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Restoration of aberrant gene expression of monocytes in systemic lupus erythematosus via a combined transcriptome-reversal and network-based drug repurposing strategy

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Abstract

Background Monocytes -key regulators of the innate immune response- are actively involved in the pathogenesis of systemic lupus erythematosus (SLE). We sought to identify novel compounds that might serve as monocyte-directed targeted therapies in SLE.

Results We performed mRNA sequencing in monocytes from 15 patients with active SLE and 10 healthy individuals. Disease activity was assessed with the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2 K). Leveraging the drug repurposing platforms iLINCS, CLUE and L1000CDS^2, we identified perturbagens capable of reversing the SLE monocyte signature. We identified transcription factors and microRNAs (miRNAs) that regulate the transcriptome of SLE monocytes, using the TRRUST and miRWalk databases, respectively. A gene regulatory network, integrating implicated transcription factors and miRNAs was constructed, and drugs targeting central components of the network were retrieved from the DGIDb database. Inhibitors of the NF-κB pathway, compounds targeting the heat shock protein 90 (HSP90), as well as a small molecule disrupting the Pim-1/NFATc1/NLRP3 signaling axis were predicted to efficiently counteract the aberrant monocyte gene signature in SLE. An additional analysis was conducted, to enhance the specificity of our drug repurposing approach on monocytes, using the iLINCS, CLUE and L1000CDS^2 platforms on publicly available datasets from circulating B-lymphocytes, CD4$^+$ and CD8$^+$ T-cells, derived from SLE patients. Through this approach we identified, small molecule compounds, that could potentially affect more selectively the transcriptome of SLE monocytes, such as, certain NF-κB pathway inhibitors, Pim-1 and SYK kinase

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inhibitors. Furthermore, according to our network-based drug repurposing approach, an IL-12/23 inhibitor and an EGFR inhibitor may represent potential drug candidates in SLE.

Conclusions Application of two independent - a transcriptome-reversal and a network-based -drug repurposing strategies uncovered novel agents that might remedy transcriptional disturbances of monocytes in SLE.

Keywords Systemic lupus erythematosus, Monocytes, Drug repurposing, Micro RNAs, Transcription factors

Background

Monocytes and macrophages constitute a major cellular compartment derived from hematopoietic myeloid precursors. Monocyte-macrophage lineage cells exhibit versatile immunoregulatory, inflammatory and tissue repairing capabilities and play an instrumental role in the development of systemic lupus erythematosus (SLE) [1]. Data from murine and human SLE studies demonstrated that the polyclonal B cell hyperreactivity, an immunological hallmark of SLE, might be at least partially attributable to aberrations in monocyte-mediated CD40/CD40L co-stimulation [1–5]. Abnormal activation of autoreactive T and B cells in SLE could also be caused by deregulated cytokine production by monocytes. Monocytes in SLE display excess production of the B-lymphocyte stimulator (BLyS) which promotes the survival and proliferation of B cells [6]. Moreover, these cells are a major source of IL-10 and IL-6 in the peripheral blood of SLE patients, which in turn augments antibody production and induces plasma cell differentiation, respectively. Despite its anti-inflammatory role in general, IL-10 derived from monocytes in SLE, can promote the production of the BLyS factor from B-lymphocytes, which is also linked with the development of autoantibodies [6]. Besides their contribution to the aberrant activation of adaptive immune system, defects in non-inflammatory phagocytosis by macrophages are implicated in the impaired clearance of cellular debris, that serves as a crucial trigger for the production of autoantibodies in SLE [1, 7–10]. Notably, monocytes in SLE not only significantly contribute to the generation of the interferon (IFN) signature *per se*, but also give rise to plasmacytoid dendritic cells which are considered as the primary type I IFN producing cells in SLE [11, 12].

Several powerful computational tools have facilitated *de novo* drug development and drug repurposing processes in a cost-effective and time-saving manner. The library of integrated network-based cellular signatures (LINCS) L1000 dataset integrated over a million gene expression profiles of human cell lines before and after exposure to more than 20,000 perturbagens. Taking a step forward, the LINCS L1000 Characteristic Direction Signatures Search engine (L1000CDS^2) enabled the prioritization of thousands of small-molecule signatures, according to their ability to counteract disease specific transcriptional profiles [13]. We have previously employed an iLINCS-based drug repurposing pipeline [14, 15], suggesting the potential therapeutic relevance of compounds targeting the PI3K/mTOR pathway in SLE.

Herein, we employed two independent drug repurposing approaches to identify novel compounds that might restore the molecular aberrancies of monocytes in SLE. Using the iLINCS, CLUE and L1000CDS^2 platforms, we propose putative novel drugs potentially capable of reversing the monocyte-related SLE gene signature. We also report FDA-approved drugs and patented compounds that might disturb the gene regulatory network of SLE monocytes, suggesting they should be tested as monocyte-targeted therapies in SLE.

