# Lipoxin A4 Selectively Shift the Tumor-Associated Macrophage Profile Leading to Control of Tumor Progression

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**INTRODUÇÃO**. In tumor microenvironments, pro-inflammatory macrophages (M1) acquire anti-inflammatory and pro-tumor characteristics. These tumor-associated macrophages (TAMs), often referred to as myeloid suppressors, exhibit an M2-like profile, with low cytotoxic properties and a deficient modulation of NO and ROS production. Lipoxins (LX) and 15-epi-lipoxins are lipid mediators inducing anti-inflammatory and pro-resolution activities in mononuclear cells, but their effects on TAMs remain to be elucidated.
**OBJETIVO:** This study tested the hypothesis that ATL-1, a synthetic analogue of 15-epi-lipoxin $A_4$, could modulate the TAM activity profile.
**MATERIAL E METODOS:** Human macrophages (MΦ) were differentiated into TAMs after incubation with conditioned medium from MV3, a human melanoma lineage cell, and then used in identification and functional tests in the presence or not of ATL-1
**DISCUSSÃO E RESULTADOS**: In contrast with the effects observed,in the other M2 subset and M1 profile macrophages, ATL-1 selectively decreased M2 surface markers in these TAM, suggesting unique behaviour of the M2d subset. The effect was dependent on VEGF signaling and importantly, reproduced by the natural lipoxins, LXA and 15-epi-$LXA_4$. In parallel, ATL-1 stimulated TAM to produce NO by increasing the iNOS/arginase ratio and activated NADPH oxidase, triggering ROS production. These alterations in TAM profile induced by ATL-1 led to the loss of the anti-apoptotic effects of TAMs on melanoma cells and increased their cytotoxic properties. Furthermore, in addition to reversing the TAM anti-apoptotic effect on MV3, ATL-1 inhibited endothelial cell tubulogenesis activated by TAM, a crucial step in the angiogenic process. Finally, ATL-1 was found to inhibit tumor progression in a murine model *in vivo*, which was accompanied by alterations in TAM profile and diminished angiogenesis.
**CONCLUSAO:** Together, the results suggest unexpectedly that the aspirin-induced lipoxin analogue down-modulates the tumor progression stimulated by TAM probably by inducing a change in the TAMs from an M2- to an M1-like profile thereby triggering tumor cell apoptosis.

Key Words: **Lipoxin, Tumor-Associated Macrophage, Inflammation, Cancer, Polarization.**

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