OXFORD

Precision Clinical Medicine, 2025, **8**: pbaf033

DOI: 10.1093/pcmedi/pbaf033
Commentary

SKP2 at the crossroads of proliferation and immune evasion: a new target in the tumor microenvironment

Panagiotis J. Vlachostergios [1,*] and Stergios Boussios [2,3,4,5]

[1]Division of Hematology and Medical Oncology, Department of Medicine, Weill Cornell Medicine, New York, NY 10054, United States
[2]Department of Medical Oncology, Ioannina University Hospital, Faculty of Medicine, School of Health Sciences, University of Ioannina, Ioannina 45110, Greece
[3]Department of Research and Innovation, Medway NHS Foundation Trust, Gillingham, ME7 5NY, United Kingdom
[4]Faculty of Medicine, Health and Social Care, Canterbury Christ Church University, Canterbury, CT1 1QU, United Kingdom
[5]Faculty of Life Sciences and Medicine, School of Cancer and Pharmaceutical Sciences, King's College London, London, WC2R 2LS, United Kingdom
*Corresponding author: Panagiotis J. Vlachostergios, pjv9003@med.cornell.edu

Editor's note: A commentary on "A pan-cancer analysis revealed as an inhibitor of the tumor immune microenvironment and a promising therapeutic target for immunotherapy"

The tumour microenvironment (TME) encompasses the dynamic interplay of malignant cells with surrounding stroma, vasculature, immune cells, and extracellular matrix. Decades of work have shown that the TME is far from a passive by-stander in oncogenesis; rather, it actively shapes tumour evolution, metastatic dissemination, and therapeutic responses [1, 2]. Immune infiltration—particularly of $CD8^+$ T cells—is a favourable prognostic marker in many cancers, but this benefit can be erased by co-existent regulatory T-cells (Tregs), tumour-associated macrophages, myeloid-derived suppressor cells, and up-regulation of immune checkpoint molecules e.g. programmed death-ligand 1 (PD-L1), cytotoxic T-lymphocyte antigen-4 (CTLA-4), V-domain immunoglobulin suppressor of T cell activation (VISTA). Collectively, these constitute an immunosuppressive TME [1, 2]. This arises from a convergence of tumour-intrinsic and host factors that blunt immune recognition and cytotoxic responses. Among several molecular circuits, neoangiogenic vasculature expresses aberrant adhesion molecules and may selectively favour Treg infiltration or exclude cytotoxic T-cells. For instance, prostate-specific membrane antigen expression in tumour neovasculature correlates with features of immune suppression (reduced cytotoxic T-cell signatures), suggesting that vascular phenotype can reflect and contribute to an immunosuppressive microenvironment [3]. This underscores how distinct molecular markers can reflect broader immune-landscape states.

S-Phase kinase-associated protein 2 and TME: mechanistic insights and implications

S-Phase kinase-associated protein 2 (SKP2), an F-box protein component of the SKP1–CUL1–Fbox (SCF) ubiquitin-ligase complex, has long been recognised as a canonical oncogene: by tagging tumour-suppressor substrates (such as p27, p21, FOXO1) for proteasomal degradation, SKP2 enables cell cycle progression from G1 to S phase, supports proliferation, and inhibits senescence or apoptosis [4]. However, the recent shift is towards understanding its non-proliferative roles in remodelling the TME and immune landscape. Liao *et al.* propose SKP2 as a dual oncogenic driver (cell-cycle, proliferation) and immunosuppressive regulator, making it a promising immunotherapy-adjunct target [5].

SKP2 inhibition was shown to down-regulate CD47 (a "don't-eat-me" signal) in gastric cancer models, thereby enhancing macrophage phagocytosis of tumour cells [6]. While Liao *et al.* did not focus on CD47, their pan-cancer analysis demonstrated that SKP2 plays a broadly inhibitory role in the tumour immune microenvironment, a finding further validated by multiplex immunofluorescence staining in *Skp2* knockout transgenic mouse models, which showed increased immune cell infiltration [5]. The companion study by Peng *et al.* showed that SKP2 targets the DNA-licensing factors CDC6 and CDT1 for degradation; when SKP2 is inhibited, these factors accumulate, cause replication stress and cytosolic DNA fragments, thereby activating the cyclic GMP-AMP synthase/stimulator of interferon genes (cGAS/STING) pathway, stimulating type I interferon responses and promoting $CD8^+$ T-cell recruitment [7].