Results

The SLE monocyte gene signature can be utilized to predict potential drug repurposing

To propose existing FDA-approved or investigational compounds that might serve as novel monocyte-targeted therapies in SLE, we sought to identify compounds with potency to reverse the monocyte gene expression profile. Differentially expressed genes (DEGs) (absolute Fold Change ≥ 1.5, P-value ≤ 0.01) of monocytes between SLE patients and healthy individuals defined the monocyte-specific signature (Supplementary Tables 1, Supplementary Fig. 1). Using the iLINCS, CLUE and L1000CDS^2 platforms, the top 50 compounds that were predicted to counteract the SLE monocyte-specific gene signature most efficiently – according to their inhibitory scores – were identified (Supplementary Tables 2–4).

Our analysis indicated several p38 MAP kinase inhibitors, such as the "L-skepinone" [16], as a potential novel strategy of tuning monocytes in SLE. Additionally, the mTOR inhibitor "sirolimus" [17], as well as the calcineurin inhibitor "tacrolimus" [18], were recognized as potent modulators of the lupus monocyte gene signature. In line with studies underlying the crucial role of NF-κB in the survival and activation of monocytes [19], NF-κB pathway inhibitors, such as the compound "parthenolide" [20, 21], were predicted to reverse the SLE monocyte gene signature, whereas agents targeting the SLE-related Pim-1/NFATc1/NLRP3 signaling axis [22] might also represent promising therapeutic approaches. The sphingosine-1 phosphate receptor modulator "fingolimod", which has shown possible efficacy in neuropsychiatric lupus manifestations in the MRL/*lpr* lupus mouse model

[23], might therapeutically interfere with the monocyte-mediated orchestration of immune responses in SLE.

The common compounds reversing the monocyte gene signature were identified by the three different platforms (Fig. 1A): the heat shock protein 90 inhibitors "geldanamycin" and "NVP-AUY922", the Insulin-like growth factor 1 receptor (IGF-1R) inhibitor "BMS-536924", the BCR-ABL and Src family tyrosine kinase receptor inhibitor "dasatinib", the Cyclin-Dependent Kinase 9 inhibitor "alvocidib", the EGFR inhibitor "lapatinib" and the MEK kinase inhibitor "PD-0325901.

Among the compounds identified by the L1000CDS[2] that were highly ranked in the other 2 tools (CLUE and iLINCS) were the HSP90 inhibitors "geldanamycin" and "NVP-AUY922", the EGFR inhibitors "gefitinib", "lapatinib" and "canertinib" the DNA damage checkpoint kinase 1 and 2 (chk-1 and chk-2) inhibitor "AZD-7765", the Insulin-like growth factor 1 receptor (IGF-1R)

