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Monoamine oxidase A (MAO-A): a signature marker of alternatively activated monocytes/macrophages

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Abstract

Monocytes/macrophages are versatile cells centrally involved in host defense and immunity. Th1 cytokines induce a classical activation program in monocytes/macrophages leading to a proinflammatory M1 macrophage phenotype while Th2 cytokines IL-4 and IL-13 promote monocyte differentiation into an alternatively activated, anti-inflammatory M2 macrophage phenotype. Although monoamine oxidase A (MAO-A) is primarily known for its action in the nervous system, several recent studies have identified MAO-A as a signature marker of alternative activation of monocytes/macrophages. In this brief review we explore the signaling pathways/molecules that regulate MAO-A expression in alternatively activated monocytes/macrophages. We further discuss the contribution of MAO-A to the resolution of inflammation and identify potential therapeutic targets for controlling inflammation. Altogether this review provides deeper insight into the role of MAO-A in alternative activation of monocytes/macrophages and their participation in the inflammatory response.

Introduction

Monocytes/macrophages are major mediators of inflammatory responses and play a key role in innate and adaptive immunity. Monocytes/macrophages can be broadly classified into two different categories based on their mode of activation. They are considered as (i) classically activated (M1 pro-inflammatory phenotype) when stimulated by LPS or IFN-γ[1, 2] and (ii) alternatively activated (M2 anti-inflammatory phenotype) when induced by Th2 cytokines like IL-4 and IL-13, IL-10, TGF-β etc.[3–5]. The M2 subset of monocytes/macrophages can be further divided into three different subcategories namely M2a, M2b and M2c; that have specialized functions and express different M2 marker genes[5]. IL-4 and IL-13 activate monocytes/macrophages toward the M2a phenotype leading to the upregulation of several gene products involved in inflammatory resolution. Among the most strongly upregulated genes in IL-4/IL-13-activated monocytes/macrophages with potential anti-inflammatory

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properties are 15-lipoxygenase (15-LO), monoamine oxidase A (MAO-A), scavenger receptor CD36, fibronectin and coagulation factor XIII[6–14].

MAO-A, a pro-oxidative enzyme encoded by the X chromosome, is located in the outer mitochondrial membrane and cytosol[15]. This enzyme is a catalytically active flavoprotein that converts biogenic amines like serotonin, dopamine and norepinephrine into their corresponding aldehydes[16, 17]. This enzyme reaction requires molecular dioxygen and generates stoichiometric amounts of hydrogen peroxide and ammonia[18, 19]. MAO-A hyperactivity has been shown to be associated with depression and previous reports implicate MAO-A inhibitors as effective therapeutics against clinical depression and anxiety[20, 21]. Previous studies also demonstrated the involvement of MAO-A in neurodegeneration including Parkinson's and Alzheimer's diseases by inducing oxidative stress-mediated apoptosis[22, 23]. MAO-A deficiency and abnormal activity has been associated with impulsive aggressive behavior[24], neuropsychiatric disorders[25], pancreatic beta cell function[26] and glucose metabolism[27]. MAO-A has also been implicated as a vital regulator of embryonic brain development[19]. In addition to neuroinflammatory syndromes, recent studies suggest that MAO-A is a useful prognostic marker in the management of cholangiocarcinoma[28] and MAO-A has also been implicated in the pathogenesis of many cardiovascular disorders. The predominant role of MAO-A has been reported in myocardial injury[29], heart failure[30], cardiac cell apoptosis[31] and vascular wall remodeling[32] and MAO-A promoter methylation has been shown to be associated with atherosclerosis[33].

In this brief review we focus on understanding the regulatory mechanisms controlling MAO-A gene expression in alternatively activated monocyte/macrophages and also the involvement of MAO-A in the inflammatory response.

Regulation of MAO-A expression during alternative activation of monocytes/macrophages

Alternatively activated monocytes/macrophages play a major role in the immune system by controlling inflammation[3, 34]. IL-4/IL-13-mediated induction of MAO-A in monocytes/macrophages suggests the involvement of this enzyme in the Th2 responses and switching naive monocytes/macrophages into a resolving phenotype. Although some recent studies focused on understanding the role of MAO-A during the alternative activation of monocytes/macrophages, much remains to be investigated about the regulation of MAO-A expression and the precise role of MAO-A during the resolution phase of inflammation.

During monocyte/macrophage activation both IL-4 and IL-13 interact with specific receptors that share a common IL-4Rα chain[3, 34, 35]. IL-4Rα can signal either using the common gamma chain receptor component, IL-2Rγc (Type I IL-4R, generally used by IL-4 signaling) or it can partner with IL-13Rα1 (Type II IL-4R, receptor for IL-13)[35–37]. The receptor-associated Jaks that are attached with the Type I and Type II IL-4R and activated by IL-4/IL-13 stimulation include Jak1, Jak2 and Tyk2[14, 35]. Although Jak3 is known to be associated with IL-2Rγc[38, 39], it is not activated in response to IL-4 signaling[14]. Jak kinase-mediated activation of Stat3 and Stat6 seems to be the common effect of IL-4 and

IL-13 signaling pathways during alternative activation of monocytes/macrophages[14, 40]. In contrast, Stat1 activity is an integral part of IL-13 signaling and contributes substantially to IL-13-driven gene expression[14].