In *Skp2*-knockout tumour models, there was an increase in total F4-80^+ macrophages, accompanied by increased expression of chemokines (e.g. CXCL9/10) that recruit effector T-cells. Liao *et al.* showed that high SKP2 correlates with a macrophage signature enriched for immunosuppressive subtypes [5]. Mechanistically, elevated SKP2 expression may contribute to widespread suppression of MHC molecules and chemoattractant cytokines and their receptors. Overall, recent findings place SKP2 as an immune-modulatory node. Inhibiting SKP2 in tumour cells triggers replication stress (via elevated CDC6, CDT1), which in turn leads to accumulation of cytosolic DNA, activation of the cGAS/STING pathway (or at least a DNA-damage/innate immune sensing signature), and enhanced tumour-cell intrinsic immune response [5, 7]. In murine tumour models, this translates into improved response to immune checkpoint blockade (ICB) [7]. Thus, SKP2 inhibition may unmask tumour cells to immune sensing, converting a 'cold' tumour into a more 'visible' one.

Received 28 October 2025; revised 5 November 2025; accepted 11 November 2025. published 18 November 2025

Additional lines of evidence from non-small cell lung cancer (NSCLC) and osteosarcoma support this notion. In NSCLC with loss of LKB1 (STK11)—a known immunotherapy-resistance background—SKP2 acts as the E3 ubiquitin ligase that catalyses K63-linked polyubiquitination of PD-L1 (on K136 and K280) and thus stabilizes PD-L1 protein [8]. LKB1 status correlates with PD-L1 protein levels and a "T cell-enriched hot" TME, translating into better patient responses with LKB1 wild-type and higher PD-L1 [8]. Conversely, inhibition of SKP2 (via shRNA or compound #25) reduced PD-L1 expression, and *in vivo* converted a "hot" TME into a "cold" TME, abrogating benefit from anti-PD-1/PD-L1 therapy [8]. There is a strong translational message emanating from these findings linking proliferation/ubiquitin-ligase biology with immune-checkpoint regulation: stratification of patients by LKB1/SKP2 status (and PD-L1) for ICB, followed by SKP2 targeting may modulate ther PD-L1/immune-checkpoint axis. Triple *Rb1/p53/Skp2* knockout (TKO) in an osteosarcoma mouse model corroborates this concept, showing increased expression of immune-microenvironment infiltration genes (especially macrophage lineage, and to a lesser extent, T cells, B cells, vascular cells) [9]. In osteosarcoma patient cohorts, high expression of the TKO-upregulated gene module (immune infiltration signature) correlated with favourable overall survival. Also, SKP2 expression negatively correlated with macrophage infiltration [9]. This is strong *in vivo* evidence that SKP2 controls the 'immune exclusion' phenotype of the TME. It connects SKP2 activity to not only tumour-intrinsic proliferation but also stromal/immune cell infiltration in the microenvironment.

The idea that SKP2 can modulate immune sensing extends beyond proliferation. Although it was not tumour-centric, a study of anti-PD-1 treatment in thyroid cells showed decreased AKT1 and SKP2 levels, leading to enhanced immunosensitivity through PD-L1 downregulation, increased IFN-γ production, and greater $CD8^+$ T-cell-mediated killing [10]. SKP2 was found to interact with PD-L1 protein (via immunoprecipitation) in thyroid cells, and SKP2 inhibition mimicked the anti-PD-1 effect in facilitating immune recognition of thyroid cells [10]. Collectively, several lines of evidence culminating in those from Liao *et al*. position SKP2 as a promising nexus between tumour proliferation and immune evasion [5]. SKP2 not only drives cell-cycle progression but also enables tumours to hide from immune attack by controlling checkpoint expression, limiting innate immune sensing, and shaping the immune-cell infiltration landscape (Table 1).

Table 1. Key studies on the role of SKP2 at the interface of tumour-cell proliferation and immune-evasion/TME biology.

