The glutamate metabotropic receptor 4 (GRM4) locus is linked to susceptibility to human osteosarcoma, through unknown mechanisms. We show that Grm4−/− gene-targeted mice demonstrate accelerated radiation-induced tumor development to an extent comparable with Rb1+/− mice. GRM4 is expressed in myeloid cells, selectively regulating expression of IL23 and the related cytokine IL12. Osteosarcoma-conditioned media induce myeloid cell Il23 expression in a GRM4-dependent fashion, while suppressing the related cytokine Il12. Both human and mouse osteosarcomas express an increased IL23:IL12 ratio, whereas higher IL23 expression is associated with worse survival in humans. Consistent with an oncogenic role, Il23−/− mice are strikingly resistant to osteosarcoma development. Agonists of GRM4 or a neutralizing antibody to IL23 suppressed osteosarcoma growth in mice. These findings identify a novel, druggable myeloid suppressor pathway linking GRM4 to the proinflammatory IL23/IL12 axis.

SIGNIFICANCE: Few novel systemic therapies targeting osteosarcoma have emerged in the last four decades. Using insights gained from a genome-wide association study and mouse modeling, we show that GRM4 plays a role in driving osteosarcoma via a non–cell-autonomous mechanism regulating IL23, opening new avenues for therapeutic intervention.
using immune-checkpoint blockade has failed so far in the treatment of advanced osteosarcoma (3).

Hereditary factors play an important role, and osteosarcoma is a feature of families with rare mutations in TP53, RB1, RECAL4, and BLM (4). A genome-wide association study (GWAS) investigating the role of common genetic variation identified a locus at 6p21.3 [rs1906953; odds ratio 1.57, 95% confidence intervals (95% CI), 1.35–1.83; \( P = 8.1 \times 10^{-9} \)] in the GRM4 gene with susceptibility to osteosarcoma (5), which was validated in two subsequent studies (6, 7). GRM4 (metabotropic glutamate receptor 4 or mGlur4) is a member of the group III family of G protein–coupled receptors that negatively regulates the cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) pathway. GRM4 plays a role in the central nervous system and is highly expressed in the cerebellum by cerebellar granule cells, but also by immune cells, and has been implicated in both neurodegenerative and autoimmune diseases (8, 9). Studies of the biological role of GRM4 in cancer are limited. Its expression has been associated with poor prognosis in several cancers, including malignant gliomas, colorectal cancer, and rhabdomyosarcoma (10), whereas GRM4 agonists have shown in vitro or xenograft activity in medulloblastoma (11) and glioblastoma cell lines (12), and recently in bladder cancer (13). In osteosarcoma, a small study has shown GRM4 expression correlates with better survival (14). Here, we sought to investigate the biological and therapeutic roles of GRM4 in vivo using genetic models of osteosarcoma.

RESULTS

**Grm4 Gene–Targeted Mice Have Accelerated Osteosarcoma Development and Identify Role for Inflammatory Cytokine IL23**

We first asked whether GRM4 had tumor-suppressive or oncogenic effects on tumor development. Wild-type (WT; \( n = 26 \)) or Grm4\(^{-/-} \) mice (\( n = 25 \)) were injected with \(^{45}\)Ca, a low-energy \( \beta \)-emitter that localizes to bone (ref. 15; Fig. 1A; Supplementary Fig. S1A–S1C). Ionizing radiation is the oncogenic stimulus for osteosarcoma (16, 17). Grm4\(^{-/-} \) mice had accelerated tumor development (Fig. 1B; hazard ratio (HR) 0.41; 95% CI, 0.22–0.76, \( P = 0.0006 \); median survival in WT mice 89 weeks vs. 65 weeks in Grm4\(^{-/-} \) mice). Outside the central nervous system, GRM4 is highly expressed by dendritic cells (DC), as well as CD4\(^{+} \) T cells (8). In the mouse osteosarcomas, we observed GRM4 is predominantly expressed by CD45\(^{+} \)CD11c\(^{+} \)MHC\( \alpha \) myeloid cells, but not by tumor cells (Fig. 1C). Too few CD4\(^{+} \) T cells were detectable to characterize GRM4 expression (not shown).

