115. MONOAMINE OXIDASE BLOCKADE THERAPY

(University of California - Los Angeles)

5TH KDDF GLOBAL C&D TECH FAIR

Asset Overview

Product Type	Protein
Disease Area	Oncology
Indication	tumors
Current Stage	Lead Optimization
Target	Monoamine Oxidase A (MAO-A)
MoA	MAO-A acts as an inhibitor of antitumor CD8 T Cell response, and also polarizes tumor-associated macrophages (TAMs) for immune suppression in a solid tumor
Brief Description	• Targeting tumor-associated macrophages (TAMs) is a promising strategy to modify the immunosuppressive tumor microenvironment and improve cancer immunotherapy. Mono-amineoxidase A (MAO-A) is an enzyme best known for its function in the brain; small molecule MAO inhibitors (MAOIs) are clinically used for treating neurological disorders. • MAO-A induction in mouse and human TAMs. MAO-A-deficient mice exhibit decreased TAM immunosuppressive functions corresponding with enhanced antitumor immunity. MAOI treatment induces TAM reprogramming and suppresses tumor growth in preclinical mouse syngeneic and human xenograft tumor models. • Combining MAOI and anti-PD-1 treatments results in synergistic tumor suppression. Clinical data correlation studies associate high intra-tumoral MAO-A expression with poor patient survival in a broad range of cancers. • MAO-A promotes TAM immunosuppressive polarization via upregulating oxidative stress. Together, these data identify MAO-A as a critical regulator of TAMs and support repurposing MAOIs for TAM reprogramming to improve cancer immunotherapy.
Intellectual Property	WO2022087361A1
Publication	Targeting monoamine oxidase A-regulated tumor-associated macrophage polarization for cancer immunotherapy, Nature Communications. (2021)
Inventors	Lili Yang, Xi Wang

Highlights

- MAO-A-deficient mice show reduced tumor growth associated with altered TAM polarization.
- MAO-A directly regulates TAM polarization and influences TAM-associated T-cell antitumor reactivity.
- MAO-A promotes macrophage immunosuppressive polarization via ROS upregulation.
- Syngeneic mouse tumor model studies provided proof-of-principle evidence for the cancer immunotherapy potential of MAOIs via targeting TAM reprogramming and thereby enhancing antitumor T-cell responses.
- Human TAM and clinical correlation studies confirmed MAO-A as a promising drug target in human TAMs and support the translational potential of MAO-A blockade for cancer immunotherapy through targeting TAM reprogramming.

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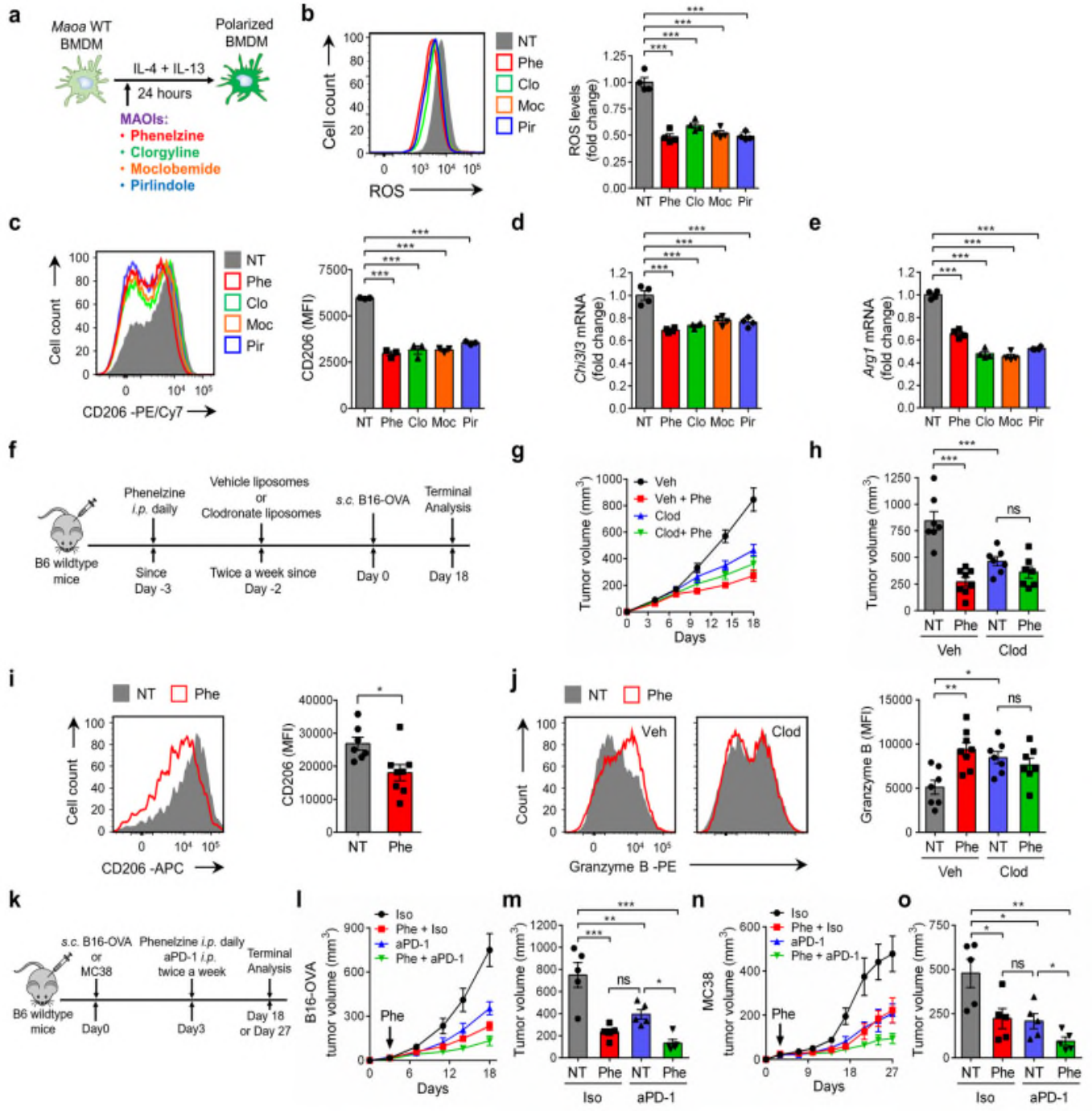
MAO-A blockade for cancer immunotherapy- syngeneic mouse tumor model studies.