Model/tumour type	Role of SKP2 in proliferation/cell-cycle	Role of SKP2 in immune/TME context	Translational/therapeutic implication
NSCLC (LKB1 WT/mutant) [4]	SKP2 stabilizes PD-L1 protein via K63-ubiquitination → may promote tumour survival/proliferation indirectly.	SKP2 required for PD-L1 expression; SKP2 inhibition converts 'hot' TME to 'cold' and reduces ICB benefit.	Screening for LKB1/SKP2 status may stratify ICB responders; SKP2 is a checkpoint-modulation target.
Pan-cancer multi-omics analysis [5]	High SKP2 expression correlates with high proliferation signatures	High SKP2 correlates with immune 'cold' microenvironment (low TILs, low antigen-presentation), poorer outcomes.	SKP2 may serve as biomarker of immune-cold status, and as an immunotherapy co-target across tumour types.
Mouse osteosarcoma model (*Rb1/p53* KO) + human OS cohort [6]	Skp2 KO delayed tumour growth	Skp2 KO → increased immune infiltration (macrophages, T/B cells), immune gene upregulation; high infiltration signature in human OS correlates with better survival.	SKP2 targeting may remodel TME from immune-excluded to immune-infiltrated, improving prognosis and immunotherapy responses.
Various tumour cell lines + murine models [7]	SKP2 inhibition → elevated CDC6/CDT1 → replication stress, genomic instability.	SKP2 inhibition → activation of cGAS/STING, increased cytosolic DNA, enhanced T cell infiltration/ICB response.	SKP2 inhibitors may sensitize tumours to checkpoint blockade by increasing tumour immunogenicity.
Thyroid cells/immune-irAE context [8]	AKT1-SKP2 downregulation → altered cell sensitivity, cell-cycle changes	SKP2 interacts with PD-L1; downregulated SKP2 → reduced PD-L1, increased CD8 + T cell killing → increased immune sensitivity.	Highlights SKP2 role in immune-sensitivity; suggests that SKP2 modulation may have implications for immune surveillance and immune-related toxicity.

Abbreviations: NSCLC – Non-small cell lung cancer; LKB1 – Liver kinase B1 (also known as STK11); WT – Wild-type; SKP2 – S-phase kinase–associated protein 2; PD-L1 – Programmed death-ligand 1; K63-ubiquitination – Lysine-63–linked ubiquitination (a type of protein tagging); TME – Tumour microenvironment; ICB – Immune checkpoint blockade; TILs – Tumour-infiltrating lymphocytes; KO – Knockout; Rb1 – Retinoblastoma gene 1; p53 – Tumour protein p53; OS – Osteosarcoma; CDC6 – Cell division cycle 6; CDT1 – Chromatin licensing and DNA replication factor 1; cGAS – Cyclic GMP–AMP synthase; STING – Stimulator of interferon genes; AKT1 – Protein kinase B alpha; $CD8^+$ – Cluster of differentiation 8 positive (cytotoxic T cells); irAE – Immune-related adverse event

Promising research directions and clinical potential

The findings of Liao *et al*. raise multiple exciting avenues for investigation and translational exploitation [5]. From a therapeutic vantage, modulating SKP2 (or its downstream pathways) offers a double-edged benefit: slowing tumour growth and enhancing immune visibility. First, the fact that SKP2 inhibition enhances $CD8^+$ T-cell infiltration and responsiveness to immune checkpoint inhibitor (ICI) suggests that small-molecule or proteolysis targeting chimera (PROTAC)-mediated SKP2 blockade may convert "cold" tumours into "hot" immune-responsive ones [11]. Pre-clinical synergy of SKP2 inhibitors with anti-PD-1/PD-L1 or anti-CTLA-4 is warranted. Second, SKP2 expression could serve as a biomarker not only of proliferative capacity, but of immune-exclusion phenotype. Patients with high SKP2 might be predicted to have poor response to ICI alone but improved benefit if SKP2 is co-targeted. Thus, correlating SKP2 with immune-signatures