GRM4 regulates DC expression of the cytokines IL1, IL6, IL12, and IL23 in experimental autoimmune encephalomyelitis (8). Using a standard strategy enriching for bone marrow DCs (18), Grm4\(^{-/-} \) DCs showed selectively increased expression of the related proinflammatory cytokines IL12 and IL23 relative to WT DCs (Fig. 1D). Sharing a common p40 subunit, both IL12 and IL23 are secreted by human and mouse DCs and tissue-resident macrophages in response to exogenous or endogenous signals (19, 20). Increased expression of IL23 is observed in many human cancers (21–23), whereas IL12 has potent antitumor activity (24). Primary \(^{45}\)Ca osteosarcomas and allografted cell lines had high IL23 expression relative to normal bone, but ex vivo–cultured osteosarcoma cell lines did not express IL23 (Supplementary Fig. S2A and S2B). In addition, IL23 is not expressed within primary tumor cells (Fig. 1E). To show that these findings were not a function of a radioa carcinogen model, the expression of IL23 was also examined in osteosarcomas from genetically defined mouse models (Ox/Cre Trp53/Rb and Ox/Cre Trp53.1224 pRb mice, ref. 25; Supplementary Fig. S3A). Again, the majority of tumors had increased IL23 compared with normal bone. \(^{45}\)Ca radiation-induced osteosarcomas from Grm4\(^{-/-} \) mice (\( n = 5 \)) have higher expression of IL23 compared with WT tumors (\( n = 6 \); \( P = 0.0358 \); Supplementary Fig. S3B). Flow-cytometry analysis of \(^{45}\)Ca spontaneous tumors identified GRM4\(^{+} \) MHC II\(^{+} \) CD11c\(^{+} \) cells as the predominant source of IL23 in the tumor microenvironment. To identify more precisely the tumor myeloid subpopulations and expression of GRM4, IL12, and IL23, we phenotyped osteosarcomas for infiltration of conventional DCs (cDC1: MHCII\(^{+} \)CD11c\(^{+} \)CD64\(^{-} \)Ly6c\(^{-} \)CD11b\(^{+} \) or cDC2: MHCII\(^{+} \)CD11c\(^{+} \)CD64\(^{+} \)Ly6c\(^{+} \)CD11b\(^{+} \) and monocyte-derived DCs (MoDC), defined as MHCII\(^{+} \)CD11c\(^{+} \)Ly6c\(^{-} \)CD14\(^{-} \)CD24\(^{+} \)CD11b\(^{+} \) (Supplementary Fig. S4 gating strategy; ref. 20). In the OS18 allograft, the predominant source of IL23 was found to be from GRM4\(^{+} \) MoDCs (Supplementary Fig. S5). Similar results were observed in primary \(^{45}\)Ca tumors (Fig. 1E; Supplementary Fig. S6A), and the non-radioa carcinogen K7M2 allograft tumors (Supplementary Fig. S6B). By contrast with IL23, IL12 was virtually undetectable in tumor-derived MoDCs, and neither IL12 nor IL23 was observed in conventional DCs. Taken together, these data suggest that both GRM4 and IL23 are expressed by MoDCs within tumors.

To determine whether osteosarcoma cells influence the expression of IL12 and IL23 in vitro, bone marrow–derived DCs (BMDC) were exposed to conditioned media from cultured mouse osteosarcoma cells (OS-CM). Lipopolysaccharide (LPS) was used as a positive control (26, 27). In WT BMDCs, LPS increased CAMP (Supplementary Fig. S7A) and IL12 and IL23. OS-CM significantly induced IL23 expression in BMDCs, while suppressing IL12 (Fig. 1F and G). The cAMP/PKA pathway mediates, and LPS increases cAMP whereas GRM4 agonists attenuate cAMP expression (Supplementary Fig. S7B). GRM4 agonist, recapitulated the effect of OS-CM by inducing IL23 expression higher than that observed for LPS alone, but not OS-CM. PHCCC also downregulated IL23 in OS-CM (Fig. S7H) and suppressed LPS-induced (Supplementary Fig. S8A) IL23 expression (Fig. 1H–K); PHCCC induced IL12 expression higher than that observed for LPS alone, but not OS-CM. PHCCC also downregulated IL23 in human peripheral blood DCs stimulated with LPS (Supplementary Fig. S8B). Collectively, these data support the interpretation that osteosarcoma cells repress IL23 production by MoDCs, an effect that is modulated by GRM4 signaling.
Grm4 have higher transcript levels of Il23a and at baseline. Bone marrow was isolated from WT or keeping genes. Values are means and SEM of triplicate determinations; duplicate experiments were performed. Flow-cytometry analysis of a 45Ca WT were treated with GRM4 agonists PHCCC or CIN (40 μmol/L) for 24 hours, and transcript levels of cytokines measured. J and K, BMDCs were treated with PHCCC (40 μmol/L) for 1 hour and stimulated with OS-CM at a 1:1 ratio for 24 hours, and transcript levels were measured. Data are means ± SEM, representative of three independent experiments. *, P < 0.05; **, P < 0.01; ***, P < 0.001; ****, P < 0.0001.
**II23 Gene-Targeted Mice Are Protected from the Development of Tumors**

