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Short Analytical Review

Novel biological networks modulated by complement

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Abstract

The almost complete deciphering of the human genome has paved the way for the application of new technology platforms in understanding the contribution of complex biological pathways to human pathophysiology and disease. In the post-genomic era, the concept of systems biology has gained significant momentum and biomedical research is now being conducted on an integrated and cross-disciplinary platform that pulls together its resources from diverse fields such as computational biology, bioinformatics, functional genomics, structural biology, and proteomics. In this perspective, the identity of established biologic systems is being re-examined in the light of novel findings that suggest novel associations between otherwise unrelated pathways and individual proteins. Complement exemplifies such a system that, transcending its innate immune identity, has forged functional associations with multiple pathways and networks in modulating basic biologic processes. In the present article, we provide a global overview of these unusual system associations of complement with the aid of a powerful and high-throughput bioinformatics platform. Using a novel approach called systems literature analysis that allows the rapid extraction of text-based associations between genes and pathways from the ever expanding scientific article database, we have selected a broad range of biologic processes modulated by complement proteins and have constructed an integrated map of complement-mediated networks that incorporates well over 85 diverse biologic pathways. Expanding the complement cascade beyond its ~35 designated components, we discuss protein–protein interactions involving novel ligands and associations with signaling cascades and cellular networks that affect both inflammatory and non-inflammatory processes. This integrated consideration of complement within a unified 'systems biology' framework underscores the concept that innate immunity goes well beyond the protection of 'self' extending links to critical developmental, homeostatic, and metabolic processes.

Keywords: Complement; Systems biology; Bioinformatics; Database mining; Systems literature analysis

Introduction

The sequencing of the human genome marked the beginning of a new era in biomedical research that has culminated over the last decade in the development of large-scale platforms for genome-wide profiling and high-throughput proteomic analysis [1]. The fields of functional genomics and proteomics have spearheaded scientific discovery by unraveling the complex and dynamic behavior of the transcriptome and proteome, respectively. In doing so, they have produced large repositories of data that lack sufficient interpretation and need to be translated into gene associations and integrated networks of protein interactions. These high-throughput experimental platforms have populated the databases with an enormous amount of biomolecular data while at the same time they have rendered the comprehensive interpretation of such experiments an immensely difficult task. Scientists across various disciplines are now faced with the challenge of integrating this universe of raw data into a context that may promote hypothesis-driven discovery and facilitate the design of effective therapeutics and potential bedside therapies [2].

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Gene regulatory networks and tightly interacting pathways constitute the core of all biological processes. The overly simplistic approach of trying to dissect molecular circuits one protein or one gene at a time is now being replaced by a multidisciplinary platform that addresses biological systems as a whole. This is achieved by the comprehensive use of diverse resources ranging from structural biology and in silico modeling to proteomics and bioinformatics [3]. In this respect, *systems biology* has emerged as the field that studies such cellular circuits in an integrated and comprehensive manner [4]. The 'systems' approach attempts to 'reconstruct' biological networks by integrating data produced on a multidisciplinary platform and aims at designing 'model biological systems' with potentially new properties by exploiting the vast computing capability of modern bioinformatics [1].

One measure of the complexity of biological systems is readily reflected by the growth of published literature that is available in the databases (e.g., well over 15,000,000 abstracts are currently listed in Medline) [5]. To a significant extent, *modern biomedical science is driven by the challenge of managing more effectively a vast inventory of biomolecular data and the corresponding textual information available in literature databases* [6].

