# Lectin-type oxidized LDL receptor 1 defines a population of polymorphonuclear myeloid-derived suppressor cells in cancer patients

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**Polymorphonuclear myeloid-derived suppressor cells (PMN-MDSC) are important regulators of immune responses and tumor progression in most types of cancer[1]. The heterogeneity of these cells and the nature of their distinction from neutrophils are major challenges in evaluation of these cells. Whole genome array of PMN-MDSC and neutrophils isolated from the same cancer patients demonstrated that PMN-MDSC had a distinct gene signature with most prominent changes in genes associated with endoplasmic reticulum (ER) stress response, whereas neutrophils from cancer patients and healthy donors had similar profile. Surprisingly, LDL was most enriched gene regulator and oxidized LDL receptor 1 *(OLR1)* was one of the most overexpressed genes in PMN-MDSC. Lectin-type oxidized LDL receptor 1 (LOX-1) encoded by *OLR1* was expressed in only 0.7% of neutrophils in peripheral blood of healthy donors, whereas 5-15% of neutrophils in cancer patients and 15-40% of neutrophils in tumor tissues were LOX-1$^+$. In contrast to their LOX-1$^-$ counterparts, LOX-1$^+$ neutrophils had PMN-MDSC gene signature, expressed ER-stress genes, arginase (*ARG 1)*, produced high levels of reactive oxygen species (ROS) and suppressed T-cell responses. Thus, LOX-1 defines the population of PMN-MDSC in cancer patients and may provide new insight to the biology and clinical evaluation of these cells.**

MDSC are an~~is~~ important component of the tumor microenvironment. In addition to their immune suppressive activity, MDSC support tumor progression by promoting angiogenesis, tumor cell survival, invasion, and metastases (reviewed in [2]). There is~~are~~ now ample evidence of the association of MDSC accumulation with negative clinical outcomes in various cancers[3]. MDSC have been implicated in resistance to anticancer therapies with kinase inhibitor[4], chemotherapy [5-8], and immune therapy [9-13]. MDSC are a heterogeneous population of immature pathologically activated myeloid cells. They include two large populations: PMN-MDSC and monocytic cells (M-MDSC) as well as smaller population of early precursors (eMDSC)[14]. PMN-MDSC form~~is~~ the most abundant population of MDSC (up to 80%) in most types of cancer, are phenotypically and morphologically similar to neutrophils (PMN) and are usually associated with high levels of ROS production and Arg1 activity[15]. These cells share $CD11b^{+}CD14^{-}CD15^{+}/CD66b^{+}$ phenotype with neutrophils but in contrast to PMN, these cells are isolated from PBMC as low density cells. Similarity of PMN-MDSC with PMN raised the questions of biological distinction of these cells and precise clinical relevance of PMN-MDSC, especially in the tumor site. Currently, these cells can be separated only in peripheral blood (PB) and only by using density gradient, which most likely results in cross-contamination of populations of PMN and PMN-MDSC.

In an attempt to characterize PMN-MDSC, we isolated PMN-MDSC and PMN from PB of the same patients with head and neck (HNC) and non-small cell lung cancer (NSCLC) using Histopaque gradient. As a control PMN from healthy donors were used. Both, low-density PMN MDSCs and high-density PMN were further purified with CD15 magnetic beads, which resulted in high purity of cells with phenotype and morphology of neutrophils **(Fig. 1a, b)**. PMN-MDSC, in contrast to PMN, suppressed T-cell proliferation in allogeneic mixed leukocyte reaction (MLR) **(Fig. 1c)** or induced by CD3/CD28 antibodies **(Fig. 1d)**.

**Commented [KSC1]:** Do you obtain PMN-MDSC from controls?

We compared global gene expression in PMN and PMN-MDSC using Illumina HumanWG 12v4 human whole-genome bead arrays. Hierarchical clustering of the samples using expression of the 985 most changed (fold > 2) significant genes (nominal $p<0.05$) revealed that PMN-MDSC samples have a unique expression profile and PMN from cancer patients are very similar to healthy donor PMN samples, as they grouped within the same cluster (**Figure 1e,f**). Specifically, of the 985 genes, the majority (74%) showed significant difference (false discovery rate, FDR<5%) between patients' PMN-MDSC and PMN, while only 12% of the genes were significantly different between PMN from healthy donors and PMN from cancer patients with nominal $p<0.05$ and none were significant when results were corrected for multiple testing (best FDR=19%) indicating high similarity of PMN samples between cancer patients and healthy donors.

