Foxp3Δ3 As A Biomarker For Treatment Response And Novel Target For Anti-Cancer Therapy

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SUMMARY

The Chin group at UCLA has discovered that an isoform of the protein Foxp3 is a robust biomarker of bladder cancer sensitivity to chemotherapy, including cisplatin- and gemcitabine-based treatments.

BACKGROUND

Urothelial carcinoma of the bladder comprises the majority of bladder cancer cases and represents the 9th leading cause of cancer mortality in the world. Resistance to chemotherapy is a major clinical problem; In patients with advanced bladder cancer, 50 to 60% do not respond to systemic cisplatin-based chemotherapy, which is the standard of care. A biomarker that can predict treatment response would assist physicians in treatment decisions and greatly benefit patients.

INNOVATION

Researcher Arnold I. Chin from UCLA has found that Foxp3Δ3, an isoform of a transcription factor Foxp3, is preferentially expressed in bladder cancer cell lines and primary tumors. His research has demonstrated that Foxp3Δ3 overexpression confers resistance to cisplatin and gemcitabine. Therefore, determining levels of this isoform can be used as a prognostic indicator and guide treatment for bladder cancer patients.

- Specifically, the inventor found that knockdown of Foxp3Δ3 sensitized bladder cancer cells to both cisplatin and gemcitabine. Therefore, Foxp3Δ3 can serve as a diagnostic biomarker for cisplatin and gemcitabine sensitivity in bladder cancer patients.
- Dr. Chin also found that Foxp3Δ3 expression is also correlated to sensitivity to HDAC inhibitors, and that Foxp3Δ3 expression levels may be used as a prognostic biomarker for this therapy as well.

APPLICATIONS

- Predict patient response to chemotherapies, such as cisplatin, gemcitabine, and HDAC inhibitors
- Assist physicians in making treatment decisions
- Non-invasively monitor patient response to therapy during treatment from urine and/or blood tests
- This biomarker may also be used as a prognostic and/or diagnostic biomarker for other cancers including but not limited to lung, ovarian, cervical, lymphomas, germ cell cancers

ADVANTAGES

Non-invasive

- Physicians can serially monitor Foxp3Δ3 levels in patients during treatment by testing urine and/or blood.

Differential expression of Foxp3Δ3 over Foxp3 in bladder cancer patients is high

- There is an 8- to 40-fold increase in expression of the Foxp3Δ3 isoform compared to full-length Foxp3 in bladder cancer.

STATE OF DEVELOPMENT

Foxp3 and Foxp3Δ3 expression has been analyzed in a tumor tissue microarray, as well as human clinical specimens. Dr. Chin has further characterized the role of Foxp3 and Foxp3Δ3 in both *in vitro* and *in vivo* model systems.

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INVENTORS

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OTHER INFORMATION

KEYWORDS

Foxp3, Foxp3D3, bladder cancer biomarker, cancer stem cells, cisplatin resistance, histone deacetylase inhibitor resistance, HDAC inhibitor resistance, companion diagnostic

CATEGORIZED AS

- **Medical**
  - Diagnostics
  - Disease: Cancer

RELATED CASES

2015-686-0

▶ Higher stage primary tumors had a higher expression of Foxp3, preferentially expressing the Foxp3Δ3 isoform

▶ Stable SW780 cell lines expressing Foxp3Δ3 demonstrated enhanced sphere formation and expression of stem cell markers *in vitro*, and larger tumors with more luminal differentiation *in vivo* xenografts

▶ Foxp3Δ3 is the predominant isoform in multiple primary bladder tumors, as well as cancer cell lines (ratios of Foxp3Δ3 to Foxp3 ranged from 8:1 to 42:1)

▶ The researchers demonstrated that while Foxp3Δ3 overexpression induced resistance to cisplatin and gemcitabine, it also surprisingly sensitized cytotoxicity to HDAC inhibition

▶ Conversely, knockdown of Foxp3 by approximately 40% showed that decreasing Foxp3 expression sensitized bladder cancer cell lines to cisplatin and induced HDAC inhibitor resistance

RELATED MATERIALS

▶ Zhang H, Prado K, Zhang KX, E. M. Peek, J. Lee, X. Wang, J. Huang, G. Li, M. Pellegrini, A. I. Chin, Biased Expression of the FOXP3D3 Isoform in Aggressive Bladder Cancer Mediates Differentiation and Cisplatin Chemotherapy Resistance, Clin. Cancer Res., 2016.

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