Ovarian Cancer

Major Finding: An antibody to CD3 and MUC16 was effective against ovarian cancer in mice and tolerable in monkeys.

Concept: The antibody specifically recruits $CD3^+$ T cells to ovarian cancer cells, which highly express MUC16.

Impact: Tolerability and efficacy in animals indicate that preliminary human studies should commence.

A BISPECIFIC ANTIBODY FOR MUC16 AND CD3 HAS PRECLINICAL ANTITUMOR ACTIVITY

Ovarian cancer owes much of its lethality to recurrences after initially successful treatment. Immunotherapies have shown some promise, but the effectiveness of existing immunotherapies, such as programmed cell death 1 protein (PD-1) inhibitors, appears limited. Crawford and colleagues developed a bispecific antibody (REGN4018) that binds both the integral membrane glycoprotein Mucin 16 (MUC16), which is highly expressed in ovarian cancer cells, and the protein CD3, expressed by $CD3^+$ T cells. In both human and cynomolgus monkey cell lines, REGN4018 bound CD3 and MUC16 T cells and tumor cells, respectively, and caused human and cynomolgus T cells to kill ovarian carcinoma cells. Demonstrating REGN4018's antitumor effects, mice injected intraperitoneally with ovarian carcinoma cells allowed to grow for six to seven days exhibited reduced tumor burden, measured via *in vivo* bioluminescence imaging, when treated with REGN4018 compared with nonbinding or CD3-binding control antibodies. This REGN4018 treatment also induced serum cytokines TNFα, IL2, IL6, IL8, and IL10 and CD25, PD-1, and granzyme B in T cells in the peritoneal cavity, indicating that the treatment activated T cells, a likely explanation for its antitumor efficacy. In immunocompetent MUC16 membrane-proximal region knockin mice expressing human CD3 on T cells, PET imaging with ^{89}Zr-labeled REGN4018 demonstrated that the bispecific antibody localized to the tumor, with some also appearing in the spleen, rather than to the MUC16-expressing tissues (trachea, ovary, and stomach). The tissues expressing MUC16 at low levels were not found to exhibit any cellular infiltration or necrosis after five days of REGN4018 treatment, demonstrating the treatment's targeted effects to the tumor rather than the normal tissues. Toxicology studies in cynomolgus monkeys also showed that the REGN4018 is tolerated well. The efficacy and tolerability of REGN4018 in mice and monkeys, respectively, indicate that clinical investigation of the treatment is warranted; to this end, a Phase I trial of REGN4018 as monotherapy and in combination with anti–PD-1 is under way. ■

Crawford A, Haber L, Kelly MP, Vazzana K, Canova L, Ram P, et al. A Mucin 16 bispecific T cell–engaging antibody for the treatment of ovarian cancer. Sci Transl Med 2019;11:eaau7534.

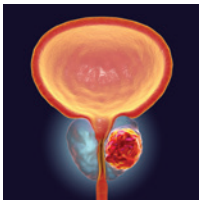
Prostate Cancer

Major Finding: The effects of prostate cancer–associated mutations in *FOXA1* depend on their position.

Mechanism: *FOXA1* mutations alter lumen structure and increase androgen receptor signaling.

Impact: *FOXA1* mutations are prevalent in prostate cancer but have distinct consequences.

MUTATIONS IN *FOXA1* CLUSTER INTO DISTINCT STRUCTURAL AND PHENOTYPIC CLASSES



FOXA1 is a transcription factor that is frequently mutated in prostate cancer, but the impact of *FOXA1* mutations is not known. Using sequencing data from 3,086 patients with primary or metastatic prostate cancer, Adams and colleagues discovered that 11% had mutations in *FOXA1*. Mutated *FOXA1* was associated with higher Gleason Scores, reduced time to biochemical recurrence, and faster metastasis. More than 50% of *FOXA1* mutations are in the Wing2 region of the forkhead DNA-binding domain, and mutations also clustered more rarely at R219. Both mutations increased growth of primary mouse prostate organoids, especially without epidermal growth factor, and exhibited histologic abnormalities, with Wing2-hotspot mutants causing increased lumen formation and size and R219 mutations leading to inability to form measurable lumens. Both types of mutations also caused a gain of function in FOXA1's pioneering activity, changing the chromatin landscape, which may contribute to oncogenesis. In a separate study of an aggregate cohort of 1,546 prostate cancers, Parolia and colleagues found *FOXA1* mutations at frequencies of 8%–9% in primary disease and 12%–13% in metastatic castration-resistant prostate cancer, and divided the mutations into three classes. Class 1 mutations were found in Wing2 or another region of the forkhead domain proximal to Wing2 in the protein's structure. These mutations were not enriched in metastatic cases, and, consistent with the work by Adams and colleagues, they are activating. Class 1 mutations enhanced nuclear mobility and caused 3–6-fold greater activation of androgen receptor signaling. Class 2 mutations, which were truncations of the protein's C-terminal domain, were also activating, and were seen at higher frequency in metastatic prostate cancers. Class 2 mutants dominantly engaged DNA and derepressed the WNT pathway that promotes metastasis. Class 3 mutations were genomic rearrangements that involve duplicating or repositioning a regulatory element that the group named FOXA1 mastermind, which caused overexpression of *FOXA1* or other oncogenes, respectively. Collectively, these results provide insight into the functional consequences of *FOXA1* alterations and highlight the central role of *FOXA1* in prostate cancer development. ■

Parolia A, Cieslik M, Chu SC, Xiao L, Ouchi T, Zhang Y, et al. Distinct structural classes of activating FOXA1 alterations in advanced prostate cancer. Nature 2019 Jun 26 [Epub ahead of print].

Adams EJ, Karthaus WR, Hoover E, Liu D, Gruet A, Zhang Z. FOXA1 mutations alter pioneering activity, differentiation and prostate cancer phenotypes. Nature 2019 Jun 26 [Epub ahead of print].