The comparison identified at least 1870 array probes significantly differentially expressed between PMN-MDSC and PMN in the same patients (FDR<5%). While the majority of probes had expression differences of less than 50%, there were 751 probes with 1.5 fold or more, mostly upregulated in PMN-MDSC (**Figure S1a**) with 36 probes (30 unique known genes) different at least 5 fold (**Figure S1b**).

Using Ingenuity Pathway Analysis, we analyzed probes with 1.5-fold differences for enrichment of cellular functions, canonical pathways and for possible upstream regulators responsible for observed target gene expression changes. There were 34 pathways with nominal statistically significant enrichment in PMN-MDSCs. They include eukaryotic Translation Initiation Factors 2 and 4 (eIF2 and eIF4) pathways, mTOR signaling **(Fig. S2a)**. The regulators of genes enriched in PMN-MDSC included regulators of ER stress response, MAPK pathway, CTNNB1 (β-catenin), HIF-1α, CSF1, IFN-γ and other **(Fig. S2b)**. Surprisingly, the most significant changes were associated with low-density lipoprotein (LDL) **(Fig. S2b)**. Thus, PMN-MDSC had enriched for

probes associated with ER stress response, which is consistent with recent observations on up-regulation of ER-stress in MDSC[16].

To search for potential marker of PMN-MDSC we evaluated differentially expressed genes, which encoded surface molecules (**Fig. 1g**) and compared expression of various surface molecules between PMN-MDSC and PMN from the same patients and PMN from healthy donors (**Fig. S3a**). Unexpectedly, the differences were found in the expression of lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1), a 50kDa transmembrane glycoprotein encoded by the *OLR1* gene (oxidized LDL receptor 1)[17]. In our analysis *OLR1* was one of the mostly up-regulated genes in PMN-MDSC (**Fig. S1 and Fig. 1g).** LOX-1 is one of the main receptor for oxidized-LDL (oxLDL)[18]. It also binds other ligands including other modified lipoproteins, advanced glycation end products, aged red blood cells, apoptotic cells and activated platelets [19]. LOX-1 is expressed on endothelial cells, macrophages, smooth muscle cells, and some intestinal cell lines[17]. However, it has not been associated with neutrophils or monocytes.

In our study, LOX-1 was practically undetectable on PMN but expressed in about 1/3 of PMN-MDSC (**Fig. S3b and Fig. 2a**). Since LOX-1 can be expressed on platelets[20] and it is known that platelets could adhere to activated PMN we asked whether increased expression of LOX-1 in PMN-MDSC fraction was the result of increased adherence of platelets. However, LOX-1$^-$ and LOX-1$^+$ cells in PMN-MDSC from cancer patients had the same small proportion of cells that express platelets markers CD41a and CD42b **(Fig. S3c)**.

These results suggested that LOX-1 could be associated with PMN-MDSC. It is likely that gradient centrifugation may enrich not only for PMN-MDSC but also for activated PMN without suppressive activity. In addition, some PMN-MDSC could retain high density. Therefore, we investigated whether LOX-1 could identify PMN-MDSC in unseparated PB. PMN in PB were

directly labeled with CD15 and LOX-1 and the proportion of LOX-1$^+$ cells among all PMN was calculated (**Fig. S4**). In preliminary experiments we compared the staining of neutrophils with CD15 and CD66b antibody and did not observe any difference (**data not shown**). The proportion of LOX-1$^+$ cells among all PMN in healthy donors was very low - 0.7% (range 0.1-1.5). In all three tested group of patients it was significantly increased. In patients with NSCLC it increased to 4.9% (range 0.9-11.9) ($p<0.001$) with 89% of patients having the proportion of LOX$^+$PMN above control values. In patients with HNC it increased to 6.4% (range 1.07-14.2) ($p<0.0001$) with 85% of patients having the proportion of LOX$^+$ PMN above control values. In patients with colon cancer (CC) it increased to 6.5% (range 0.31-26.8) ($p=0.0035$) with 71.4% of patients with LOX$^+$PMN above control values **(Fig. 2b)**. We assessed the changes in LOX-1$^+$ PMN in tumor-free patients with intestinal inflammatory conditions: eosinophilic colitis, ulcerative colitis, and Crohn's disease. No changes in the presence of LOX-1$^+$ cells among PMN were observed in patients with eosinophilic and ulcerative colitis. Patients with Crohn's disease, however, had moderate increase in the proportion of these cells (**Fig. 2c**).

