A B cell burden in prostate cancer

By Kai-Jye Lou, Staff Writer

Although castration therapies such as androgen ablation are standard prostate cancer treatments, many patients develop resistance in 12–18 months.¹ Now, researchers from the **University of California, San Diego** and **Scripps Florida** have found that castration therapies themselves trigger an inflammatory response that could be partly responsible for such resistance. The findings make the case for complementing castration therapies with marketed biologics that can deplete B cells or block lymphotoxin signaling.

In a mouse model of prostate cancer, tumor cells killed by androgen deprivation released proinflammatory factors. This in turn led to infiltration by leukocytes, including B and T cells. A series of mouse allograft and genetic studies specifically implicated the B cells and the lymphotoxin they produced as promoters of castration-resistant prostate cancer.²

The researchers showed that mice with a B cell-specific deficiency in lymphotoxin- β (LT β) had delayed growth of castration-resistant prostate cancer. In contrast, mice with a T cell-specific LT β deficiency failed to show delayed growth of castration-resistant prostate cancer.

B cell depletion via either a CD20 antibody, small interfering RNA-mediated LT β receptor knockdown or an LT β decoy receptor all delayed the growth of castration-resistant prostate cancer in mice compared with that in controls.

Results were published in *Nature*.

“We show for the first time that B cells infiltrate the prostate tumors after castration and help the growth of castration-resistant prostate cancer, which is the most malignant and aggressive form,” said Michael Karin, corresponding author on the paper and a professor of

Figure 1. Promoting castration-resistant prostate cancer through B cell-derived lymphotoxin.

Castration therapy is routinely used to treat patients with androgen-dependent prostate cancers. In *Nature*, researchers show how castration therapy itself could promote the development of castration-resistant prostate cancer.

[a] Castration therapy in mice with androgen-dependent prostate cancer triggers tumor cell death. Dying cells release proinflammatory factors (green circles) that lead to chemokine induction and infiltration by leukocytes, including B and T cells.

[b] Infiltrating B cells produce lymphotoxin and other factors (small red circles) that activate conserved helix-loop-helix ubiquitous kinase (CHUK; IKK- α) and signal transducer and activator of transcription 3 (STAT3) signaling (red circles) in the surviving prostate cancer cells, which promotes their hormone-free survival.

B cell depletion with a CD20 antibody **[c(1)]** and treatment with an LT β receptor (LTBR)-Ig decoy **[c(2)]** both delayed the growth of castration-resistant prostate cancer. Mice with a B cell-specific deficiency in lymphotoxin also had delayed growth of castration-resistant prostate cancer cells. In contrast, mice with a T cell-specific deficiency in lymphotoxin failed to show delayed growth of castration-resistant prostate cancer cells.

pharmacology at UCSD. “In our paper we have used two mouse models, but we have since validated our findings with human prostate cancer specimens.”

The researchers wrote that an extrapolation of their mouse data to humans “suggests that interventions that prevent lymphotoxin production or signaling may delay the appearance of castration-resistant prostate cancer in patients undergoing androgen ablation therapy by 2.3–3.1 years.”

“This paper convincingly identified a key role for lymphotoxin in castration-resistant prostate cancer,” said Jan van de Winkel, president of R&D and CSO of **Genmab A/S**. “The mechanism behind the role of B lymphocytes in castration-resistant prostate cancer has also been elegantly characterized.”

Two-pronged attacks

The results point to a pair of therapeutic strategies that could help delay the development of castration-resistant prostate cancer in patients receiving androgen ablation therapy: inhibiting B cell–specific lymphotoxin signaling or depleting the overall population of B cells (see **Figure 1**, “Promoting castration-resistant prostate cancer through B cell–derived lymphotoxin”).

“Blocking LTβ signaling in B cells can help to improve the currently used androgen ablation therapy by delaying the growth of the castration-resistant prostate cancer and increasing the quality of life for prostate cancer patients,” Karin told *SciBX*.

van de Winkel noted that treating other types of solid tumors by neutralizing B cells or their downstream effector pathways has been suggested in previous studies.^{3–5}

“Genmab has been following this area closely,” he said.

Massimo Ammirante, a lead author on the *Nature* paper and a post-doctoral fellow at UCSD, thinks blocking lymphotoxin signaling could be safer than B cell depletion, as B cells play a major role in normal immune system function.

Jun-Li Luo is the other lead author on the *Nature* paper and is an assistant professor in the Department of Cancer Biology at Scripps Florida.

Regardless, testing both approaches in the clinic could proceed quickly as drugs that employ either strategy already are marketed to treat hematologic cancers and autoimmune diseases.

However, van de Winkel noted that “better documentation and quantitation of B cells in late-stage patients with castration-resistant prostate cancer will be essential before moving to the next step of evaluating B cell depletion strategies in prostate cancer. The key data missing are quantitative data on the presence of B cells in castration-resistant prostate cancer. That would further support the rationale to evaluate B cell–depleting

antibodies or, alternatively, therapeutic approaches directed to lymphotoxin itself, such as Enbrel, in human patients.”

There are at least four approved antibodies against CD20, which work by depleting B cells. These include Arzerra ofatumumab, a human mAb against CD20 from Genmab and partner **GlaxoSmithKline plc**, which is marketed to treat chronic lymphocytic leukemia (CLL). The mAb also is in Phase III testing for diffuse large B cell lymphoma (DLBCL) and rheumatoid arthritis (RA) and is in Phase II for relapsing-remitting multiple sclerosis (RRMS).

The other approved anti-CD20 therapies include Rituxan rituximab from **Biogen Idec Inc.** and **Roche**, which is approved for multiple cancer and autoimmune indications, and a pair of radiolabeled antibodies for non-Hodgkin's lymphoma—**Spectrum Pharmaceuticals Inc.**'s Zevalin ibritumomab tiuxetan and GlaxoSmithKline's Bexxar tositumomab.

Enbrel etanercept, a soluble tumor necrosis factor receptor 2 (TNFR2) from **Amgen Inc.** and the **Wyeth** unit of **Pfizer Inc.**, blocks lymphotoxin signaling.⁶ The companies market the biologic to treat multiple autoimmune diseases.

Karin and Ammirante said the group is now trying to elucidate the molecular mechanisms and signaling pathways in prostate cancer cells that promote the development of castration resistance. “This will help find new therapeutic targets to prevent the growth of castration-resistant prostate cancer,” Karin told *SciBX*.

Karin said the university holds a pending patent that covers targeting B cells to treat prostate cancer. The work is not available for licensing.

Lou, K.-J. *SciBX* 3(12); doi:10.1038/scibx.2010.361
Published online March 25, 2010

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COMPANIES AND INSTITUTIONS MENTIONED

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