Accepted Manuscript

Acetyl-L-carnitine is an anti-angiogenic agent targeting the VEGFR2 and CXCR4 pathways

Denisa Baci, Antonino Bruno, Barbara Bassani, Matilde Tramacere, Lorenzo Mortara, Adriana Albini, Douglas M. Noonan

PII: S0304-3835(18)30279-9

DOI: 10.1016/j.canlet.2018.04.018

Reference: CAN 13858

To appear in: *Cancer Letters*

Received Date: 29 November 2017

Revised Date: 12 April 2018

Accepted Date: 13 April 2018

Please cite this article as: D. Baci, A. Bruno, B. Bassani, M. Tramacere, L. Mortara, A. Albini, D.M. Noonan, Acetyl-L-carnitine is an anti-angiogenic agent targeting the VEGFR2 and CXCR4 pathways, *Cancer Letters* (2018), doi: 10.1016/j.canlet.2018.04.018.

ABSTRACT

Carnitines play an important role in the energy exchange in cells, involved in the transport of fatty acids across the inner mitochondrial membrane. L-Acetylcarnitine (ALCAR) is an acetic acid ester of carnitine that has higher bioavailability than carnitine and is considered a fat-burning energizer supplement. We previously found that in serum samples from prostate cancer (PCa) patients, 3 carnitine family members were significantly decreased, suggesting a potential protective role of carnitine against PCa. Several studies support beneficial effects of carnitines on cancer, no study has investigated the activities of carnitine on tumor angiogenesis.

We examined whether ALCAR act as an "angiopreventive" compound and studied the molecular mechanisms involved. We found that ALCAR was able to limit inflammatory angiogenesis by reducing stimulated endothelial cell and macrophage infiltration *in vitro* and *in vivo*. Molecularly, we showed that ALCAR downregulates VEGF, VEGFR2, CXCL12, CXCR4 and FAK pathways. ALCAR blocked the activation of NF-κB and ICAM-1 and reduced the adhesion of a monocyte cell line to endothelial cells. This is the first study showing that ALCAR has anti-angiogenesis and anti-inflammatory properties and might be attractive candidate for cancer angioprevention.