Next, we addressed the question whether LOX-1$^+$ PMN were true PMN-MDSC. LOX-1$^+$ and LOX-1$^-$ PMN were sorted directly from PB of patients with NSCLC and CC. LOX-1$^-$PMN had typical morphology of mature neutrophils, whereas LOX-1$^+$ PMN displayed more immature morphology with band shape nuclei (**Fig. 2d**). Whole genome array was performed on LOX-1$^+$ and LOX-1$^-$ PMN and compared with that of PMN and PMN-MDSC (**Fig. 1**). Analysis of gene expression showed that LOX-1$^+$ PMN clustered together with PMN-MDSC, whereas LOX-1$^-$ PMN were very similar to healthy donor PMN (**Fig. 2e**). Ninety three genes (FDR <5%) overlapped between PMN-MDSC and LOX-1$^+$ PMN (**Fig. 2f**). Thus, LOX-1$^+$ PMN from cancer patients had similar genomic signature to PMN-MDSC. LOX-1$^+$ PMN had significantly higher

expression of *ARG1* (>5-fold), the gene directly associated with PMN-MDSC function, than LOX-1$^-$ PMN **(Fig. 2f)**. No differences were found in the expression of *NOS2* (**data not shown)**, which was consistent with relatively low role of iNOS in PMN-MDSC[1].

The hallmark of PMN-MDSC is their ability to suppress T-cell function. We isolated LOX-1$^-$ and LOX-1$^+$ PMN directly from PB of cancer patients and used them in T-cell suppression assay. LOX-1$^+$ PMN suppressed T-cell proliferation, whereas LOX-1$^-$ PMN did not (**Fig. 2g**). LOX-1$^+$ PMN had significantly higher ROS production than LOX-1$^-$ PMN MDSC (**Fig. 2h**), another hallmark of PMN-MDSC. Thus, taken together these data demonstrate that LOX-1$^+$ PMN indeed represent the population of PMN-MDSC.

We asked whether LOX-1 antibody used for isolation of PMN-MDSC could directly affect functional activity of PMN. PMN from cancer patients were cultured with T cells in the presence of LOX-1 antibody or IgG. LOX-1 antibody did not make PMN immune suppressive (**Fig. S5**).

Next, we tested the contribution of ROS to immune suppression mediated by LOX-1$^+$ PMN-MDSC. Both, ROS scavenger *N*-acetylcysteine (NAC) and catalase cancelled LOX-1$^+$PMN-MDSC mediated suppression (**Fig. 3a**).

What could induce LOX-1 up-regulation in PMN-MDSC? Based on the fact that in endothelial cells LOX-1 can be induced by pro-inflammatory cytokines[21], we tested the effect of several pro-inflammatory cytokines as well as tumor-cell conditioned medium (TCM) on LOX-1 expression in PMN obtained from healthy donors. None of tested pro-inflammatory cytokines (IL-1β, TNFα, IL-6) or TCM induced upregulation of LOX-1 in PMN after 24 hr culture with GM-CSF (**Fig. 3b**).

Our previous observations[16] and data obtained in this study demonstrated that PMN-MDSC in cancer patients displayed signs of ER stress response. It was recently demonstrated that in human endothelial cells oxLDL induced expression of LOX-1 through activation of ER stress sensors

IRE1 and PERK[22]. In contrast, ER stress induced by tunicamycin (TM) in hepatic L02 cells caused down-regulation of LOX-1. Knock down of IRE1 or XBP-1 restored LOX-1 expression in TM-treated cells[23]. To test whether ER stress is directly associated with PMN-MDSC, LOX-1$^+$ and LOX-1$^-$ PMN were isolated from PB of cancer patients and expression of genes associated with ER-stress were evaluated. LOX-1$^+$PMN-MDSC had significantly ($p<0.01$) higher expression of *sXBP1* and less prominent up-regulation of *ATF4* than LOX-1$^-$ PMN. No changes in the expression of *CHOP* were observed (**Fig. 3c**). To test the effect of ER-stress on expression of LOX-1, PMN from healthy donors were treated with ER stress inducers: thapsigardin (THG) or dithiothreitol (DTT) overnight in the presence of GM-CSF. At selected doses (THG -1 μM, DTT – 1mM) cell viability remained above 95%. Both, THG and DTT caused dramatic up-regulation of LOX-1 expression in PMN **(Fig. 3d)**. THG treatment of PMN overnight caused acquisition of potent immune suppressive activity by PMN (**Fig. 3e**). To verify the role of ER stress in this phenomenon we used recently developed selective inhibitor of sXBP – BI09[24]. In the presence of BI09 THG failed to induce up-regulation of LOX-1 (**Fig. 3f**) and suppressive activity of PMN (**Fig. 3g**).