Given that GRM4 suppresses tumor development (Fig. 1B), and IL23 is negatively regulated by GRM4, we tested whether IL23 itself had oncogenic properties in the osteosarcoma model. II23p19−/− (II23−/−) mice were strikingly protected from tumor development, with 24/30 (80%) of II23−/− mice tumor-free at 104 weeks compared with 0 control mice at 90.7 weeks (Fig. 2A; HR 9.4; 95% CI, 3.3–27; P < 0.0001). To enhance sensitivity, a subset of II23−/− mice >2 years of age were screened by 18F 2-deoxyglucose PET scanning, without any subclinical evidence of tumors (data not shown). IL6 drives the generation of IL17-expressing T-helper cells (TH17), and IL23 differentiates IL17-expressing T-helper cells (31, 32). How- ever, unlike II6−/− mice (16), II17a−/− mice did not display accelerated tumor development (Fig. 2B; HR 0.95; 95% CI, 0.47–1.9, P = 0.89). These findings recapitulate our observations in a mouse model of soft-tissue sarcoma (31). To put our findings of a protumorigenic role for IL23 in context, we tested 15 mouse genotypes of pathways implicated in immune control of cancer development (II11r+/+, II6+/+, II17+/+, Pdl1+/+ (Cd74+/+), Ifnar1−/−, Ifnar2−/−, Ifnγ+/+/ perforin−/−, Trail−/−, Ccl2−/−, Ccr2−/−, Ja18−/−, and Cd14−/−), apoptosis (Bim−/−), and adenosine metabolism (Cd73/NTES−/−; Supplementary Fig. S9A-S9J). Among these, only II23−/− mice were protected against osteosarcoma development (Fig. 2C). Notably, the effect sizes observed in this model in both II23−/− and Grm4−/− mice were comparable with or greater than those observed in Rb−/− mice (16).

**High IL23 in the Tumor Correlates with Worse Overall Survival in Humans**

We next examined the expression of IL23 in a series of human osteosarcomas using in situ hybridization. More than 60% of samples demonstrated focal staining for IL23A (p19) expression (12% high, 24% medium), whereas little staining was observed in normal human bone (NHB; Fig. 2A; Supplementary Fig. S10). In an independent cohort quantitated by qRT-PCR, increased IL23A expression was noted in tumors compared with NHB, accompanied by reduced IL12A (p35) expression. More than 70% of samples exhibited significantly increased expression of IL23A over NHB, with 53% having >2-fold increase and 34% having >5-fold greater expression. By contrast, IL12A (p35) transcript expression was significantly lower in tumor samples relative to NHB (Fig. 2B). Finally, high IL23 expression (>8-fold) was associated with worse survival (Fig. 2C; HR 0.33; 95% CI, 0.06–1.69; P = 0.0427).