MAO-A is one of the signature genes that is modulated by both IL-4 and IL-13 in monocytes/macrophages[34]. Recently we identified Hck, a non-receptor tyrosine kinase of the Src family, as an essential upstream regulator of a panel of genes including both 15-LO and MAO-A in alternatively activated monocytes/macrophages[12]. Moreover, we presented evidence that Stat transcription factors, that control 15-LO gene expression[14, 40, 41], are also involved in regulating MAO-A expression[14] in response to IL-4/IL-13 stimulation. Altogether our data indicated the participation of several signaling pathways including IL-4Rα/Jak1/Stat3, IL-4Rα/Jak1/Stat6, IL-4Rα/Jak2/Stat3, IL-13Rα1/Tyk2/Stat1 and IL-13Rα1/Tyk2/Stat6 in the upregulation of both 15-LO and MAO-A during alternative monocyte/macrophage activation as illustrated in our proposed models[12, 14, 40, 41].

In addition to requiring tyrosine phosphorylation for activation, Stat transcriptional activity is also enhanced by serine phosphorylation. In this regard, our group further demonstrated the involvement of several Ser/Thr kinases including p38MAPK, ERK1/2 and PKCδ in regulating Stat serine phosphorylation and Stat-dependent gene transcription leading to the expression of both 15-LO[40–43] and MAO-A (A. Bhattacharjee and M.K. Cathcart, unpublished observations).

Two other critical regulators involved in the transcriptional control of 15-LO, CREB and EGR-1[43], were also found to act as essential regulators of MAO-A gene expression (A. Bhattacharjee and M.K. Cathcart, unpublished observations). The existence of Stat, EGR-1 and CREB transcription factor binding sequences in the promoter of 15-LO gene and our demonstration of their regulatory role in 15-LO gene transcription in alternatively activated monocytes/macrophages (A. Bhattacharjee and M.K. Cathcart, unpublished observations)[41, 43] led us to speculate the presence of the cognate binding sequences for these transcription factors in the promoter of the MAO-A gene but this speculation needs further confirmation; however, our unpublished observations showed significant inhibition of MAO-A gene expression by transfecting 15-LO antisense oligonucleotides in IL-13-stimulated monocytes thus suggesting that MAO-A gene expression is directly dependent on 15-LO expression/activity in alternatively activated monocytes/macrophages (A. Bhattacharjee and M.K. Cathcart, unpublished observations).

Recent investigations introduce Kruppel-like factors (KLFs), members of the zinc finger family of transcriptional regulators, as major contributors to the regulation of M1/M2 polarization and specifically identify KLF4 and KLF6 as the critical regulators of this process[44, 45]. Macrophage KLF4 expression is strongly induced in M2 macrophages and significantly downregulated in M1 macrophages[44]. In contrast, KLF6 expression is robustly stimulated by M1 stimuli and substantially reduced by M2 stimuli[45]. Mechanistically KLF4 cooperates with Stat6 and acts as a positive regulator of the M2 genetic program, whereas it inhibits M1 targets probably by competing with NFkB for the key coactivators required for its transcriptional activity[44]. In contrast, KLF6 suppresses the M2 phenotype by negatively regulating PPARγ expression while promoting the M1

phenotype through cooperation with NFkB[45]. Therefore, a balance between KLF4 and KLF6 is required for optimal M2 gene expression in alternatively activated monocytes/macrophages via modulation of Stat6. Furthermore, these findings also identify both KLF4 and KLF6 as probable transcriptional regulators of Stat6-mediated MAO-A gene expression which needs to be verified by further experimentation.

Integrins are adhesion receptor molecules that control monocyte migration and macrophage differentiation. During inflammation, integrin activation mediates adhesion of monocytes to endothelial cells and subsequent migration through the extracellular matrix (ECM) to sites of inflammation[46]. The β_2 subfamily of integrins plays a significant role in monocyte migration and the immune-inflammatory response. Recently we investigated how β_2 integrins regulate monocyte activation in response to IL-13 stimulation. In this study we found that IL-13 induction of 15-LO expression is inhibited during β_2 integrin activation or clustering through α_M integrin[13]. We also demonstrated that whereas IL-13 stimulation promotes the surface expression of scavenger receptor CD36, a key protein for the development of inflammation and atherosclerosis, activation of β_2 integrin substantially blocks this effect[13]. We further focused on exploring the molecular mechanisms that inhibit CD36 expression and CD36-mediated foam cell formation in IL-13-stimulated monocytes/macrophages after $\alpha_M\beta_2$ integrin activation. Our data showed that, $\alpha_M\beta_2$ integrin activation controls CD36 expression and foam cell formation in alternatively activated monocyte/macrophages via a 15-LO-dependent pathway involving peroxisome proliferator-activated receptor-γ (PPARγ) activation[47]. As our unpublished observations support the fact that MAO-A expression is controlled by 15-LO in alternatively activated monocyte/macrophages, we predict at this stage that $\alpha_M\beta_2$ integrin activation may inhibit MAO-A expression in these cells. Moreover, like 15-LO products (13-HPODE/13-HODE, 15-HPETE/15-HETE) which are PPARγ ligands and regulate CD36 expression[48], PPARγ activation by the products of MAO-A (e.g., the serotonin metabolite 5-methoxy-indole acetate)[49] may influence the expression of M2 markers including CD36 in alternatively activated monocytes/macrophages[50, 51].