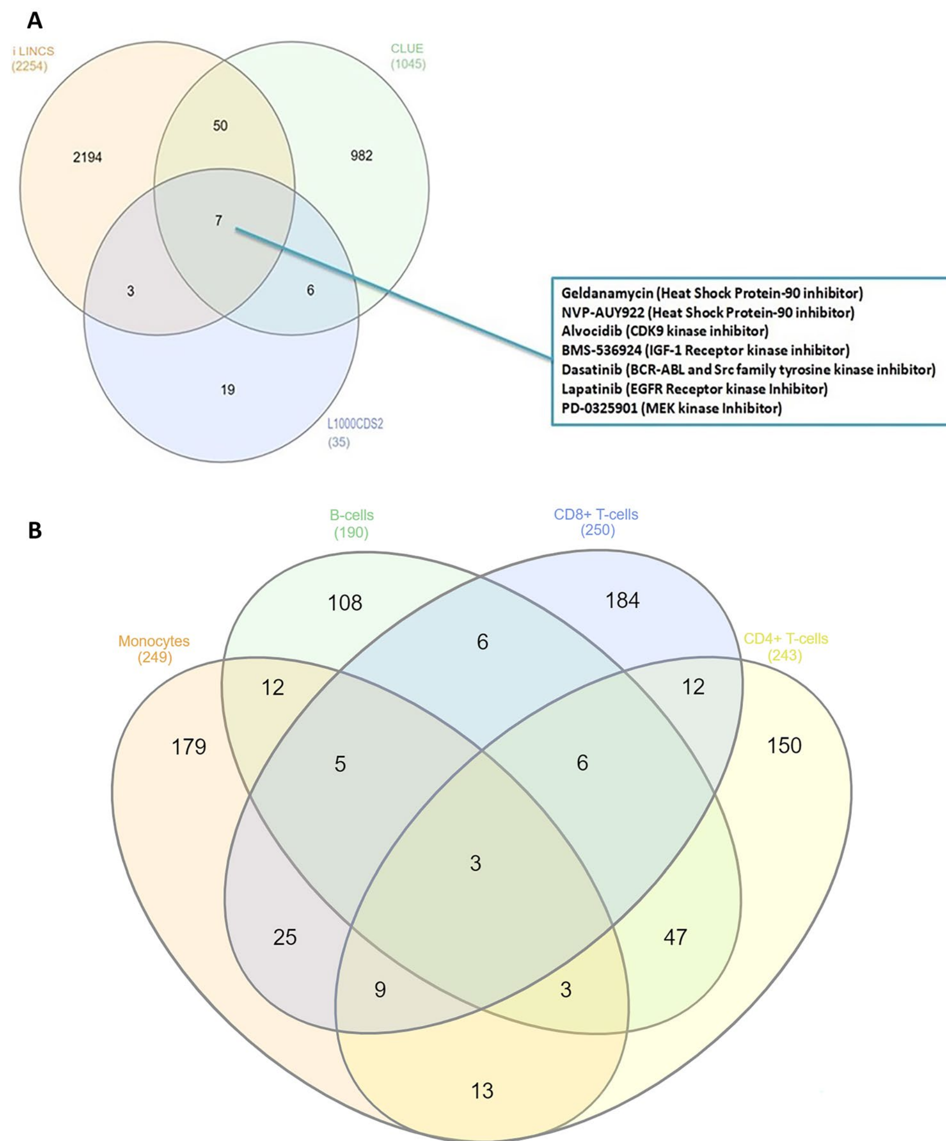

Fig. 1 (**A**) Venn diagram demonstrating the common compounds identified by the three different drug repurposing platforms, iLINCS, CLUE and L1000CDS[2], that could reverse the monocytes signature. To identify the 7 common compounds between the 3 different tools, all compounds derived from each different tool (iLINCS, CLUE and L1000), that could reverse the monocytes signature, were included in the Venn diagram. (**B**) Venn diagram to determine the top ranked drugs from all the three different drug repurposing platforms, that reverse exclusively our monocytes signature and not the signatures of B-cells, $CD4^+$ and $CD8^+$-T cells. For this Venn diagram the top-50 ranked compounds derived exclusively from each different tool (iLINCS, CLUE and L1000) that could reverse the monocytes, the B-cells, $CD4^+$ and $CD8^+$-T cells signature respectively, were included. Concerning the iLINCS tool the top-50 ranked compounds from each of the 5 different libraries were included. Conclusively, via this Venn diagram, 179 compounds were identified to reverse exclusively the monocytes signature

inhibitor “BMS-536924”, the Cyclin-Dependent Kinase 9 inhibitor “alvocidib”, the glucogen synthase inhibitor “TWS-119” and the Src/ABL dual kinase inhibitor “saracatinib”.

To enhance the specificity of our drug repurposing approach, leveraging the iLINCS, CLUE and $L1000CDS^2$ platforms, we identified the 50 top-ranked compounds, that could reverse the publicly available transcriptional signatures of circulating $CD4^+$ [56], $CD8^+$-T [56] and B-cells [57] obtained from SLE patients and we determined the agents that were exclusively related to the monocytes (Fig. 1B). The NF-κB pathway inhibitor “parthenolide”, inhibitors of the Pim-1/NFATc1/NLRP3 signaling axis, the EGFR inhibitors “gefitinib” and “afatinib”, the spleen tyrosine kinase (SYK) inhibitor “fostamatinib”, the TGF-beta inhibitor “pirfenidone”, the dual Src/ABL kinase inhibitor saracatinib, the antioxidant “L-sulphoraphane” as well as the “AZD-7765”, a compound inhibiting the DNA damage checkpoint kinase chk-1 and chk-2 were identified as monocyte specific.

Gene interaction network analysis as a guide for drug repurposing

Next, we sought to propose compounds that modulate the expression of multiple targets in the gene regulatory network of SLE monocytes. To this end, the transcription factors that regulate the transcriptional landscape of monocytes in SLE were retrieved from the TRRUST database (Supplementary Table 5). To reveal post-transcriptional regulators, the miRNAs that could regulate the gene expression profile of SLE monocytes were yielded using the miRWalk database (Supplementary Table 6). Thus, a comprehensive miRNA-gene interaction network - inferred using the monocytes gene signature, transcription factors and miRNAs - was constructed (Fig. 2).

Topological analysis of the constructed network uncovered a high degree of interconnectivity of genes encoding the proinflammatory mediators IL-6 and IL-1b. In line with studies underscoring the pivotal contribution of monocytes as IFN-producing cells in SLE, genes linked to type I IFN pathway, such as *IRF7*, *IFIT3*, as well as the transcription factor *STAT1* emerged as hub nodes [24]. Top-ranked hub miRNAs included the miR-124-3p, which has been found significantly upregulated in peripheral blood mononuclear cells and serum from SLE patients [25], as well as several miRNAs, with still largely unknown function in the context of SLE, such as miR-24-3p, miR-302c-3p and miR-302d-3p.

