Beta Adrenergic Signaling Promotes Drug Resistance in Sarcomas

Kathryn Fox\(^1\) and Erin B. Dickerson\(^2,3\)

\(^1\)College of Food, Agricultural and Natural Resource Sciences, University of Minnesota, St. Paul, MN; \(^2\)Veterinary Clinical Sciences, College of Veterinary Medicine, University of Minnesota, St. Paul, MN; \(^3\)Masonic Cancer Center, University of Minnesota, Minneapolis, MN

Abstract

Tumor cells often hijack metabolic pathways to promote tumor growth and chemoresistance. Recent studies by our group show that human angiosarcomas and canine hemangiosarcomas express \(\beta\)-adrenergic receptors (\(\beta\)-ARs). Treatment with \(\beta\)-AR antagonists (beta blockers) inhibited tumor growth and sensitized cells to chemotherapy agents. Because \(\beta\)-ARs modulate the expression of the co-transcription factor PGC-1\(\alpha\), a key regulator of gluconeogenesis, mitochondrial metabolism, and fatty acid oxidation, expression of PGC-1\(\alpha\) may be essential for sarcoma growth. Furthermore, chemoresistance has been shown to induce PGC-1\(\alpha\)-dependent increases in mitochondrial metabolism and promote tumor cell survival, leading us to hypothesize that knockdown of PGC-1\(\alpha\) would mimic the effects of beta blockade and increase the sensitivity of angiosarcoma and hemangiosarcoma cells to chemotherapy. We found that non-specific and receptor-specific \(\beta\)-AR antagonists reduced the viability of AS5 cells; however, an inhibitor specific for the \(\beta\)-3 AR reduced viability to the greatest extent. Treatment of AS5 cells with the generic beta blocker, propranolol, and the chemotherapy drug, doxorubicin, sensitized AS5 cells to chemotherapy when compared to doxorubicin treatment alone. Propranolol also reduced the expression of PGC-1\(\alpha\), and knockdown of PGC-1\(\alpha\) with siRNAs reduced the expression of the co-transcription factor. Our data suggest that \(\beta\)-AR signaling is important for angiosarcoma cell viability, and that beta blockers used in combination with standard-of-care chemotherapies may increase therapeutic efficacy. Knockdown of PGC-1\(\alpha\) in angiosarcoma and hemangiosarcoma cell lines followed by treatment with doxorubicin will need to be performed to confirm the role of PGC-1\(\alpha\) in chemoresistance.

Introduction

Hemangiosarcoma is an aggressive and essentially incurable cancer in dogs, with an estimated 50,000 cases per year in the United States. Although these tumors can arise almost anywhere in the body, they are most prevalent in the spleen, liver, heart and skin (MacEwen, 2001). In contrast, angiosarcomas, a similar disease found in humans, are rare (~2-3% of all soft tissue sarcomas) and extremely aggressive with fewer than 300 cases diagnosed in the United States each year (Condie et al., 2001; Lurkin et al., 2010; Penel et al., 2008). The fact that angiosarcomas are very uncommon makes them difficult to study. Because the pathology and disease progression of these tumors are virtually indistinguishable, a comparative approach can be used wherein studies of hemangiosarcomas in dogs are used to advance treatment approaches for angiosarcomas in humans. Most dogs succumb to their tumors within approximately 6 months of diagnosis (Clifford et al., 2000), often due to tumor rupture and metastatic spread. Most human patients survive less than 2 years (Fury et al., 2005). The current treatment for both humans and dogs includes chemotherapy and, if applicable, removal of the tumor. Because micrometastases may be present at the time of surgery and these tumors are often resistant to chemotherapy treatment, outcomes remain poor and new approaches are needed to treat these diseases.

Conclusions

- \(\beta\)-AR antagonists decreased the viability of AS5 cells; however, the AS5 cells were more susceptible to the \(\beta\)-3-antagonist, SR-592308. This suggests that angiosarcomas may rely more heavily on \(\beta\)-3-AR signaling pathways for survival.
- Propranolol reduced the expression of PGC-1\(\alpha\), indicating that \(\beta\)-AR antagonists may modulate certain metabolic pathways.
- \(\beta\)-AR antagonists may work with chemotherapy drugs to disrupt essential metabolic processes and induce chemosensitivity.
- Knockdown of PGC-1\(\alpha\) was achieved with siRNAs against PPARGC1A, and optimal knockdown was achieved at 72 hours. Knockdown in the presence of doxorubicin will need to be performed to determine if loss of PGC-1\(\alpha\) mimics the effects of propranolol.
- Future studies will focus on combining \(\beta\)-AR antagonists with chemotherapeutic drugs to improve the overall treatments for hemangiosarcomas and angiosarcomas.

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