IL-13-activated pathways in human macrophages can additionally be modulated by microRNA-155[52]. MicroRNA-155 (miR-155) has been extensively studied during inflammation and immune function[53–55] and is known to be upregulated by several pro-Th1 factors during inflammation. MicroRNA-155 directly targets IL-13Rα1 3'-UTR to diminish IL-13Rα1 protein expression leading to the downregulation of Stat6 activation and Stat6-dependent gene expression[52]. Hence miR-155 regulates Th1/Th2 equilibrium, facilitating the classical activation of macrophages to the M1 phenotype by reducing the expression of several IL-13-dependent M2 genes. As Stat6 is the major regulator of the signaling cascades triggered by IL-13[14, 56, 57] and controls IL-13-driven MAO-A gene expression[14], it is very likely that miR-155 will prove to be an essential regulator of MAO-A gene expression in alternatively activated macrophages.

MAO-A-mediated ROS generation in alternatively activated monocytes/ macrophages and its implication

Although MAO-A expression is strongly upregulated in alternatively activated monocytes/ macrophages[9, 10, 12, 14, 58], the biological importance of MAO-A for monocyte physiology has not been determined. In peripheral tissues, MAO-A is involved in the oxidative catabolism of biogenic amines thereby preventing those amines from entering the circulation. Unfortunately, the metabolism of dietary amines in inflamed tissues during the acute inflammation has not been thoroughly studied. As biogenic amines such as histamines and serotonin are well-known inflammatory mediators[59–61] and preferentially oxidized by MAO-A, removal of these pro-inflammatory mediators from the site of inflammation may switch naive monocytes from pro-to anti-inflammatory phenotypes and thereby reverse the inflammatory symptoms.

Recently we demonstrated for the first time that MAO-A is involved in generating ROS (H_2O_2) in alternatively activated monocytes/macrophages[14]. Interesting studies have shown that MAO-generated H_2O_2 is an important inhibitor of inducible nitric oxide synthase (NOS2) expression[62]. Although NOS2 generation of NO is differently regulated in murine and human macrophages, we speculate that the expression of MAO-A in M2 macrophages may stabilize this anti-inflammatory phenotype in part by preventing the expression of NOS2 and generation of NO. In other studies, H_2O_2 was shown to inhibit macrophage IL-12 expression, an M1 macrophage marker, by inhibiting c-Rel translocation to the nucleus[63] and mitochondria-derived H_2O_2 was shown to inhibit the transcription factors SP-1 and AP-1 in macrophages[64]. Thus there are many potential avenues by which MAO-A and MAO-A-derived H_2O_2 may influence gene expression in M2 macrophages.

ROS generated during the oxidation of biogenic amines can trigger various signaling pathways that ultimately lead to oxidative stress. Although superoxide anion production and oxidative stress have been implicated in proinflammatory pathways, e.g. LDL oxidation and atherogenesis, the formation of ROS and their biologic effects are in delicate balance with their catabolism (via SOD/catalase) thus influencing physiologic effects.

Role in potential endogenous PPARγ ligand production

PPARγ, a lipid activated nuclear receptor, is a critical regulator of cellular lipid metabolism and shows anti-inflammatory activities[65, 66]. Although alternative activation of monocytes/ macrophages by IL-4/IL-13 and PPARγ-mediated transcriptional regulation are interlinked, the underlying mechanisms that connect these two processes are not well understood. A recent study proposed the requirement of PPARγ activity for alternative activation of macrophages *in vivo*[67]. It further showed that the IL-4-Stat6-PPARγ signaling axis in monocytes is crucial for their differentiation into alternatively activated macrophages and for innate immunity[67]. Although a later study reported substantial enhancement of PPARγ signaling by IL-4 in human monocyte derived macrophages or mouse bone marrow derived macrophages, the direct involvement of PPARγ in IL-4-stimulated alternative activation could not be demonstrated since the markers of alternative activation were not changed in PPARγ-deficient cells[68]. This study thus recognized PPARγ as a downstream target of

IL-4 signaling rather than a direct regulator of alternatively activated monocytes/macrophages[68].

There are several possible mechanisms that could be responsible for the interaction between IL-4/IL-13 signaling and PPARγ transcriptional activities during alternative macrophage activation. PPARγ is a ligand activated transcription factor which can prime the native monocytes (in presence of an appropriate M2 stimulus such as IL-4 or IL-13) to an enhanced M2 phenotype. Therefore we speculate that IL-4/IL-13 stimulation not only leads to PPARγ activation but also can induce mechanisms that are involved in the generation of PPARγ ligands. This type of mechanism has been described in alternatively activated monocytes/macrophages where IL-4/IL-13 induces the expression of 15-lipoxygenase, which metabolizes arachidonic and linoleic acids to produce 15-HETE/13-HODE that serve as endogenous ligands of PPARγ[47, 48, 69]. As mentioned above, IL-4 and IL-13 also enhance MAO-A expression which may lead to an enhanced serotonin metabolism in alternatively activated macrophages. The serotonin metabolite 5-methoxy-indole acetate was shown to be a PPARγ activator[49, 50]. Serotonin was also shown to induce PPARγ target gene expression like FABP4 in differentiating macrophages in the presence of IL-4[50]. The ability of serotonin to induce *in vitro* PPARγ transcriptional activity is interesting and requires further studies involving pharmacological or genetic manipulations of the specific PPARγ ligand producing enzymes.