We investigated the possible role of LOX-1 in mouse PMN-MDSC. Similar to human PMN, CD11b$^+$Ly6C$^{lo}$Ly6G$^+$ mouse PMN had very low expression of LOX-1. However, in contrast to human PMN-MDSC, spleen, BM, or tumor PMN-MDSC from mice bearing EL-4 lymphoma, Lewis Lung Carcinoma (LLC) or transgenic Ret melanoma did not up-regulate LOX-1 (**data not shown).** Lethally irradiated wild-type recipients were reconstituted with congenic bone marrow cells isolated from wild-type or LOX-1 knockout *(Olr1$^{-/}$)* mice. Ten weeks after reconstitution donor's cells represented more than 95% of all myeloid cells (**data not shown**). LLC tumor was implanted s.c. and mice evaluated 3 weeks later. No differences in the presence of PMN-MDSC in spleens or tumors were observed between mice reconstituted with WT and LOX-1 KO BM (**Fig.**

**S6a**). WT and *Olr1*$^{-/-}$ PMN-MDSC equally well suppressed T-cell proliferation (**Fig. S6b**). Gene expression profile demonstrated no differences between WT and *Olr1*$^{-/-}$ PMN-MDSC. Most importantly WT PMN-MDSC had the same undetectable level of *Olr1* as *Olr1*$^{-/-}$ PMN-MDSC (**data not shown**). Thus, in contrast to humans, mouse LOX-1 is not associated with PMN-MDSC.

It is known that LOX-1 is shaded from the surface of the cells and can be detected in plasma[25]. Since LOX-1$^+$ PMN-MDSC represent large number of cells in cancer patients, we evaluated correlation between the presence of LOX-1$^+$ PMN-MDSC and soluble LOX-1. In NSCLC and CC patients the proportion of PMN-MDSC strongly correlated with soluble LOX-1 (**Fig. 4a**) suggesting that these cells may be an important source of LOX-1 in plasma of cancer patients.

There are now enough evidence demonstrating that tumor MDSC are more suppressive than cells in PB (rev. in[26]). We asked whether population of PMN-MDSC is more prevalent among PMN in tumors than in PB. The proportion of LOX-1$^+$ cells among CD15$^+$ neutrophils isolated from tumors of patients with HNC and NSCLC was more than 3-fold higher than in CD15$^+$ neutrophils from PB of the same patients (**Fig. 4b**). Cells in blood and tumor tissues were subjected to the same digestion protocol. However, to exclude possible effect of tissue digestions and isolation on LOX-1 expression, we also evaluated patients with multiple myeloma (MM) where tumor is located in BM. Similar to solid tumors, the proportion of LOX-1$^+$ PMN-MDSC in BM was 3-4-fold higher than in PB of the same patients (**Fig. 4c**). LOX-1$^+$ PMN-MDSC isolated from BM of patients with MM had profound suppressive activity, whereas LOX-1$^-$ PMN did not suppress T cells (**Fig. 4d**) supporting the conclusion that LOX-1$^+$ PMN represent PMN-MDSC in tumor site.

We evaluated the link between stage of NSCLC patients and the proportion of PMN-MDSC. Patients with early (I/II) and late (III/IV) stages of the disease had significant increase in the proportion of LOX-1$^+$ PMN-MDSC ($p<0.01$). There was no statistical significant difference

between two groups of patients (**Fig. 4e**). However, patients with late stages of NSCLC had consistent increase in the presence of LOX-1$^+$PMN-MDSC (83.3% of all patients), whereas patients with early stages showed substantial heterogeneity (only 50% of patients had elevated proportion of PMN-MDSC). Further prospective studies are needed to determine whether this heterogeneity in PMN-MDSC accumulation is associated with clinical outcome.

