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RAGE Re-Expressed at Myofibre Level Drives Muscle Wasting in Cancer Conditions

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ABSTRACT

Background: Cancer cachexia (CC) is a highly debilitating syndrome characterized by loss of body and muscle weight affecting most advanced cancer patients. The receptor for advanced glycation end-products (RAGE) is expressed by several cell types and sustains the inflammatory response in acute and chronic diseases. Total ablation of RAGE (*Ager*$^{-/-}$ mice) translates into restrained CC and increased survival in tumour-bearing mice. RAGE, which is not expressed in adult healthy myofibres, is re-expressed in atrophying myofibres in cancer conditions. However, the specific contribution of muscular RAGE to CC was unknown.

Methods: Using an HSA/Cre-*loxP* system, we generated a tamoxifen-inducible conditional *Ager*^{mKO} mouse model in which RAGE is selectively ablated in myofibres. Tamoxifen-treated *Ager*^{mKO}, *Ager*^{flox} and *Ager*$^{-/-}$ mice were subcutaneously injected with Lewis lung carcinoma (LLC) cells, and body changes and survival were monitored until 25 dpi, when histological, molecular and proteomic analyses were performed in tumour-bearing and control mice. Muscle samples of pre-cachectic and cachectic pancreatic cancer patients were analysed to validate the results.

Results: Compared with LLC-*Ager*^{flox} mice, LLC-*Ager*^{mKO} mice showed reduced (7.5% [$p = 0.004$] vs. 15.1% [$p < 0.0001$]) body weight loss, no significant reduction of hind-limb muscle mass and strength and myofibre cross-sectional areas, increased survival (69.2% vs. 42.9% mice alive at 25 dpi) and restrained muscle and serum pro-inflammatory factors. Mechanistically, *Ager*^{mKO} muscles resist cancer-induced atrophy by maintaining an active Akt-GSK-3β-PGC-1α pathway, and increasing the synthesis of myosin heavy chain (MyHC)-I and -IIa (71.8% [$p = 0.008$] and 73.9% [$p = 0.002$] increase, respectively) along with a 76.3% ($p = 0.008$) increase in hybrid MyHC-I/IIa myofibres. Distinct proteomic signatures characterize muscles of tumour-bearing mice in dependence on RAGE expression, supporting a protective effect of RAGE ablation in muscles. LLC/*Ager*^{mKO} muscles showed increased amounts of several enzymes involved in glycolysis and glucose catabolism, typical of Warburg metabolism. Noteworthy, muscles of pre-cachectic and cachectic cancer patients showed ~3-fold increase ($p < 0.05$) in RAGE amounts and reduced Akt-GSK-3β-PGC-1α pathway, compared with healthy control subjects.

Conclusions: Our data provide evidence that RAGE engagement at myofibre level drives loss of body and muscle weights and inflammation in cancer conditions. RAGE ablation in muscles confers resistance to CC through myofibre remodeling and glycolytic