Conclusion

IL-4/IL-13 stimulation leads to the induction of 15-LO and MAO-A genes whose protein products are already recognized as critical markers of alternatively activated monocytes/macrophages. 15-LO and its products can directly control MAO-A gene expression in monocytes/macrophages during alternative activation. It is well known that 15-LO metabolites can act as endogenous ligands of PPARγ and control the expression and function of scavenger receptor CD36 in a PPARγ-dependent manner to affect inflammatory signaling pathways in pathophysiologic responses. As MAO-A-generated metabolites can also act as endogenous ligands of PPARγ and can regulate PPARγ-dependent gene expression, it is quite likely that MAO-A-generated metabolites also control CD36 expression level. Thus, the coordinated action of the 15-LO/MAO-A → PPARγ → CD36 axis may prove to be of central importance for monocyte/macrophage physiology and function during alternative activation and resolution of inflammation. The components of this pathway may prove to be important targets for controlling the pathogenesis of atherosclerosis and chronic inflammation.

Although MAO-A is associated with the resolution of inflammation in M2 macrophages, MAO-A-mediated ROS generation in alternatively activated monocytes/macrophages and subsequent oxidative stress could promote inflammation in cardiovascular diseases like atherosclerosis. Hence the participation of MAO-A in promoting or resolving inflammation appears to rely on the delicate balance of ROS formation and catabolism as well as the influence of MAO-A on regulating bioactive amine levels and generating PPARγ ligands. This balance is determined by the cellular and tissue microenvironment of MAO-A expression and is altered in different disease states. It is clear that M1 and M2 are the two

extreme cases of an entire spectrum of macrophage activation and function which needs further characterization of marker genes that can differentiate between the subtypes of activation states. In this context it is imperative to perform additional detailed investigations to fully understand the role of MAO-A during alternative activation of monocytes/macrophages and its contribution to the resolution of inflammation.

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References

1. Dalton DK, Pitts-Meek S, Keshav S, Figari IS, Bradley A, Stewart TA. Multiple defects of immune cell function in mice with disrupted interferon-γ genes. Science. 1993; 259:1739–1742. http://dx.doi.org/10.1126/science.8456300 PMid:8456300. [PubMed: 8456300]
2. Martinez FO, Helming L, Gordon S. Alternative activation of macrophages: an immunologic functional perspective. Annu Rev Immunol. 2009; 27:451–483. http://dx.doi.org/10.1146/annurev.immunol.021908.132532 PMid:19105661. [PubMed: 19105661]
3. Gordon S. Alternative activation of macrophages. Nat Rev Immunol. 2003; 3:23–35. http://dx.doi.org/10.1038/nri978 PMid:12511873. [PubMed: 12511873]
4. Mantovani A, Sica A, Sozzani S, Allavena P, Vecchi A, Locati M. The chemokine system in diverse forms of macrophage activation and polarization. Trends Immunol. 2004; 25:677–686. http://dx.doi.org/10.1016/j.it.2004.09.015 PMid:15530839. [PubMed: 15530839]
5. Mosser DM, Edwards JP. Exploring the full spectrum of macrophage activation. Nat Rev Immunol. 2008; 8:958–969. http://dx.doi.org/10.1038/nri2448 PMid:19029990 PMCid:PMC2724991. [PubMed: 19029990]
6. Conrad DJ, Kuhn H, Mulkins M, Highland E, Sigal E. Specific inflammatory cytokines regulate the expression of human monocyte 15-lipoxygenase. Proc. Natl. Acad. Sci. USA. 1992; 89:217–221. http://dx.doi.org/10.1073/pnas.89.1.217. [PubMed: 1729692]
7. Nassar GM, Morrow JD, Roberts LJ 2nd, Lakkis FG, Badr KF. Induction of 15-lipoxygenase by interleukin-13 in human blood monocytes. J Biol Chem. 1994; 269:27631–27634. PMid:7961680. [PubMed: 7961680]
8. Gratchev A, Guillot P, Hakiy N, Politz O, Orfanos CE, Schledzewski K, et al. Alternatively activated macrophages differentially express fibronectin and its splice variants and the extracellular matrix protein betaIG-H3. Scand J Immunol. 2001; 53:386–392. http://dx.doi.org/10.1046/j.1365-3083.2001.00885.x PMid:11285119. [PubMed: 11285119]
9. Chaitidis P, Billett EE, O'Donnell VB, Fajardo AB, Fitzgerald J, Kuban RJ, et al. Th2 response of human peripheral monocytes involves isoform-specific induction of monoamine oxidase-A. J Immunol. 2004; 173:4821–4827. http://dx.doi.org/10.4049/jimmunol.173.8.4821 PMid:15470022. [PubMed: 15470022]
10. Chaitidis P, O'Donnell V, Kuban RJ, Bermudez-Fajardo A, Ungethuem U, Kuhn H. Gene expression alterations of human peripheral blood monocytes induced by medium-term treatment with the TH2-cytokines interleukin-4 and-13. Cytokine. 2005; 30:366–377. http://dx.doi.org/10.1016/j.cyto.2005.02.004 PMid:15869882. [PubMed: 15869882]
11. Berry A, Balard P, Coste A, Olagnier D, Lagane C, Authier H, et al. IL-13 induces expression of CD36 in human monocytes through PPARgamma activation. Eur J Immunol. 2007; 37:1642–1652. http://dx.doi.org/10.1002/eji.200636625 PMid:17458857. [PubMed: 17458857]
12. Bhattacharjee A, Pal S, Feldman GM, Cathcart MK. Hck is a key regulator of gene expression in alternatively activated human monocytes. J Biol Chem. 2011; 286:36709–36723. http://dx.doi.org/10.1074/jbc.M111.291492 PMid:21878628 PMCid:PMC3196116. [PubMed: 21878628]

