The oncolytic peptide LTX-315 enhances tumor-specific immune responses and tumor regression in murine 4T1 breast cancer when combined with doxorubicin

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Introduction

There is an increased focus on the combination of different treatment modalities to achieve an enhanced antitumor efficacy.

LTX-315 is a novel oncolytic peptide derived from the naturally occurring host defense peptide, bovine lactalbumin [1]. LTX-315 interacts electrostatically with anionic components of negatively charged cancer cell membranes as well as intracellular targets such as mitochondria, causing cellular lysis and a subsequent release of endogenous cellular content such as danger signals and high-mobility group box 1 (HMGB1) for tumor-specific immune responses to be achieved in the highly aggressive 4T1 breast cancer model when combining LTX-315 with doxorubicin [2-7].

Doxorubicin is a widely used chemotherapy and works by intercalating DNA and topoisomerase II inhibitors, causing cytotoxicity and inducing apoptosis. A single dose of doxorubicin (8 mg/kg) has been shown to induce tumor regression in an orthotopic 4T1 breast cancer model but also induces substantial side effects [8].

There is an increased focus on the combination of different treatment modalities to achieve an enhanced antitumor efficacy compared to either treatment alone in an A2B2 cell lymphoma model [9]. Thus, we hypothesized that an enhanced antitumor effect and augmented tumor-specific immune responses could be achieved in the highly aggressive 4T1 breast cancer model when combining LTX-315 with doxorubicin.

Aim

To investigate the antitumor efficacy of LTX-315 alone or in combination with doxorubicin in the murine 4T1 breast carcinoma model.

LTX-315

Mode of action

Subcutaneous model

Fig. 1 - LTX-315 induces complete regression of established 4T1 tumors when used in combination with doxorubicin

Orthotopic model

Fig. 3 - LTX-315 in combination with doxorubicin induces complete regression of orthotopic 4T1 tumors established in the mammary fat pad

Results

Experimental setup 1

Experimental setup 2

Fig. 2 - Inhibition of tumor growth in animals previously cured with LTX-315 and doxorubicin rechallenged with tumor cells

Fig. 4 - Animals previously cured with LTX-315 in combination with doxorubicin showed protection against tumor growth when rechallenged through left ventricular injection (IV)

Conclusion

• LTX-315 in combination with doxorubicin induced complete regression of both subcutaneous and orthotopic aggressive 4T1 tumors
• Animals treated with the combination therapy demonstrated protective immune responses when rechallenged with 4T1 tumor cells
• LTX-315 is currently in clinical phase 1/2a studies

References

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