**IL23 and GRM4 Are Therapeutically Targetable in Osteosarcoma**

Both IL23 and GRM4 are potential therapeutic targets, and IL23 blockade has been successful in treating psoriasis (32, 33). The antitumor activity of a neutralizing antibody (16E5)
Myeloid GRM4 Regulates IL23 in Tumor Progression

A

Normal human bone Osteosarcoma

B

C

Figure 3. High IL23A in the tumor correlates with worse overall survival in humans. A, In situ hybridization was used to evaluate IL23A expression in a human osteosarcoma tissue microarray (40 samples in duplicate) and normal human bone (10 samples in duplicate). A representative image of human osteosarcoma and normal human bone expressing IL23A. B, IL23A and IL12A transcript levels were measured relative to normal human bone using qRT-PCR in an independent cohort with corresponding survival data. C, High IL23A expression trends with worse overall survival in human osteosarcoma. Kaplan–Meier curve of high IL23A expressors shown in B (P = 0.0427).

Similar effects were observed with another specific GRM4 agonist, LSP2-9166 (Supplementary Fig. S15). Taken together, these data support the therapeutic potential of targeting the GRM4–IL23 axis (Fig. 4E). Neither an IL23 blocking antibody nor GRM4 agonists affected the growth of primary osteosarcoma cells cultured ex vivo, consistent with a key role for the host immune system in mediating their antitumor effects (Supplementary Fig. S16).

DISCUSSION

Cancer immunoediting studies over two decades suggest the immune system has secondary modifier effects on tumor development relative to the contribution of cell-autonomous, classic tumor suppressors and oncogenes (36). Here, we present direct human and mouse genetic evidence for a non-cell-autonomous role for GRM4 and IL23 within MoDCs in spontaneous tumor development. Strikingly, the magnitude of the effect of loss of GRM4 is comparable with the loss of the canonical tumor suppressor RB1. The modest disease association of polymorphisms in GWAS, presumably due to weak effects on gene expression, does not predict the biological or therapeutic effect due to complete loss-of-function mutations in mice. Of the 17 gene-targeted genotypes tested, the size of the oncogenic effect of IL23 in tumor development was marked. Although the oncogenic effects of IL23 have been reported in multiple cancer types (2, 21, 22, 37), it is interesting that subjects with psoriasis, an autoimmune disease driven by IL23, are specifically at risk of osteosarcoma and chondrosarcomas (HR 4.97; 95% CI, 2.32–10.62; P < 0.0001; ref. 38).

We propose that tumor-infiltrating MoDCs responding to inflammatory signals in the tumor microenvironment secrete IL23, contributing to an immune-suppressed environment. GRM4 and IL23 are primarily coexpressed within monocyte dendritic cells, and do not appear to be expressed by tumor cells. This is consistent with our previous observations (39), although we cannot exclude the role of other stromal cells in tumor development. GRM4 activation downregulates IL23 and suppresses tumor growth. In human osteosarcomas, tumor-infiltrating myeloid cells, including dendritic cells and macrophages, connote a worse survival outcome (40). DCs comprise diverse progeny of the myeloid lineage, including antigen-presenting cells (APC) required for efficient activation of T cells and maintenance of immune tolerance (41, 42). APCs are best known in cancer through their pivotal role in therapeutic vaccination strategies (43). Distinct DC populations have shown opposing effects on tumor immunity, driving antitumor immunity or contributing to immune nonresponsiveness in cancer (20). The understanding of myeloid subpopulations within tumors and their functional role is a rapidly evolving field (20, 42). Our data linking GRM4 to IL23 build on emerging evidence that glutamate signaling regulates IL23 expression (44), probably via GRM4 (8).

It is important to note that IL23 is likely regulated by other mechanisms than GRM4, and also that GRM4 has actions independent of IL23. There are significant therapeutic implications of these findings. To date, immune-checkpoint inhibitors targeting PD-1/PD-L1 have been disappointing in osteosarcoma (3).
The therapeutic effect of both IL23 antagonists and GRM4 agonists appeared comparable in our system to doxorubicin (DOX). The first-generation agent geting these genes may be well tolerated. IL23 antagonists are already approved for the treatment of plaque psoriasis, our findings identify a non–cell-autonomous pathway linking GRM4 to the proinflammatory IL23–IL12 axis, with the potential to be therapeutically targeted in osteosarcoma.