In this direction, bioinformatics researchers have developed a variety of 'mining' tools that can rapidly survey the biomedical literature and extract bibliographic correlations between different biological entities [7]. Showing significant promise is the integrative approach referred to as systems literature analysis (SLA) [8]. SLA replaces traditional Boolean searches with an integrated approach that, instead of retrieving large and unmanageable lists of papers, returns networks of all literature-reported correlations between research parameters. With SLA systems, it is possible to navigate across genes, diseases, biological events, post-translational modifications, and even experimental procedures and specific reagents. New text-mining algorithms are being developed in an effort to enable scientists to efficiently extract biological information from text databases, refine their search queries, manage complex ontologies, and cluster biologic entities in a meaningful manner that can shed light onto novel systems associations [9]. The use of such SLA strategies essentially supplements genome and proteome profiling approaches by providing an integrative context within which putative gene networks can be designed or even predicted based on the co-occurrence of genes, proteins and pathways within scientific articles.

A 'systems biology' approach to immunologic processes

Immunological processes epitomize in many ways the inherent complexity of biological systems. Even though the immune response has been extensively studied over the years, very little is known about the way in which different components of this response interact in a 'systems' perspective.

Complement, a key component of innate immunity that exhibits great versatility in terms of function, serves as an ideal paradigm of how traditional immunology is revisiting basic immune processes in a 'systems' approach [10]. In the post-genomic era, our knowledge of complement is enriched by findings that point to novel functions that do not strictly correlate with immunological defense and surveillance, immune modulation, or inflammation [11]. Moreover, structural, biochemical, and in vivo studies have revealed novel associations of complement with diverse molecular pathways and intracellular signaling cascades.

To date, there has been no comprehensive account of the global system associations of complement.

To integrate complement into a broader 'systems' context and gain new insight into its remarkable adaptability in different pathophysiological settings, our laboratory has adopted a multidisciplinary platform of research in elucidating diverse interactions of complement components with pathways that affect basic biological processes [10]. To this end, using a combination of high-throughput screening techniques, biophysical methods, molecular modeling and simulation, as well as protein profiling coupled to sensitive mass spectrometric approaches, we have mapped critical protein–protein interactions and identified structure–function relationships for various complement components [10,12]. Using such an integrative experimental strategy, we have documented the engagement of complement in molecular circuits that regulate the growth response of the regenerating liver and in signaling pathways that dictate the early development and deployment of hematopoietic precursors to various tissues [13,14]. This integrative approach has revealed novel aspects of complement function that can lead, through further manipulation, to the design of effective therapeutics and also contribute to the understanding of complex pathological processes. Furthermore, this plethora of complement-modulated functions illustrates the necessity for a unified, 'systems-driven' platform that can promote knowledge discovery in immunology through the integration of both experimental and literature-based biological information.

In an effort to map for the first time the global network of complement-mediated interactions and shed light on the elusive 'systems'-driven perspective of complement, we have employed an SLA approach [8] that allows the rational extraction of pathway and gene-specific correlations from the literature databases. Here, we outline the powerful capacity of such a bioinformatics technology to retrieve parameter-guided literature and correlate biological entities and biological processes based on the frequency and strength of term co-occurrences within the scientific literature. We discuss the literature-based, comprehensive analysis of global complement interactions and illustrate the ability of such a 'mining' platform to provide a 'systems biology' profile for any biological pathway. Complement proteins C3 and C5a serve as a paradigm of how such a literature-mining platform can help elucidate complex

pathway interactions and construct putative gene regulatory networks using as 'building blocks' text-based correlations that involve complement genes and a wide spectrum of Gene ontology-based biological processes.

Unraveling a network of system associations through systems literature analysis: the case of complement component C3

The complement system comprises more than 35 components that participate in various aspects of innate immunity [15,16]. C3 marks the convergence point of all pathways of complement activation and constitutes one of the most versatile and multifaceted proteins of the complement system. It physically interacts with more than 20 proteins, including complement receptors, membrane-bound and soluble complement regulators and inactivators, viral glycoproteins, bacterial products, and cell adhesion molecules [16]. The role of C3 in target cell opsonization, pathogen clearance, and the propagation of various inflammatory responses is well established and numerous studies have dissected critical aspects of its immunologic functions in normal physiology and disease. Despite this plethora of natural C3 ligands and the diversity of interactions, C3 has been mainly associated by the broader scientific community with the maintenance of 'first line' host defense against infection. This persistent consideration of complement as a system that merely wards off infection is attributed to the lack of an integrative 'systems' platform that will enable scientists to address complement as a component within a dynamic network of interacting biologic pathways.