To identify agents with potentially unrecognized efficacy in SLE, we next determined drugs targeting hub genes of the miRNA-gene interaction network. Using the DGIdb database, a detailed drug-gene interaction network was constructed (Fig. 3A, Supplementary Table 7), revealing the anti-IL-12/IL-23 antibody “ustekinumab” and the epidermal growth factor receptor (EGFR) inhibitor “cetuximab”. Interestingly, the recombinant human TNF receptor Fc fusion protein “etanercept” as well as the chimeric monoclonal anti-TNFa antibody “infliximab” were identified as highly interconnected nodes.

Considering the extensive alterations of transcriptional regulation in SLE monocytes, we additionally constructed the drug-transcription factor interaction network (Fig. 4). The proteasome inhibitor “bortezomib” was yielded as potential drug candidate, whereas several natural compounds and plant extracts, such as “resveratrol”, “quercetin” and “curcumin” might efficiently modulate the activity of the dysregulated transcription factors in SLE monocytes [26–30].

Discussion

Herein, we applied a transcriptome-reversal combined with a network-based drug repurposing approach to identify novel compounds which might represent putative therapeutic options in SLE, through targeting transcriptional disturbances of monocytes. Using high-throughput drug repurposing tools, we identified agents predictive of reversing the molecular aberrations of SLE monocytes. By employing a gene network-based analysis, we propose agents, that might target essential regulators of the monocyte transcriptional landscape.

Several *in silico* drug repurposing studies have deployed whole blood gene expression profiling to suggest tailored SLE treatment choices [14, 31]. For example, Toro-Dominguez et al. employed a longitudinal stratification strategy to propose endotype tailored drug candidates [31]. In view of the central role of monocytes in several aspects of SLE pathogenesis [1], it is tempting to speculate that the targeted manipulation of monocytes might confer some therapeutic benefit in SLE. Furthermore, it was shown that selective depletion of monocytes in SLE patients by cytapheresis could lead to clinical remission, while inhibition of monocytes activation, differentiation and migration in in vivo models of SLE could have a beneficial impact on the disease manifestations such as nephritis and neuropsychiatric symptoms [53–55].To this end, we proposed putative novel drugs or small-molecule compounds that may reverse the transcriptional signatures of SLE monocytes. The inhibitor of the serine/threonine kinase Pim-1 “SGI-1776” was identified as a promising therapy, corroborating experimental data which suggest that inhibition of the Pim-1/NFATc1/NLRP3 pathway ameliorates nephritis in lupus mouse models [22]. Interestingly, the antioxidant “L-sulphoraphane” improved the renal damage in lupus-like mice through suppression of oxidative stress, enabling a mechanistic insight into our findings [49]. In the same context, the administration of “fostamatinib” in lupus prone