13. Yakubenko VP, Bhattacharjee A, Pluskota E, Cathcart MK. αMβ2 integrin activation prevents alternative activation of human and murine macrophages and impedes foam cell formation. Circ Res. 2011; 108:544–554. http://dx.doi.org/10.1161/CIRCRESAHA.110.231803 PMid:21252155 PMCid:PMC3080038. [PubMed: 21252155]
14. Bhattacharjee A, Shukla M, Yakubenko VP, Mulya A, Kundu S, Cathcart MK. IL-4 and IL-13 employ discrete signaling pathways for target gene expression in alternatively activated monocytes/macrophages. Free Radic Biol Med. 2013; 54:1–16. http://dx.doi.org/10.1016/j.freeradbiomed.2012.10.553 PMid:23124025 PMCid:PMC3534796. [PubMed: 23124025]
15. Moskvitina TA, Medvedev AE. Different sensitivity of mitochondrial and cytosolic monoamine oxidases to in vivo but not in vitro inhibition by specific irreversible inhibitors. Med Sci Monit. 2001; 7:17–19. PMid:11208486. [PubMed: 11208486]
16. Singer TP, Ramsay RR. Flavoprotein structure and mechanism 2. Monoamine oxidases: old friends hold many surprises. FASEB J. 1995; 9:605–610. PMid:7768351. [PubMed: 7768351]
17. Wouters J. Structural aspects of monoamine oxidase and its reversible inhibition. Curr Med Chem. 1998; 5:137–162. PMid:9481038. [PubMed: 9481038]
18. Scrutton NS. Chemical aspects of amine oxidation by flavoprotein enzymes. Nat Prod Rep. 2004; 21:722–730. http://dx.doi.org/10.1039/b306788m PMid:15565251. [PubMed: 15565251]
19. Wang CC, Borchert A, Ugun-Klusek A, Tang LY, Lui WT, Chu CY, et al. Monoamine oxidase A expression is vital for embryonic brain development by modulating developmental apoptosis. J Biol Chem. 2011; 286:28322–28330. http://dx.doi.org/10.1074/jbc.M111.241422 PMid:21697081 PMCid:PMC3151076. [PubMed: 21697081]
20. Meyer JH, Ginovart N, Boovariwala A, Sagrati S, Hussey D, Garcia A, et al. Elevated monoamine oxidase a levels in the brain: an explanation for the monoamine imbalance of major depression. Arch Gen Psychiatry. 2006; 63:1209–1216. http://dx.doi.org/10.1001/archpsyc.63.11.1209 PMid:17088501. [PubMed: 17088501]
21. Schwartz TL. A neuroscientific update on monoamine oxidase and its inhibitors. CNS Spectr. 2013; (Suppl 1):25–32. PMid:24252505. [PubMed: 24252505]
22. Naoi M, Maruyama W, Akao Y, Yi H, Yamaoka Y. Involvement of type A monoamine oxidase in neurodegeneration: regulation of mitochondrial signaling leading to cell death or neuroprotection. J Neural Transm Suppl. 2006; 71:67–77. http://dx.doi.org/10.1007/978-3-211-33328-0_8 PMid:17447417. [PubMed: 17447417]
23. Ou XM, Chen K, Shih JC. Monoamine oxidase A and repressor R1 are involved in apoptotic signaling pathway. Proc Natl Acad Sci USA. 2006; 103:10923–10928. http://dx.doi.org/10.1073/pnas.0601515103 PMid:16829576 PMCid:PMC1544150. [PubMed: 16829576]
24. Brunner HG, Nelen M, Breakefield XO, Ropers HH, van Oost BA. Abnormal behavior associated with a point mutation in the structural gene for monoamine oxidase A. Science. 1993; 262:578–580. http://dx.doi.org/10.1126/science.8211186 PMid:8211186. [PubMed: 8211186]
25. Shih JC, Chen K, Ridd MJ. Role of mao a and b in neurotransmitter metabolism and behavior. Pol J Pharmacol. 1999; 51:25–29. PMid:10389141. [PubMed: 10389141]
26. Adeghate E, Parvez H. The effect of diabetes mellitus on the morphology and physiology of monoamine oxidase in the pancreas. NeuroToxicology. 2004; 25:167–173. http://dx.doi.org/10.1016/S0161-813X(03)00091-3. [PubMed: 14697891]
27. Panagiotidis G, Lindstrom P, Stenstrom A, Lundquist I. Glucose modulation of islet monoamine oxidase activity in lean and obese hyperglycemic mice. Metabolism. 1993; 42:1398–1404. http://dx.doi.org/10.1016/0026-0495(93)90189-U. [PubMed: 8231833]
28. Huang L, Frampton G, Rao A, Zhang KS, Chen W, Lai JM, et al. Monoamine oxidase A expression is suppressed in human cholangiocarcinoma via coordinated epigenetic and IL-6-driven events. Laboratory Investigation. 2012; 92:1451–1460. http://dx.doi.org/10.1038/labinvest.2012.110 PMid:22906985 PMCid:PMC3959781. [PubMed: 22906985]
29. Bianchi P, Kunduzova O, Masini E, Cambon C, Bani D, Raimondi L, et al. Oxidative stress by monoamine oxidase mediates receptor-independent cardiomyocyte apoptosis by serotonin and postischemic myocardial injury. Circulation. 2005; 112:3297–3305. http://dx.doi.org/10.1161/CIRCULATIONAHA.104.528133 PMid:16286591. [PubMed: 16286591]

