Summary: GRM4, a GWAS-suspected tumor suppressor, is tested in a mouse model of osteosarcomagenesis as well as the putative oncogene it suppresses, IL23. Both are expressed in and exert the bulk of their influence among tumor-infiltrating myeloid-derived antigen-presenting cells, rather than osteosarcoma cells.

See related article by Kansara et al., p. 1511 (1).

In this issue of Cancer Discovery, Kansara and colleagues (1) interrogate potential mechanisms for the association between development of osteosarcoma and a polymorphism in the GRM4 locus. The link between this polymorphism and osteosarcoma was first reported in 2013, identified through a genome-wide association study of almost a thousand patients with osteosarcoma and more than triplette controls (2). It was also independently confirmed in two subsequently published Chinese osteosarcoma populations (3, 4).

As an initial test of this hypothetical link between locus and disease, Kansara and colleagues employed experiments that induced osteosarcomagenesis by a calcium-45 radioisotope that incorporates into bone mineral, then emits low-energy beta particles to affect and ultimately transform nearby osteoblasts. One could certainly argue that this model is prone to artifact, because a small minority of osteosarcomas follow traceable radiation exposure, but the model offers an appropriately pathway-agnostic generation of osteosarcomas that likely recapitulate the breadth of genetic driver variation observed in human osteosarcomas. Serendipitously, it is an ideal model for the testing of germline variants that may have non–cell-autonomous effects on osteosarcomagenesis, as it depends on no guided somatic genetic perturbation. Also serendipitously, germline homozygous disruption of Grm4 is well-tolerated developmentally in mice. It may be criticized that complete loss of GRM4 in the whole organism does not model well a polymorphism that results in only slightly reduced expression, but when this kind of over-the-top gene knockout experiment actually renders the result predicted by the polymorphism identified in a genome-wide association study, it merits more celebration than criticism.

This mouse genetic confirmation of the osteosarcoma-suppressing impact of GRM4 was only the beginning of the interesting findings reported by Kansara and colleagues. Although others have identified detectable expression of GRM4 in some osteosarcoma cell lines, Kansara and colleagues noted that measureable expression of GRM4 was almost exclusively outside of malignant osteoblasts. This suggests a non–cell-autonomous impact of the germline variant. Their increasingly complex sorting of myeloid-derived cell populations from whole tumors ultimately identified monocyte-derived dendritic cells as the source of most GRM4, as well as its targets, IL23 and IL12.

Most genetic loci associated with osteosarcoma development have implicated pathways whose disruption led to increased accumulation of DNA damage and chromosomal instability in the cells of origin for the tumor. This history of discoveries highlights the contrasting significance of a germline variant with disease penetrance mediated by the innate immune system, instead of the tumor cells.

Of note, a role for aberrant immune surveillance in osteosarcomagenesis has long been suspected. The very concept of immunotherapy for cancer began from the efforts of William B. Coley, who noted more than a hundred years ago that his patients who developed infections occasionally survived even inoperable sarcomas, if they managed to avoid death by sepsis in that preantibiotic era (5). Importantly, the treatments that he promoted, and that came to bear his name as Coley’s toxins, stimulated innate immunity through heat-inactivated bacteria. Although T cell–mediated immunotherapy has dominated the world of oncology in the last decade, for osteosarcoma, the thinking has continued to hearken back to those findings that suggested myeloid-derived inflammation instead. In 2007, prompted by observations that infectious complications of surgical reconstructions in canine osteosarcomas improved survival (6–8), a review of human patients with osteosarcoma identified a similar survival advantage following infections (9). This reanimated the discussion of the immune system as a potential inroad in the fight against osteosarcoma.

In spite of all these suggestions that the relationship between osteosarcoma and the immune system may represent a key to its undoing, osteosarcomas have proved recalcitrant to most recently developed immunotherapies. There was modest success in systemic administration of the immune stimulant mifamurtide (liposomal muramyl tripeptide; ref. 10),
of IL23 to IL12 by RT-PCR associated with poor survival in human osteosarcomas, also supportive of their hypothesis, but by correlation alone.

Kansara and colleagues returned to their stride with the potentially therapeutic manipulations of GRM4 and IL23. Agonists of GRM4 pathway activity inhibited osteosarcoma progression, as did therapeutic antibodies against IL23. The latter have been developed for clinical utility against psoriasis, which both is driven by overactive IL23 signaling and associates with elevated risk for osteosarcoma. Confirming that neither approach affected osteosarcoma cells in independent culture, experiments in engrafted tumors or in cocultures of tumor cells with bone marrow–derived myeloid cells had the predicted effects on tumor growth. Although complete tumor remissions would be desirable and were not observed by any regimen tested, we in the world of sarcoma have resigned ourselves to be enthusiastic about even minor wins. It is a sad fact that the evidence-based best practice for osteosarcoma chemotherapy still uses drug combinations of high-dose methotrexate, doxorubicin, and cisplatin that were first tried more than 35 years ago.

Work certainly remains to be done in the testing of clinically relevant combinations of IL23 antagonism or GRM4 agonism with other cytotoxic or targeted drugs, but the foundation is laid for potential efficacy. Most profoundly, a strong tumor suppressor and another oncogene have been identified that transfer smoothly between experimental osteosarcomagenesis in the mouse and genetic perturbations identified in human osteosarcoma. The mechanism of IL23-mediated promotion of osteosarcomagenesis is likely complex and will require a number of pathway–cell type–, and activation state–isolating experiments for elucidation. IL23 expression and myeloid-derived dendritic cells more generally have demonstrated both activating and suppressing effects on cytotoxic T cells, as well as direct impacts on osteoblasts or associated osteoclasts. Potential mechanisms are myriad; we can only hope data are forthcoming.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Dendritic Cells Drive Osteosarcomagenesis through Newly Identified Oncogene and Tumor Suppressor

Kevin B. Jones


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