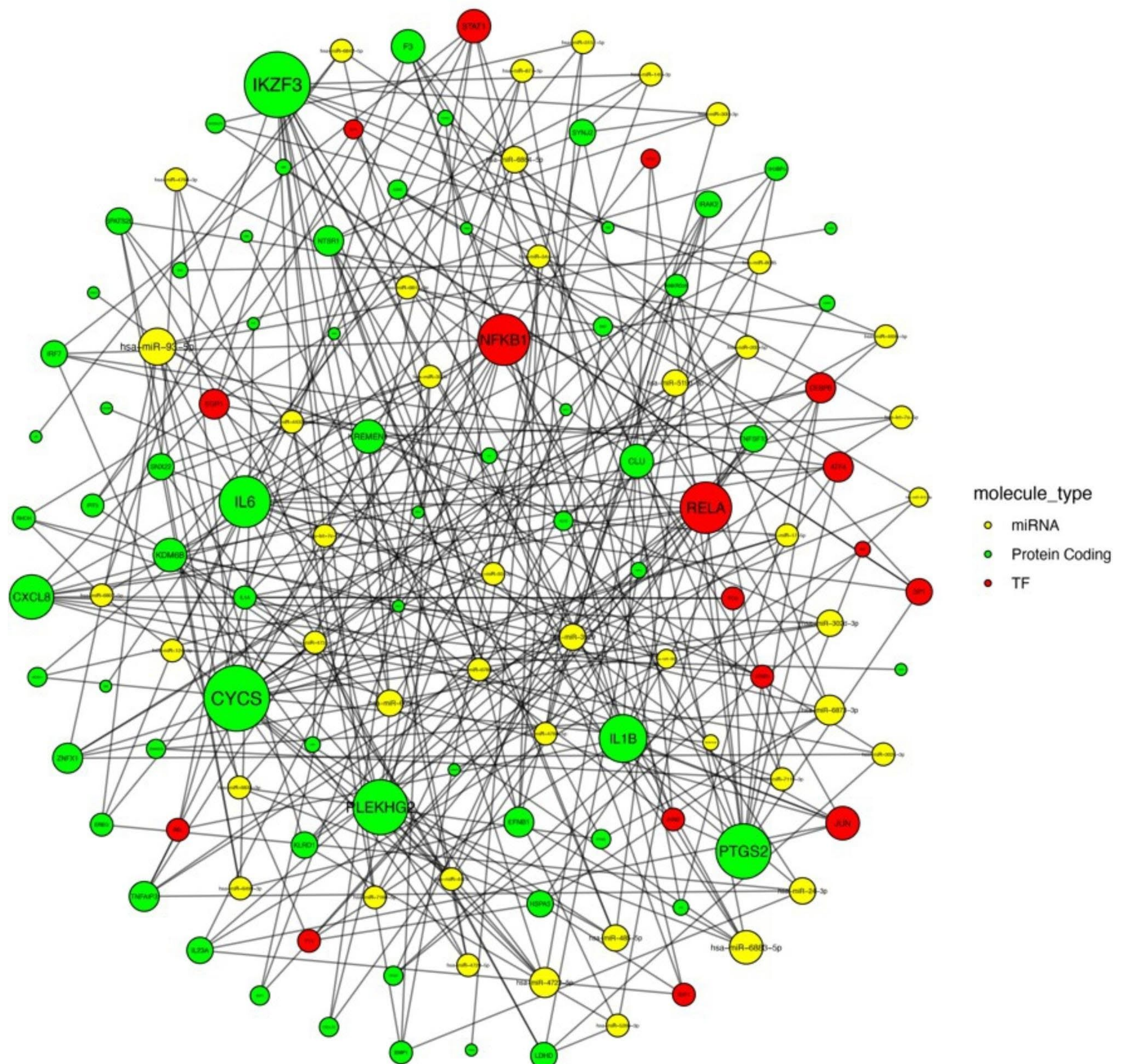

Fig. 2 Interaction network integrating the protein coding differentially expressed genes (DEGs) identified by the differential expression analysis of the monocytes from SLE patients versus healthy individuals, the transcription factors identified to regulate their expression and the miRNAs that are associated with them. The size of each node is scaled according to the degree of its interconnectivity, with highly interconnected nodes depicted larger. Only nodes with degree > 3 were depicted. Genes encoding the interleukins IL-6, IL-1b as well as genes implicated in the JAK/STAT pathway were among the most highly interconnected nodes

mouse models prevented the development of nephritis, providing evidence for the therapeutic potential of targeting the Spleen tyrosine kinase (Syk) in SLE [47, 48, 61].

Serum IL-23 levels were significantly elevated in patients with SLE compared to healthy individuals and correlated with overall SLE disease activity as measured by SLEDAI [60]. Furthermore, the increased c-reactive protein levels observed in inflammatory conditions, especially during flares of the disease can be linked specifically with the IL-23 production in monocytes [58]. Despite the recently published phase 3 trial [33, 34], our findings indicate that the IL-12/IL-23 inhibitor "ustekinumab" may efficiently disrupt the molecular interaction network of monocytes and therefore some patients might indeed benefit from this drug. Although proteasome inhibitors effectively deplete autoreactive plasma cells and proved to be therapeutically effective in preclinical mouse models of LN, there is compelling evidence suggesting that