may refine patient stratification. Third, while historic efforts to target SKP2 focused on inhibiting its F-box function (e.g. compounds C25) or disrupting SCF assembly, more recently PROTACs that degrade SKP2 (e.g. Skp2-PRO-1) have emerged [11]. Given the immune-remodelling benefit, drug development should prioritize tumour models with immune-cold microenvironments. Additionally, one must assess on-target toxicity given SKP2's role in normal proliferative tissues. Fourth, while the pan-cancer study gives associative data and proof-of-concept in murine models, detailed mechanistic interrogation is needed in specific human tumour types (e.g. bladder, lung, melanoma) [5]. Determining whether SKP2's immune role is mediated primarily via tumour cells (intrinsic) vs stromal/immune cells (extrinsic) will guide therapeutic design. One might ask whether SKP2 in tumour-associated macrophages independently contributes to immunosuppression. Overall, the TME is multifactorial: hypoxia, metabolic dysregulation, ECM remodelling, and angiogenesis all link to immune suppression. Investigating how SKP2 intersects with these axes (e.g., does SKP2 regulate hypoxia-responsive elements or affect lactate metabolism?) may broaden its relevance. Indeed, SKP2's link to glucose metabolism in hepatoblastoma (via isocitrate dehydrogenase 1) points to cross-talk between metabolism and immune evasion [12]. Nonetheless, not all cancers may equally depend on SKP2 for immune evasion. Exceptions were observed in kidney renal clear cell carcinoma and lower-grade glioma, where SKP2 overexpression correlated with increased immune infiltration and possibly better clinical outcomes. These anomalies highlight the context-dependent role of SKP2 in shaping the tumor immune microenvironment, likely influenced by cancer-specific genetic and immunological landscapes. Future research should explore how SKP2 interacts with other molecular and immune modulators in these tumour types. Using the pan-cancer atlas of Liao *et al.*, tumour types with the strongest SKP2–immune signature coupling (e.g., head and neck, pancreatic) should be prioritized for translational work [5]. Tailoring strategies by tumour immunophenotype will be key. As with many immunotherapy adjuncts, one must anticipate compensatory resistance mechanisms. Does SKP2 inhibition lead to up-regulation of other F-box proteins, or alternative immune-escape pathways (e.g. up-regulation of VISTA, TIM-3, or alternative metabolic checkpoints)? Pre-clinical modelling of acquired resistance will be important.

Clinical translation and challenges

From a clinical perspective, the concept of targeting SKP2 is compelling but will face hurdles. Drug specificity, on-target toxicities (given SKP2's role in normal proliferative tissues), delivery into immune-excluded tumours, and biomarker-driven patient selection are all considerations. Recently, a novel high–throughput screening system called DEFUSE (death fusion/cell survival escaper) was reported, which converts the degradation of a protein of interest into a cell–survival read–out [13]. Applying this to the oncogenic protein SKP2 led to the identification of a small molecule degrader named SKPer1. SKPer1 functions by inducing proximity between SKP2 and the E3 ligase STUB1, leading to SKP2 ubiquitination and subsequent proteasomal degradation [13]. In *in vivo* models, SKPer1 showed tumour–suppressive activity with a favourable safety profile [13]. Furthermore, a 10–amino–acid tag derived from SKP2 can serve as a "degradation tag" to confer induced–proximity degradation capability when fused to other client proteins [13]. This chemical strategy to experimentally manipulate SKP2 levels could be harnessed in evaluating how SKP2 degradation influences immune cell infiltration, antigen presentation, chemokine expression, or response to immunotherapy in model systems. It therefore offers a potential mechanistic and translational tool to move beyond correlative bioinformatics findings into functional perturbation. Moreover, the immune-effects of SKP2 inhibition—though robust in mouse models—must be confirmed in human TMEs and in combination with ICIs in clinical trials. Safety in combination with standard of care (chemotherapy, radiotherapy) must also be assessed, given that SKP2 may influence DNA damage responses [7]. Nevertheless, the dual role of SKP2 in driving proliferation and immune suppression gives a high therapeutic index: tumours dependent on SKP2 may be uniquely vulnerable, as SKP2 may serve as both a mechanistic target and biomarker.