30. Kaludercic N, Carpi A, Menabo R, Di Lisa F, Paolocci N. Monoamine oxidases (MAO) in the pathogenesis of heart failure and ischemia/reperfusion injury. Biochim Biophys Acta. 2011; 1813:1323–1332. http://dx.doi.org/10.1016/j.bbamcr.2010.09.010 PMid:20869994 PMCid:PMC3030628. [PubMed: 20869994]

31. Pchejetski D, Kunduzova O, Dayon A, Calise D, Seguelas MH, Leducq N, et al. Oxidative stress-dependent sphingosine kinase-1 inhibition mediates monoamine oxidase A-associated cardiac cell apoptosis. Circ Res. 2007; 100:41–49. http://dx.doi.org/10.1161/01.RES.0000253900.66640.34 PMid:17158340. [PubMed: 17158340]

32. Coatrieux C, Sanson M, Negre-Salvayre A, Parini A, Hannun Y, Itohara S, et al. MAO-A-induced mitogenic signaling is mediated by reactive oxygen species, MMP-2, and the sphingolipid pathway. Free Radic Biol Med. 2007; 43:80–89. http://dx.doi.org/10.1016/j.freeradbiomed.2007.03.036 PMid:17561096. [PubMed: 17561096]

33. Zhao J, Forsberg CW, Goldberg J, Smith NL, Vaccarino V. MAO-A promoter methylation and susceptibility to carotid atherosclerosis: role of familial factors in a monozygotic twin sample. BMC Med Genet. 2012; 13:100. http://dx.doi.org/10.1186/1471-2350-13-100 PMid:23116433 PMCid:PMC3532355. [PubMed: 23116433]

34. Gordon S, Martinez FO. Alternative activation of macrophages. Mechanism and functions. Immunity. 2010; 32:593–604. http://dx.doi.org/10.1016/j.immuni.2010.05.007 PMid:20510870. [PubMed: 20510870]

35. Roy B, Bhattacharjee A, Xu B, Ford D, Maizel AL, Cathcart MK. IL-13 signal transduction in human monocytes: phosphorylation of receptor components, association with Jaks, and phosphorylation/activation of Stats. J Leukocyte Biol. 2002; 72:580–589. PMid:12223527. [PubMed: 12223527]

36. Heller NM, Qi X, Junttila IS, Shirey KA, Vogel SN, Paul WE, et al. Type I. IL-4Rs selectively activate IRS-2 to induce target gene expression in macrophages. Sci Signaling. 2008; 1:ra17. http://dx.doi.org/10.1126/scisignal.1164795 PMid:19109239 PMCid:PMC2739727.

37. LaPorte SL, Juo ZS, Vaclavikova J, Colf LA, Qi X, Heller NM, et al. Molecular and structural basis of cytokine receptor pleiotropy in the interleukin-4/13 system. Cell. 2008; 132:259–272. http://dx.doi.org/10.1016/j.cell.2007.12.030 PMid:18243101 PMCid:PMC2265076. [PubMed: 18243101]

38. Miyazaki T, Kawahara A, Fujii H, Nakagawa Y, Minami Y, Liu ZJ, et al. Functional activation of Jak1 and Jak3 by selective association with IL-2 receptor subunits. Science. 1994; 266:1045–1047. http://dx.doi.org/10.1126/science.7973659 PMid:7973659. [PubMed: 7973659]

39. Dawson CH, Brown BL, Dobson PR. A 70-kDa protein facilitates interleukin-4 signal transduction in the absence of the common γ receptor chain. Biochem Biophys Res Commun. 1997; 233:279–282. http://dx.doi.org/10.1006/bbrc.1997.6397 PMid:9144438. [PubMed: 9144438]

40. Bhattacharjee A, Xu B, Frank DA, Feldman GM, Cathcart MK. Monocyte 15-lipoxygenase expression is regulated by a novel cytosolic signaling complex with protein kinase C delta and tyrosine-phosphorylated Stat3. J Immunol. 2006; 177:3771–3781. http://dx.doi.org/10.4049/jimmunol.177.6.3771 PMid:16951338. [PubMed: 16951338]