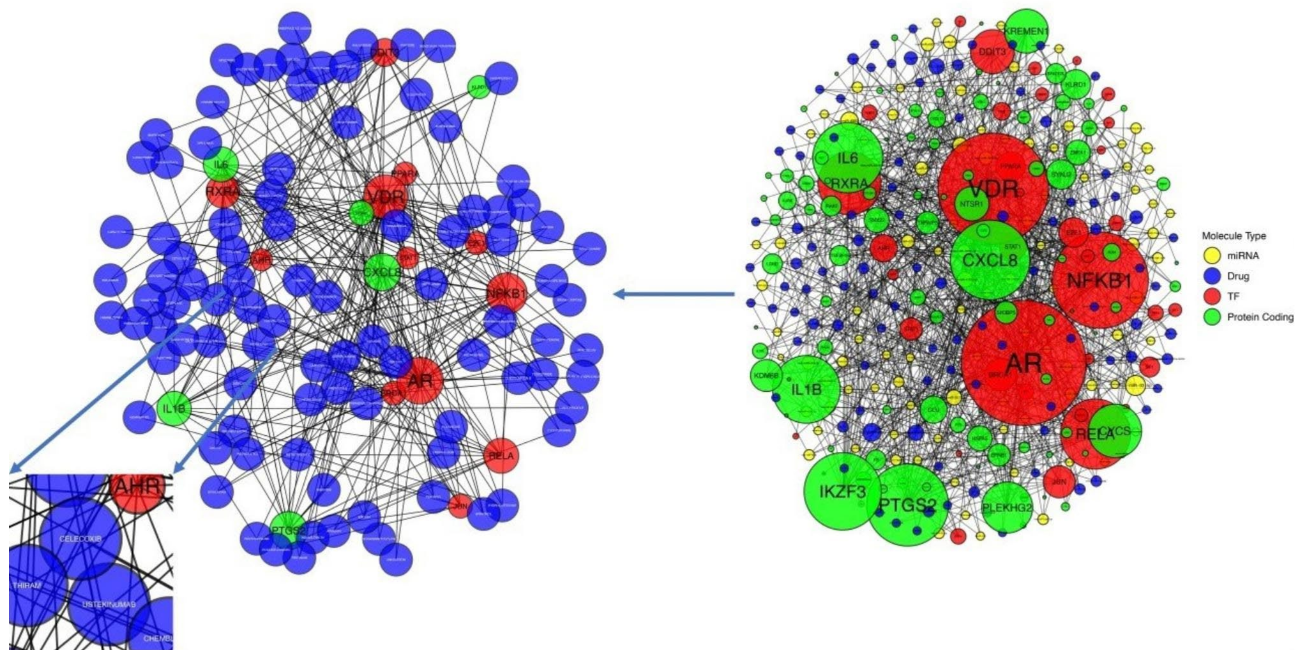

Fig. 3 Interaction network combining the protein coding differentially expressed genes (DEGs), the transcription factors and the miRNAs as defined in Fig. 2 and the drugs that are predicted to interact with the DEGs, according to the DGIdb database. Nodes with degree > 2 were included in the network on the right side of the graph. From the nodes included in the network on the right side of the graph, we selected the DEGs, transcription factors and miRNAs with degree > 10, as depicted in the network on the left side of the graph. Among others, the monoclonal antibodies targeting the IL12/IL23 as well as the TNF pathways were identified

immunoproteasome inhibition might selectively induces apoptosis in CD14+monocytes, leading to suppression of IL-23-driven autoimmunity [52].

EGF is a chemoattractant for monocytes, implicated with the recruitment of monocytes at the sites of inflammation [50], whereas urine epidermal growth factor (EGF) levels might serve as a potential biomarker of response to treatment in patients with Lupus Nephritis (LN) [51]. Notably, monocytes are abundantly present in renal biopsies from patients with LN, therefore EGF receptor inhibitors, such as cetuximab might represent a potential new therapeutic avenue in LN through preventing abnormal migration of monocytes to LN inflammatory lesions.

Previous in vitro and in vivo data support the notion that HSP90 might represent a potential drug target in SLE [35–37]. Interestingly, HSP90 facilitates the TLR7/9-mediated nucleic acid recognition in SLE, therefore promoting IFN-α production from plasmacytoid dendritic cells [35]. To this end, the potential therapeutic application of the HSP90 inhibitor, "geldanamycin", revealed by our analysis could merit further clinical investigation.

Complete understanding of miRNA regulation in SLE still remains elusive. Herein, we detected novel miRNAs, which might possess regulatory properties in the gene network of SLE monocytes. Given that each miRNA could concurrently influence multiple effectors of pathways, targeting the dysregulated miRNAs may also show promise for the future treatment of SLE. Accordingly, therapeutic modulation of the highly interconnected miR-124-3p and miR-302d, which has been designated as predictor of remission in SLE [25] and may participate in regulation of the IFN-induced gene expression in SLE through targeting the *IRF9* [59], respectively, might shed new insights into SLE treatment.

Our study has certain limitations, related to the function and topology of the cell subset and the methods used. Tissue macrophage compartment in steady state is mainly derived from embryonic precursors and actively contributes to maintenance of tissue homeostasis and resolution of inflammation [32]. Therefore, targeted pharmacological manipulation of tissue resident macrophage populations that might be driving pathology in SLE needs to be evaluated. Notably, the majority of the patients included in our study were receiving immunosuppressive treatment at sampling. Although cytotoxic agents, which can easily alter the composition of the whole-blood cells and potentially generate misleading results, were only rarely administrated in our study population, we can not exclude the possibility that therapy-induced transcriptional changes may interfere with our findings. Additionally, in our analysis we identified agents that might restore the transcriptional aberrations of SLE monocytes, however an effect of these agents on