**METHODS**

**Mice**

Inbred wild-type C57Bl/6J (C57BL/6 WT) and C57BL6 GRM4-deficient (Grm4−/−) mice were purchased from The Jackson Laboratory; C57BL/6 Il12p39-deficient (Il12p39−/−), C57BL/6 Gld1-deficient (Gld1−/−), C57BL/6 Il17a-deficient (Il17a−/−), C57BL/6 Il17d-deficient (Il17d−/−), C57BL/6 perforin and Il17r-deficient (pif1−/−), C57BL/6 Cld4-deficient (Cld4−/−), C57BL/6 Ifnr1-deficient (Ifnr1−/−), C57BL/6 Cld2-deficient (Cld2−/−), C57BL/6 Cld3-deficient (Cld3−/−), C57BL/6 Cld42-deficient (Cld42−/−), and C57BL/6 If11r-deficient (If11r−/−) mice were either generated using C57BL/6 embryonic stem cells or back-crossed to at least 10 generations to C57BL/6. All mice were genotyped using published protocols. Mice were bred at Australian BioResources (Moss Vale, NSW, Australia) and...
maintained at the Garvan Institute Biological Testing Facility, with all animal experiments carried out according to guidelines contained within the NSW (Australia) Animal Research Act 1985, the NSW (Australia) Animal Research Regulation 2010, and the Australian code of practice for the care and use of animals for scientific purposes (8th Edition, 2013, National Health and Medical Research Council, Australia) and approved by Garvan/St. Vincent’s Animal Ethics and Experimentation Committee (approval number 15/21, 15/30, 18/31, 18/38). Some experiments were performed at the Peter MacCallum Cancer, Melbourne, Australia; all procedures using mice were reviewed and approved by the Peter MacCallum animal ethics experimentation committee.

**Mouse Models of Osteosarcoma**

The experiments using the radiocarcinogen model were conducted as previously described (15, 16). Briefly, mice were injected with 1 μCi/g 4⁰Ca (GE Healthcare) or 0.9% saline intraperitoneally at 28, 35, 42, and 49 days postpartum. Mice were aged and monitored for signs of tumorogenesis (limping, paralysis, loss of condition, poor feeding or grooming, or weight loss) twice weekly for up to two years. Mice developed tumors in the spine (70%) and limbs (18%), and then pelvis, cranium, scapula, and clavicle (12%). In some instances, X-ray imaging was conducted using a Faxitron system. Mice were sedated with isoflurane inhalation and scanned.

**Tumor Implantation Model and Treatment Studies**

Osteosarcoma cell lines were derived from tumors from 4⁰Ca experiments (OS18, OS25); these cell lines generate osteosarcoma when implanted into C57BL/6 mice. The OS cell lines were derived by culturing tumor pieces in Minimum Essential Medium with alpha modification, 10% heat-inactivated fetal calf serum, 100 U/mL penicillin/streptomycin, 2 mM/L Glutamax, and 1 mM/L sodium pyruvate until a monolayer grew out. Cells were passaged 20 to 25 times and were checked for Mycoplasma contamination by qRT-PCR, and aliquots were frozen. Mycoplasma grew out. Cells were passaged 20 to 25 times and were checked for Mycoplasma contamination by qRT-PCR, and aliquots were frozen. New aliquots were thawed for each experiment and passaged up to 8 times. OS lines cultured in vitro were mixed with 1:1 Matrigel:media (Becton Dickinson), and a total volume of 100 μL (10⁵ cells) was injected subcutaneously in the flank. Mice were monitored for tumor growth relative to adjacent non–tumor cell injected leg using digital calipers (Unique Precision Machine, Inc.). Mice were treated as described in the legends; mice were treated intraperitoneally with anti-IL23p19 (mGlu3) or control antibody (αGAP3) at 500 μg/mouse (Amgen) weekly, liposomal doxorubicin (Calyx) 2.5–5 mg/kg or PHCCC in vehicle DMSO 20% 10 mg/kg or LSP2-9166 10 mg/kg in saline as described in the legends.

