE, Cinahl, and Scopus using key phrases. Four main search domains were used, which were combined with the Boolean operator AND, whereas each box represents a main search domain connected by the Boolean operator OR. Asterisk (*) utilized as wildcard symbol to broaden search by finding words that start with the same letters.

The retrieved literature was screened by title and abstract for inclusion. If the suitability of an article was unclear, the full text was assessed. Studies were selected if they met the following inclusion criteria: i) English language, ii) focus on cSCC, iii) study sample of ISPs, OTRs, or representative model, iv) data focusing on epigenetic or genetic alterations or gene expression, and v) full text available. Articles were excluded if: i) original data were not reported, ii) no data was reported regarding ISPs or OTRs, iii) articles solely reported isolated cases, iv) articles did not discuss genetic or epigenetic alterations or gene expression, iv) data were not reported for cSCC, or v) the article was not written in the English language. Human cell lines and animal models representative of human ISPs were not excluded. Additional articles discovered during the completion of full-text review of the selected articles were added to the review if they met the inclusion criteria, did not meet exclusion criteria, and were not duplicates.

Data availability statement
We do not have any additional data or materials to share.

ORCIDs
Elliot D Blue: http://orcid.org/0000-0002-8683-5599
S. Caleb Freeman: http://orcid.org/0000-0003-1357-8656
Marissa B. Lobl: http://orcid.org/0000-0002-8128-613X
Dillon D. Clarey: http://orcid.org/0000-0003-1076-2781
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Ashley Wysong: http://orcid.org/0000-0001-5131-1149

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