The Liao *et al.* study represents a timely and innovative contribution to the field by positioning SKP2 not solely as a cell-cycle oncogene but as a regulator of tumour immune microenvironment [5]. Future work should aim to delineate the tumour-type specificity of SKP2's immune modulatory role, validate SKP2 as a predictive biomarker, and pursue early-phase trials combining SKP2 modulation and immune checkpoint blockade. If successful, SKP2 might well join the emerging cadre of "immune-modifier" targets that complement conventional immunotherapy and shift the therapeutic paradigm for otherwise refractory cancers.

Author contributions

Panagiotis J. Vlachostergios (Writing—original draft, Data curation, Writing—review & editing), and Stergios Boussios (Writing—review & editing, Resources, Supervision).

Conflict of interest

None declared.

References

1. Anderson NM, Simon MC. The tumor microenvironment. *Curr Biol* 2020;**30**:R921–5. https://doi.org/10.1016/j.cub.2020.06.081
2. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011;**144**:646–74. https://doi.org/10.1016/j.cell.2011.02.013
3. Vlachostergios PJ, Karathanasis A, Dimitropoulos K *et al.* High PSMA expression is associated with immunosuppressive tumor microenvironment in clear cell renal cell carcinoma. *Precis Clin Med* 2024;**7**:pbae010. https://doi.org/10.1093/pcmedi/pbae010
4. Wu T, Gu X, Cui H. Emerging roles of SKP2 in cancer drug resistance. *Cells* 2021;**10**:1147. https://doi.org/10.3390/cells10051147
5. Liao X, Zhang Y, Yu X *et al.* A pan-cancer analysis revealed SKP2 as an inhibitor of the tumor immune microenvironment and a promising therapeutic target for immunotherapy. *Precis Clin Med* 2025;**8**:pbaf022. https://doi.org/10.1093/pcmedi/pbaf022
6. Hu K, Zhao L, Miao P *et al.* Inhibition of Skp2 enhances antitumor immunity of macrophages by regulating CD47 in gastric cancer. *Int Immunopharmacol* 2025;**163**:115262. https://doi.org/10.1016/j.intimp.2025.115262
7. Peng Y, Qi X, Ding L *et al.* SKP2 inhibition activates tumor cell-intrinsic immunity by inducing DNA replication stress and genomic instability. *Br J Cancer* 2025;**132**:81–92. https://doi.org/10.1038/s41416-024-02909-y

8. Lv L, Miao Q, Zhan S *et al.* LKB1 dictates sensitivity to immunotherapy through Skp2-mediated ubiquitination of PD-L1 protein in non-small cell lung cancer. *J Immunother Cancer* 2024;**12**:e009444. https://doi.org/10.1136/jitc-2024-009444
9. Ferrena A, Wang J, Zhang R *et al.* SKP2 Knockout in Rb1/p53-deficient mouse models of osteosarcoma induces immune infiltration and drives a transcriptional program with a favorable prognosis. *Mol Cancer Ther* 2024;**23**:223–34. https://doi.org/10.1158/1535-7163.MCT-23-0173
10. Wu Y, Li J, Yang X *et al.* Immunosensitivity mediated by down-regulated AKT1-SKP2 induces anti-PD-1-associated thyroid immune injury. *Int Immunopharmacol* 2023;**121**:110452. https://doi.org/10.1016/j.intimp.2023.110452
11. Kamel EM, Khadrawy SM, Allam AA *et al.* Targeting the Skp2-Cks1 protein-protein interaction: structures, assays, and preclinical inhibitors. *Eur J Pharmacol* 2025;**1006**:178129. https://doi.org/10.1016/j.ejphar.2025.178129
12. Yu P, Li J, Feng W *et al.* SKP2 ubiquitylation modifies IDH1 to regulate hepatoblastoma cell cycle and glucose metabolism. *BMC Cancer* 2025;**25**:1304. https://doi.org/10.1186/s12885-025-14644-5
13. Chu Y, Chen S, Yang M *et al.* A rapid imaging-based screen for induced-proximity degraders identifies a potent degrader of oncoprotein SKP2. *Nat Biotechnol* 2025. https://doi.org/10.1038/s41587-025-02793-8

Received 28 October 2025; revised 5 November 2025; accepted 11 November 2025. published 18 November 2025