41. Xu B, Bhattacharjee A, Roy B, Xu HM, Anthony D, Frank DA, et al. Interleukin-13 induction of 15-lipoxygenase gene expression requires p38 mitogen-activated protein kinase mediated serine 727 phosphorylation of Stat1 and Stat3. Mol Cell Biol. 2003; 23:3918–3928. http://dx.doi.org/10.1128/MCB.23.11.3918-3928.2003 PMid:12748293 PMCid:PMC155212. [PubMed: 12748293]

42. Xu B, Bhattacharjee A, Roy B, Feldman GM, Cathcart MK. Role of protein kinase C isoforms in the regulation of interleukin-13-induced 15-lipoxygenase gene expression in human monocytes. J Biol Chem. 2004; 279:15954–15960. http://dx.doi.org/10.1074/jbc.M400413200 PMid:14757756. [PubMed: 14757756]

43. Bhattacharjee A, Mulya A, Pal S, Roy B, Feldman GM, Cathcart MK. Monocyte 15-lipoxygenase gene expression requires ERK1/2 MAPK activity. J Immunol. 2010; 185:5211–5224. http://dx.doi.org/10.4049/jimmunol.1000514 PMid:20861348 PMCid:PMC3061395. [PubMed: 20861348]

44. Liao X, Sharma N, Kapadia F, Zhou G, Lu Y, Hong H, et al. Kruppel-like factor 4 regulates macrophage polarization. J Clin Invest. 2011; 121:2736–2749. http://dx.doi.org/10.1172/JCI45444 PMid:21670502 PMCid:PMC3223832. [PubMed: 21670502]

45. Date D, Das R, Narla G, Simon DI, Jain MK, Mahabeleshwar GH. Kruppel-like transcription factor 6 regulates inflammatory macrophage polarization. J Biol Chem. 2014; 289:10318–10329. http://dx.doi.org/10.1074/jbc.M113.526749 PMid:24385430. [PubMed: 24385430]
46. Krieglstein CF, Granger DN. Adhesion molecules and their role in vascular disease. Am J Hypertens. 2001; 14:44S–54S. http://dx.doi.org/10.1016/S0895-7061(01)02069-6. [PubMed: 11411765]
47. Yakubenko VP, Hsi LC, Cathcart MK, Bhattacharjee A. From macrophage interleukin-13 receptor to foam cell formation: mechanisms for αMβ2 integrin interference. J Biol Chem. 2013; 288:2778–2788. http://dx.doi.org/10.1074/jbc.M112.381343 PMid:23184931 PMCid:PMC3554943. [PubMed: 23184931]
48. Huang JT, Welch JS, Ricote M, Binder CJ, Willson TM, Kelly C, et al. Interleukin-4-dependent production of PPAR-γ ligands in macrophages by 12/15-lipoxygenase. Nature. 1999; 400:378–382. http://dx.doi.org/10.1038/22572 PMid:10432118. [PubMed: 10432118]
49. Waku T, Shiraki T, Oyama T, Maebara K, Nakamori R, Morikawa K. The nuclear receptor PPARgamma individually responds to serotonin- and fatty acid-metabolites. EMBO J. 2010; 29:3395–3407. http://dx.doi.org/10.1038/emboj.2010.197 PMid:20717101 PMCid:PMC2957204. [PubMed: 20717101]
50. Czimmerer Z, Varga T, Poliska S, Nemet I, Szanto A, Nagy L. Identification of novel markers of alternative activation and potential endogenous PPARγ ligand production mechanisms in human IL-4 stimulated differentiating macrophages. Immunobiology. 2012; 217:1301–1314. http://dx.doi.org/10.1016/j.imbio.2012.08.270 PMid:22954708. [PubMed: 22954708]
51. Bouhlel MA, Derudas B, Rigamonti E, Dièvart R, Brozek J, Haulon S, et al. PPARgamma activation primes human monocytes into alternative M2 macrophages with anti-inflammatory properties. Cell Metab. 2007; 6:137–143. http://dx.doi.org/10.1016/j.cmet.2007.06.010 PMid:17681149. [PubMed: 17681149]
52. Martinez-Nunez RT, Louafi F, Sanchez-Elsner T. The interleukin 13 (IL-13) pathway in human macrophages is modulated by microRNA-155 via direct targeting of interleukin 13 receptor alpha1 (IL13R{alpha}1). J Biol Chem. 2011; 286:1786–1794. http://dx.doi.org/10.1074/jbc.M110.169367 PMid:21097505 PMCid:PMC3023473. [PubMed: 21097505]
53. O'Connell RM, Taganov KD, Boldin MP, Cheng G, Baltimore D. MicroRNA-155 is induced during the macrophage inflammatory response. Proc Natl Acad Sci USA. 2007; 104:1604–1609. http://dx.doi.org/10.1073/pnas.0610731104 PMid:17242365 PMCid:PMC1780072. [PubMed: 17242365]
54. Lu LF, Thai TH, Calado DP, Chaudhry A, Kubo M, Tanaka K, et al. Foxp3-dependent microRNA155 confers competitive fitness to regulatory T cells by targeting SOCS1 protein. Immunity. 2009; 30:80–91. http://dx.doi.org/10.1016/j.immuni.2008.11.010 PMid:19144316 PMCid:PMC2654249. [PubMed: 19144316]
55. McCoy CE, Sheedy FJ, Qualls JE, Doyle SL, Quinn SR, Murray PJ, et al. IL-10 inhibits miR-155 induction by toll-like receptors. J Biol Chem. 2010; 285:20492–20498. http://dx.doi.org/10.1074/jbc.M110.102111 PMid:20435894 PMCid:PMC2898307. [PubMed: 20435894]
56. Heydeck D, Thomas L, Schnurr K, Trebus F, Thierfelder WE, Ihle JN, et al. Interleukin-4 and -13 induce upregulation of the murine macrophage 12/15-lipoxygenase activity: evidence for the involvement of transcription factor STAT6. Blood. 1998; 92:2503–2510. PMid:9746791. [PubMed: 9746791]
57. Conrad DJ, Lu M. Regulation of human 12/15-lipoxygenase by Stat6-dependent transcription. Am J Respir Cell Mol Biol. 2000; 22:226–234. http://dx.doi.org/10.1165/ajrcmb.22.2.3786. [PubMed: 10657944]
58. Chaitidis P, Billett E, Kuban RJ, Ungethuem U, Kuhn H. Expression regulation of MAO isoforms in monocytic cells in response to Th2 cytokines. Med Sci Monit. 2005; 11:BR259–BR265. PMid: 16049371. [PubMed: 16049371]
59. Pichler R, Maschek W, Krieglsteiner S, Raml A, Schmekal B, Berg J. Pro-inflammatory role of serotonin and interleukin-6 in arthritis and spondyloarthropathies-measurement of disease activity by bone scan and effect of steroids. Scand J Rheumatol. 2002; 31:41–43. http://dx.doi.org/10.1080/030097402317255363 PMid:11922199. [PubMed: 11922199]