**Gene-Expression Analysis and Statistical Methods**

Transcript levels of cytokines were determined using quantitative RT-PCR. Total RNA was extracted from cells using TRIzol and Qagen RNEasy Mini Kit per the manufacturer’s instructions. RNA was converted to cDNA using standard techniques. Real-time RT-PCR was carried out using SYBR Green (Applied Biosystems) according to the manufacturer’s instructions using an ABI Prism 7000 Sequence Detection System. All primer sequences are listed in Supplementary Table S1. Statistical analysis was performed using GraphPad Prism software (V7.0a, GraphPad). Values are reported as means ± SEM. When comparing two groups, P values were calculated using two-tailed Student t tests. For time to event and survival analysis, P values for the Kaplan-Meier survival curves were calculated with a log-rank (Mantel-Cox) test. Significance was conventionally accepted at P values equal to or less than 0.05. For multiple treatment group comparisons, significance was determined by one-way analysis of variance, followed by the Tukey post hoc multiple comparisons test, where *, P < 0.05; **, P < 0.01; ***, P < 0.001; ****, P < 0.0001.

**Cytokine Assay**

Cell culture media from control and treated cells were frozen at −80°C. The concentration of cytokines was quantitatively determined using Cytometric Bead Array (CBA) Cytokine Kits, mouse or human (BD Biosciences), as per kit instructions. A standard calibration curve was established for each kit. The maximum and minimum detection limits for cytokines were 1 to 5,000 pg/mL.

**Flow-Cytometry Immune Cell–Infiltration Analysis**

Tumors were washed in PBS and cut into 1-mm³ pieces, and tissue was digested in DMEM supplemented with 2% FCS and 5 μg/mL collagenase A for 50 minutes at 37°C. Cells were passed through a 70-μm cellular sieve and labeled with surface antibodies and intracellular antibodies. Mouse splenocytes were used as positive controls for immune cells. Cells were analyzed using a FlowJo software. Antibodies are listed in Supplementary Table S2.

**Histology**

Tissue was fixed in 10% neutral buffered formalin, embedded in paraffin, and sectioned and stained with hematoxylin and eosin, via routine method. Human bone and osteosarcoma tissue microarrays were purchased from Biomax (BO244b, OS080). In situ hybridization was carried out using probes for mouse and human IL23-encoding RNA (ACD Bio-Techne). Slides were scanned on ScanScope XT (Aperio).

**DC Enrichment and Stimulation**

BMDCs were generated as described (Abcam protocol modified from ref. 18). Briefly, bone marrow was flushed out of mouse tibia and femur and single cell suspension–plated in the presence of 50 ng/mL GM-CSF and 50 ng/mL IL4 (PeproTech); 80% of the medium was removed, and new medium added at day 3; assays were conducted on day 7. Flow cytometry analysis of enriched dendritic cells was conducted. Cells were plated in 6-well plates and treated.

**Statistical Analysis**

Statistical analysis was performed using GraphPad Prism software (V7.0a, GraphPad). Values are reported as means ± SEM. When comparing two groups, P values were calculated using two-tailed Student t tests. For time to event and survival analysis, P values for the Kaplan-Meier survival curves were calculated with a log-rank (Mantel-Cox) test. Significance was conventionally accepted at P values equal to or less than 0.05. For multiple treatment group comparisons, significance was determined by one-way analysis of variance, followed by the Tukey post hoc multiple comparisons test, where *, P < 0.05; **, P < 0.01; ***, P < 0.001; ****, P < 0.0001.

**Data and Materials Availability**

All data are available in the main text or the supplementary materials.

**Disclosure of Potential Conflicts of Interest**

J.-P. Pin reports receiving a commercial research grant from CisBio Bioassays and has ownership interest in patents on mGlu4 assays and pharmacological compounds. E.G. Demicco is a consultant/advisory board member for Bayer. M.W.L. Teng has received honoraria from the speakers bureaus of Bristol-Myers Squibb, Roche, and Merck. M.J. Smyth reports receiving commercial research grants from Bristol-Myers Squibb and Tizona Therapeutics, has ownership interest (including patents) in Tizona Therapeutics, and is a consultant/advisory board member for Tizona Therapeutics and Compass Therapeutics. D.M. Thomas reports receiving commercial research support from Amgen. No potential conflicts of interest were disclosed by the other authors.

**Authors’ Contributions**

Conception and design: M. Kansara, M.J. Smyth, D.M. Thomas

Development of methodology: M. Kansara, J.-P. Pin, D.M. Thomas

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