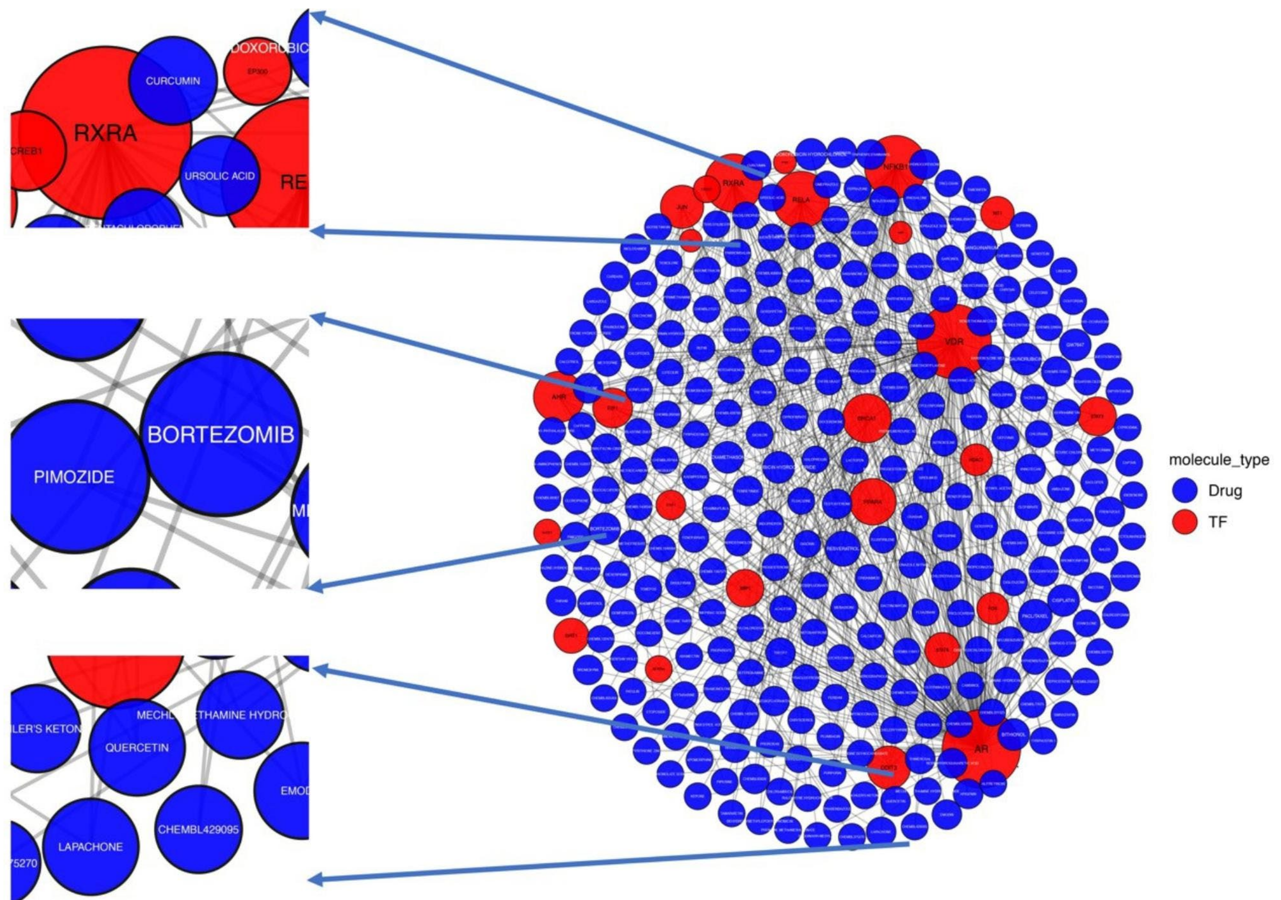

Fig. 4 Interaction network showing the transcription factors that regulate the expression of the monocyte gene signature in SLE and the compounds that interfere with their function. Only nodes with degree > 2 were demonstrated. The proteasome inhibitor "bortezomib" as well as several natural products emerged as potential drug candidates

other cell types as well, cannot be completely excluded. Lastly, our analysis is a computational approach and further experimental and clinical investigation is required to validate our findings.

Conclusion

In summary, using two independent computational system biology approaches, we identified novel compounds that are predicted to restore the function of monocytes in SLE. The therapeutic implications of our findings need to be further defined in animal models of SLE models and then tested in clinical trials.

Methods

Patients

Monocytes were isolated ($CD14^+$ cells through FACS technology, BD FACS ARIA IIu) from peripheral blood samples of 15 SLE patients fulfilling the 2019 EULAR/ACR classification criteria for SLE [38]. Patients were recruited from the Rheumatology Outpatient Department of the Attikon University Hospital and the University Hospital of Heraklion [38] (supplementary Table 9). Ten age- and sex-matched healthy individuals were used as controls. Disease activity was evaluated using the modified Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2 K); SLEDAI-2 K ≥ 4 defined active disease [39, 40]. All participants provided informed consent and the study approval was obtained from the local institutional review boards.

RNA sequencing and differential expression analysis

RNA libraries were prepared using the Illumina TruSeq kit. Paired-end mRNA sequencing was performed on the Illumina HiSeq2000 platform. The reads were aligned to the human reference genome (GRCh38.p12) by STAR RNA-Seq aligner [41]. Differential expression analysis was conducted using the edgeR Bioconductor R package [42].