Using ONCOMINE and TCGA databases we evaluated association of *OLR1* expression with clinical parameters in different types of cancer. Significant upregulation of *OLR1* was observed in many types of cancer (**Fig S7a**). Notable exception was lung cancer where normal lung tissues showed dramatically higher expression of *OLR1* than other normal tissues (**Fig. S7b**), apparently due to the presence of cells with high expression of *OLR1* (possibly lung epithelium). *OLR1* expression positively correlated with clinical stage in patients with bladder cancer, colon adenocarcinoma, and clear cell kidney cancer. Positive correlation with tumor size was found in patients with prostate adenocarcinoma and rectum adenocarcinoma. Higher expression of *OLR1* was associated with worse survival in patients with HNC (**Fig. S7c**). However, this analysis has rather limited value due to the fact that *OLR1* can be expressed on different cells in tumor microenvironment including tumors. Therefore, we have developed method of immune fluorescent staining of tissues with combination of LOX-1 and CD15 antibody (**Fig. 4f**). Control tissues from normal skin, colon and lymph nodes had similar amount of LOX-1$^+$CD15$^+$ PMN-MDSC (**Fig. 4g**). No statistical differences were found in the presence of these cells in melanoma samples, which is consistent with findings that M-MDSC but not PMN-MDSC were the predominant population of MDSC in these patients[3]. The number of LOX-1$^+$CD15$^+$ PMN-MDSC in colon carcinoma increased more than 8-fold, in HNC more than 10-fold, and in NSCLC almost 8-fold (**Fig. 4g**). The changes in CD15$^+$ cells were much less pronounced (**Fig. 4g**). Using NSCLC adenocarcinoma

tissue array we evaluated the association between PMN-MDSC and tumor size. Similar to the data obtained in PB no significant association was found with stage of the disease (**data not shown**). However, the number of LOX-1$^+$ PMN-MDSC was significantly higher in larger (T2 vs. T1) tumors. Such association was absent for total CD15$^+$ cells (**Fig. 4h**).

Thus, our data indicate that PMN-MDSC have unique gene expression signature different from that of PMN. This underscores the fact that PMN-MDSC represent the distinct functional state of pathological activation of neutrophils in cancer. Unexpectedly, genes regulated by LDL and specifically *OLR1* were prominently overexpressed in PMN-MDSC and LOX-1 was found to be specifically up-regulated on PMN-MDSC. Moreover, our analysis of gene expression signature, ROS production, and functional activity of these cells indicate that LOX-1 expression can define the population of PMN-MDSC in cancer patients. This allows for direct identification of PMN-MDSC in PB and tumor tissues without any additional purification steps and suggests an opportunity for more precise evaluation of these cells in pathological conditions.

These results open a question of potential role of LOX-1 mediated signaling in PMN pathology. Engagement of LOX-1 can lead to induction of oxidative stress, apoptosis, and activation of the NFκB pathway[17]. These pathways are ~~known to be~~ important for PMN-MDSC function. Interestingly, LOX-1 ~~has~~ also ~~been described to~~ plays a role in tumorigenesis [27]. LOX-1 up-regulation has been observed during cellular transformation into cancer cell and can have a pro-oncogenic effect by activating the NFκB pathway, by increasing DNA damage through increase ROS production and by promoting angiogenesis and cell dissemination [27,28]. It is possible that LOX-1 signaling may drive pathological activation of PMN towards PMN-MDSC. This hypothesis needs to be tested directly.

**Materials and Methods**

***Human Samples.*** Samples were collected from patients at H. Lee Moffitt Cancer Center and Helen F. Graham Cancer Center. The study was approved by Institutional Review Boards of the Christiana Care Health System at the Helen F. Graham Cancer Center, and The Wistar Institute. All patients signed approved consent forms. Peripheral blood and Tissue were collected from ?? subjects with previously untreated stage I-IV non-small cell lung cancer (NSCLC), head and neck cancer (HNC) and colon cancer (CC) at Helen F. Graham Cancer Center and the University of Pennsylvania. PB from ?? healthy donors was used as control.