60. Mossner R, Lesch KP. Role of serotonin in the immune system and in neuroimmune interactions. Brain Behav Immun. 1998; 12:249–271. http://dx.doi.org/10.1006/brbi.1998.0532 PMid: 10080856. [PubMed: 10080856]

61. Freire-Garabal M, Nunez MJ, Balboa J, Lopez-Delgado P, Gallego R, Garcia-Caballero T, et al. Serotonin upregulates the activity of phagocytosis through 5-HT1A receptors. Br J Pharmacol. 2003; 139:457–463. http://dx.doi.org/10.1038/sj.bjp.0705188 PMid:12770951 PMCid:PMC1573834. [PubMed: 12770951]

62. Vega A, Chacón P, Monteseirín J, El Bekay R, Alvarez M, Alba G, et al. A new role for monoamine oxidases in the modulation of macrophage-inducible nitric oxide synthase gene expression. J Leukoc Biol. 2004; 75:1093–1101. http://dx.doi.org/10.1189/jlb.1003459 PMid: 15075350. [PubMed: 15075350]

63. Khan N, Rahim SS, Boddupalli CS, Ghousunnissa S, Padma S, Pathak N, et al. Hydrogen peroxide inhibits IL-12 p40 induction in macrophages by inhibiting c-rel translocation to the nucleus through activation of calmodulin protein. Blood. 2006; 107:1513–1520. http://dx.doi.org/10.1182/blood-2005-04-1707 PMid:16249388. [PubMed: 16249388]

64. Murthy S, Ryan A, He C, Mallampalli RK, Carter AB. Rac1-mediated Mitochondrial H2O2, Generation Regulates MMP-9 Gene Expression in Macrophages via Inhibition of SP-1 and AP-1. J Biol Chem. 2010; 285:25062–25073. http://dx.doi.org/10.1074/jbc.M109.099655 PMid:20529870 PMCid:PMC2915742. [PubMed: 20529870]

65. Varga T, Czimmerer Z, Nagy L. PPARs are a unique set of fatty acid regulated transcription factors controlling both lipid metabolism and inflammation. Biochim. Biophys. Acta. 2011; 1812:1007–1022. [PubMed: 21382489]

66. Nagy L, Szanto A, Szatmari I, Széles L. Nuclear hormone receptors enable macrophages and dendritic cells to sense their lipid environment and shape their immune response. Physiol Rev. 2012; 92:739–789. http://dx.doi.org/10.1152/physrev.00004.2011 PMid:22535896. [PubMed: 22535896]

67. Odegaard JI, Ricardo-Gonzalez RR, Goforth MH, Morel CR, Subramanian V, Mukundan L, et al. Macrophage-specific PPARgamma controls alternative activation and improves insulin resistance. Nature. 2007; 447:1116–1120. http://dx.doi.org/10.1038/nature05894 PMid:17515919 PMCid:PMC2587297. [PubMed: 17515919]

68. Szanto A, Balint BL, Nagy ZS, Barta E, Dezso B, Pap A, et al. STAT6 transcription factor is a facilitator of the nuclear receptor PPARgamma-regulated gene expression in macrophages and dendritic cells. Immunity. 2010; 33:699–712. http://dx.doi.org/10.1016/j.immuni.2010.11.009 PMid:21093321 PMCid:PMC3052437. [PubMed: 21093321]

69. Martinez FO, Gordon S, Locati M, Mantovani A. Transcriptional profiling of the human monocyte-to-macrophage differentiation and polarization: new molecules and patterns of gene expression. J Immunol. 2006; 177:7303–7311. http://dx.doi.org/10.4049/jimmunol.177.10.7303 PMid:17082649. [PubMed: 17082649]