Drug repurposing analysis

Using the iLINCS [43], CLUE [44] and L1000CDS^2 [13] platforms, we identified compounds that reverse the SLE monocyte signature. The following libraries were used for search in the iLINCS platform: (a) iLincs chemical

perturbagen library (LINCSCP); (b) Connectivity map signatures library (CMAP); (c) Drug matrix signatures library (DM); (d) Cancer therapeutics response signatures library (CTRS); and (e) Pharmacogenomics transcriptional signatures library (PG). Through extensive literature review, the top-ranked compounds derived from each platform, were re-evaluated based on their functional relation to SLE-associated gene or protein targets (supplementary Fig. 2).

Network analysis

The transcription factors and the microRNAs (miRNAs) that regulate the expression of the statistically significant, differentially expressed protein-coding genes were identified using the databases TRRUST and miRWalk, respectively. The drug-protein interactions were retrieved from the DGIdb database. Networks were constructed using the igraph package and their visualizations using the ggraph and qgraph packages in R [45, 46] (supplementary Fig. 3).

List of abbreviations

SLE	Systemic lupus erythematosus
SLEDAI-2 K	Systemic Lupus Erythematosus Disease Activity Index 2000
miRNAs	MicroRNAs
HSP90	Heat shock protein 90
BLyS	B-lymphocyte stimulator
IFN	Interferon
LINCS	Library of integrated network-based cellular signatures
L1000CDS^2	L1000 Characteristic Direction Signatures Search engine
DEGs	Differentially expressed genes
IGF-1R	Insulin-like growth factor 1 receptor
EGFR	Epidermal growth factor receptor
LN	Lupus Nephritis

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12864-023-09275-8.

Supplementary **Table 1.** List of the statistically significant differentially expressed genes (DEGs) resulting from the comparison of the monocytes from SLE patients versus healthy controls.

Supplementary **Table 2.** List of Compounds that are predicted to reverse the monocytes signature in SLE, derived from the iLINCS platform-based drug repurposing analysis.

Supplementary **Table 3.** List of Compounds that are predicted to reverse the monocytes signature in SLE, derived from the CLUE platform-based drug repurposing analysis.

Supplementary **Table 4.** List of Compounds that are predicted to reverse the monocytes signature in SLE, derived from the L1000CDS2 platform-based drug repurposing analysis.

Supplementary **Table 5.** List of the transcription factors that are predicted to regulate the monocytes gene expression signature in SLE, as retrieved from the TRRUST database.

Supplementary **Table 6.** List of the miRNAs that are predicted to regulate the expression of the monocytes gene signature in SLE, as retrieved from the miRWalk database.

Supplementary **Table 7.** Topological analysis of the interaction network of Figure 3A

Supplementary **Table 8.** Full list of DEGs of monocytes, derived from the comparison of SLE patients versus healthy control individuals, without cut-off values.

Supplementary **Table 9.** Clinical parameters (including disease activity and concominant treatments) of the patients participated in the study. Abbreviations: MMF (mycophenolate-mofetil), AZA(azathioprine), GC(glucocorticoids), HCQ(hydroxychloroquine), CY(cyclophosphamide), ANA (anti-nuclear antibodies).

Supplementary **Table 10.** List of monocyte specific small molecule compounds, as identified via the iLINCS, CLUE io and L1000CDS2 platforms, in line with figure 1B.

Supplementary 11 **Figure 1.** Volcano plot, including the full list of DEGs from monocytes of SLE patients vs healthy controls.

Supplementary 12 **Figure 2.** Analysis methodology steps for the identification of small molecule compounds via the iLINCS, CLUE io and L1000CDS2.

Supplementary 13 **Figure 3.** Analysis methodology steps for the identification of small molecule compounds and biologic agents via the construction of Drug-Protein-miRNA interaction networks.

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Not Applicable.

Author contributions

D.N.(Dimitrios Nikolakis): Conceptualization, experiments, data analysis, writing-original draft preparation, review and editing.
P.G.: Conceptualization, experiments, data analysis, writing-original draft preparation, review and editing.
G. S.: Visualization, data analysis, editing.
A.F.: Review and editing.
G.B.: Review and editing.
E.F.: Editing.
D.N.(Dionysis Nikolopoulos): Patient Recruitment.
A.B.: RNA sequencing experiments and editing.
D.B.: Supervision, review and editing.

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Data Availability

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Declarations

Ethics approval and consent to participate

This study has received approval by the Medical School Ethics committee of the National and Kapodistrian University of Athens and all patients have signed an informed consent form to participate in the study. All methods were carried out in accordance with relevant guidelines and regulations in the Declaration of Helsinki.

Consent for publication

Not Applicable.

Competing interest

The authors declare no competing interests.

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