Source: NATURE COMMUNICATIONS | (2021) 12:3530. Fig5.

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a–e Studying the effect of MAOI treatment on IL-4/IL-13-induced BMDM polarization in vitro (n = 4). a Experimental design. Wild-type BMDMs were stimulated with IL-4/IL-13 with or without MAOI treatment.
MAOIs (monoamine oxidase inhibitors) studied were phenelzine (Phe; 20 μM), clorgyline (Clo; 20 μM), moclobemide (Moc; 200 μM), and pirlindole (Pir; 20 μM). NT no MAOI treatment. b FACS analyses of ROS levels in BMDMs. c FACS analyses of CD206 expression on BMDMs. d, e QPCR analyses of Chi3l3 (d) and Arg1 (e) mRNA expression in BMDMs. ***p < 0.001. f–j Studying the TAM-related cancer immunotherapy potential of MAOI treatment in a B16-OVA melanoma syngeneic mouse tumor model. f Experimental design. B6 wild-type mice were treated with clodronate liposomes (Clod) to serve as TAM-depleted experimental mice or treated with vehicle liposomes (Veh) to serve as TAM-intact control mice. Phe phenelzine treatment, NT no phenelzine treatment. g Tumor growth. h Tumor volume at day 18 (***p < 0.001). i FACS analyses of CD206 expression on TAMs of TAM-intact experimental mice (*p = 0.0164). j FACS analyses of intracellular Granzyme B production in tumor-infiltrating CD8+ T cells of all experimental mice (NT, *p = 0.0257; Veh, **p = 0.0025). Veh NT, n = 7; Veh Phe, n= 8; Clod NT, n = 7; Clod Phe, n =7. k–o Studying the cancer therapy potential of MAOI treatment in combination with anti-PD-1 treatment in the B16-OVA melanoma and MC38 colon cancer syngeneic mouse tumor models (n = 5). k Experimental design. Tumor-bearing mice were treated with anti-PD-1 antibody (aPD-1) or isotype control (Iso), together with or without phenelzine (Phe) treatment. NT no Phe treatment. l B16-OVA tumor growth. m B16-OVA tumor volume at day 18. n MC38 tumor growth. o MC38 tumor volume at day 27. *p < 0.05, **p < 0.01 and ***p < 0.001. Representative of three experiments. Analysed by one-way ANOVA (b–e, h, j, m, o) or by Student's t test (i). Statistics are all two-sided.