All cell samples were analyzed within 3 hours following collection. PMN-MDSC were evaluated in mononuclear fraction of peripheral blood after ficoll density gradient. Neutrophils were evaluated from cell fraction remaining~~ed~~ after removal of mononuclear cells. The cells were resuspended in PBS and loaded on a step density gradient (Percoll 63% on top of Percoll 72%) to separate PMN in a monolayer in between the 2 Percoll phases.

***Cell isolation and culture:*** Human PMN-MDSC were isolated on gradient [29] followed by labeling with CD15-PE mAb (BD Biosciences) and then separated using anti-PE beads and MACS column (Miltenyi). Tissues were first digested with human tumor dissociation kit (Miltenyi) and then red blood cell lysed. Cells were then culture in RPMI (Biosource International) supplemented with 10% FBS, 5 mM glutamine, 25 mM HEPES, 50μM β-mercaptoethanol and 1% antibiotics (Invitrogen). In some experiments, recombinant GM-CSF was added to the culture media at a concentration of 10 ng/mL (peprotech).

***Flow cytometry:*** Flow cytometry data were acquired using a BD LSR II flow cytometer and analyzed using FlowJo software (Tree Star).

***Microarray analysis:*** For sample preparation and hybridization, total RNA from purified cells was isolated with TRIzol reagent according to the manufacturer's recommendations. RNA quality was assessed with a Bioanalyzer (Agilent). Only samples with RIN numbers>8 were used. Equal amounts (400 ng) of total RNA was amplified as recommended by Illumina and was hybridized to the Illumina HumanWG 12v4 human whole-genome bead arrays.

For data preprocessing, Illumina GenomeStudio software was used to export expression values and calculated detection p-values for each probe of each sample. Signal-intensity data were log2 transformed and quantile-normalized. Only probes with a significant detection p-value ($p < 0.05$) in at least one of sample were considered. The data was submitted to GEO and is accessible using accession number GSExxxx.

Differential expression for probes was tested using SAM ('significance analysis of microarrays') method [ref1]. Multiple groups were compared using "Multiclass" option and any two groups were compared using "Two sample unpaired" option. False discovery rate was estimated using Storey et. al procedure [ref2]. Genes with a false-discovery rate of <5% were considered significant unless stated otherwise. Enrichment analyses were done using QIAGEN's Ingenuity Pathway Analysis software (IPA®, QIAGEN Redwood City, www.qiagen.com/ingenuity).

***Statistics:*** Statistical analysis was performed using a 2-tailed Student's t-test and GraphPad Prism 5 software (GraphPad Software Inc.), with significance determined at $p < 0.05$.

Tumor measurements were analyzed using 2-way ANOVA test and t-test, with significance determined at $p<0.05$.

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**Figure Legend**

**Figure 1:**

**A.** Phenotype of PMN-MDSC and PMN from cancer patients

**B.** Microarray analysis. Samples clustering.

**C.** Microarray analysis. Pathway analysis.

**D.** Microarray analysis. Top genes upregulated in PMN-MDSC (surface receptor only).

**Figure 2:**

A-B. Expression of LOX1 in PMN and PMN-MDSC separated using Ficoll/percoll. A. one representative sample B. average of 15 patients and 3 healthy donors.

C-D. Whole blood analysis of LOX1 expression in PMN in Head and Neck cancer (HNC) patients. C. One representative patient. D. average of 14 HNC patients and 7 healthy donors.

E. LOX1 induction in PMN by pro-inflammatory factor.

F. Analysis of LOX1 expression in PMN from blood and tumor of matching patients.

G. Suppressive activity of PMN from blood versus PMN from tumor.

**Figure 3:**

A. Suppressive activity of LOX1+ versus LOX1- PMN from cancer patients. One experiment representative of 5 different one.

B. ROS production in LOX1+ versus LOX1- PMN from cancer patients (n=7).

C. Inhibition of suppressive activity with NAC.

D. microarray analysis of LOX1+ versus LOX1- PMN.

**Figure 4:**

A. LOX1 expression in patients with early or late stage lung cancer.

B. LOX1 expression in patients with early or late stage Colon cancer.

C. LOX1 expression in patients with inflammatory condition.

D. Correlation of soluble LOX1 in plasma of lung cancer patients with accumulation of PMN-MDSC (% of CD15+ cells in PBMC).

E. Correlation of soluble LOX1 in plasma of colon cancer patients with accumulation of PMN-MDSC (% of CD15+ cells in PBMC).

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