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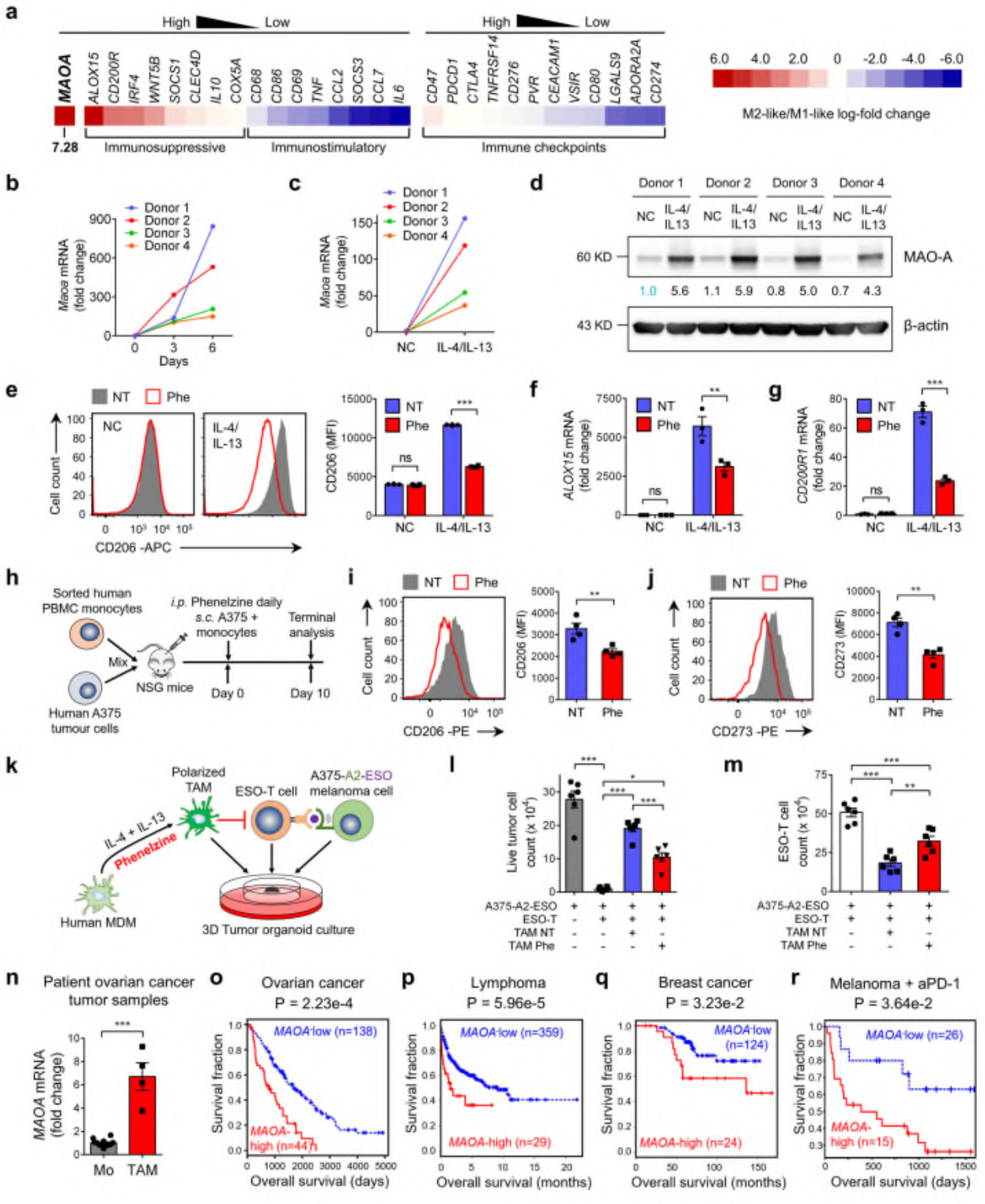

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a Heatmap showing the mRNA expression fold change of the indicated genes in human M2-like/M1-like macrophages. b–d Studying the MAO-A expression in in vitro-cultured human monocyte-derived macrophages (MDMs) (n = 4). b, c QPCR analyses of MAOA mRNA expression in MDMs over the 6-day differentiation culture (b) and post the IL-4/IL-13-induced polarization (c). d Western blot analyses of MAO-A protein expression in IL-4/IL-13-polarized MDMs. e–g Studying the IL-4/IL-13-induced polarization of human MDMs (n= 3). e FACS analyses of CD206 expression (***p < 0.001). f, g QPCR analyses of ALOX15 (f) (**p = 0.0012) and CD200R1 (g) (***p < 0.001) mRNA expression. h–j Studying the in vivo polarization of human macrophages in a human tumor-TAM co-inoculation xenograft mouse model (n = 4). h Experimental design. i, j FACS analyses of CD206 (i) (**p= 0.0093) and CD273 (j) (**p =0.0013) expression on TAMs (gated as hCD45+hCD11b+hCD14+ cells of TIIs). k–m Studying the in vitro efficacy of phenelzine in reprogramming human TAMs and enhancing human T-cell antitumor reactivity (n=6). k Experimental design. l, m FACS quantification of live tumor cells (gated as hCD45− cells) and ESO-T cells (gated as hCD45+hCD8+ESO-TCR+cells). NT no phenelzine treatment. *p<0.05, **p < 0.01 and ***p<0.001. n QPCR analyses of MAOA mRNA expression in human TAMs isolated from ovarian cancer patient tumor samples (n=4). Mo, monocytes isolated from random healthy donor peripheral blood (n=10). ***p < 0.001. o–r Clinical data correlation studies. Kaplan–Meier plots are presented, showing the association between the intratumoral MAOA gene expression levels and overall survival (OS) of cancer patients, in an ovarian cancer patient cohort (GSE26712, n=182; o), a lymphoma patient cohort (GSE10846, n=388; p), a breast cancers patient cohort (GSE9893, n=148; q) and a melanoma patient cohort with anti-PD-1 therapy (PRJEB23709, n=41; r). Phe phenelzine, NC no cytokine stimulation, NT no phenelzine treatment. Representative of one (n), two (b–d, h–j) and three (e–g, k–m) experiments. Analysed by one-way ANOVA (l, m), two-way ANOVA (e–g), Student's t test (i, j, n), or by two-sided Wald test in a Cox-PH regression (o–r). Statistics are all two-sided.