The advent of high-throughput proteome and genome profiling together with the availability of appropriate animal (transgenic and knock out) models has led to novel discoveries that implicate C3 in basic biologic processes that do not correlate with immunological defense per se [11]. Such reports still remain unappreciated partly due to the lack of a comprehensive systems platform that can provide an integrative context for efficient interpretation and rational planning of follow-up studies.

The literature databases are constantly populated with articles that discuss such novel findings but the mining of text databases for a global map of complement-mediated interactions and pathways resembles to some extent the laborious search for 'a needle in a haystack'. Indeed, a simple Boolean query using 'complement' and 'C3' as combined keywords (through NCBI's PubMed) returns more that 10,000 abstracts from Medline [5]. The sheer size of C3-related bibliography is an inherent drawback in any attempt to extract meaningful information linking C3 to a network of biologic processes.

To circumvent this enormous complexity and gain insight into the global network of system associations of C3, we decided to perform a text-based survey using a novel literature analysis platform (SLA) that treats the entire body of biomedical literature as a system of interrelated terms representing diverse biologic entities such as genes, biologic processes, and diseases [8]. The Biolab Experiment Assistant (BEA) tool that was used in this study offers the advantage of 'mining' the textual databases with a combination of domain concepts and integrating this text-based analysis into a software environment that supports the graphic representation of gene–gene or gene–pathway networks.

SLA was performed by scanning the entire Medline database and produced a network of more than 85 biological processes that are modulated by complement C3 (Fig. 1, panel A; also, Table 1). C3 was found to correlate with processes that range from innate immune response and inflammation to cell differentiation, cell growth and survival, cell activation, and tissue regeneration. It is of particular note that our analysis across Medline revealed several links between C3 and non-inflammatory pathways that affect human reproduction, fertilization, and bone development (osteogenesis), as well as associations with signaling pathways that modulate several metabolic processes (e.g., glucose metabolism, lipid storage, and metabolism) (see Fig. 1, panel A). The links between C3 and various biologic processes represent the strength/frequency of term co-occurrence within the literature and each link included several articles that qualified as positive selections in our search (indicative literature is cited as follows: [17–20]). The co-occurrence of C3 with terms representing diverse biological processes was validated though independent inspection of the relevant literature. To a great extent, these C3-mediated interactions have been validated by experimental evidence while others remain putative and need further investigation to support a direct link between complement and the respective process.

It is of particular note that several putative links were identified between C3 and signaling pathways that affect cell differentiation and various metabolic processes (e.g., lipid metabolism, lipid storage, triacylglycerol synthesis) (Fig. 1). For example, our literature-mining survey revealed a link between C3 and adipocyte differentiation. This link is supported by several articles that indicate a potential role for C3, and its activation fragment C3adesArg (ASP-acylation stimulating protein), in adipocyte physiology, metabolism, and differentiation [21,22]. Experimental evidence suggests that ASP production is differentially regulated during adipocyte development and that the temporal upregulation of ASP secretion correlates with an increase in triacylglycerol synthesis in mature adipocytes [21]. Furthermore, a recent proteomic study has identified C3, its parental molecule, as one of those factors that are secreted by 3T3-L1 cells during their differentiation to adipocytes [22]. Integrating the 'textual' information that is extracted through our systems literature analysis with all the relevant experimental data that are available on the C3-adipocyte interaction may provide a comprehensive framework for further investigation of a putative role of complement C3 in adipocyte differentiation and lipid metabolism.

Our study aimed at providing a global overview of these C3-mediated interactions and highlights the importance of

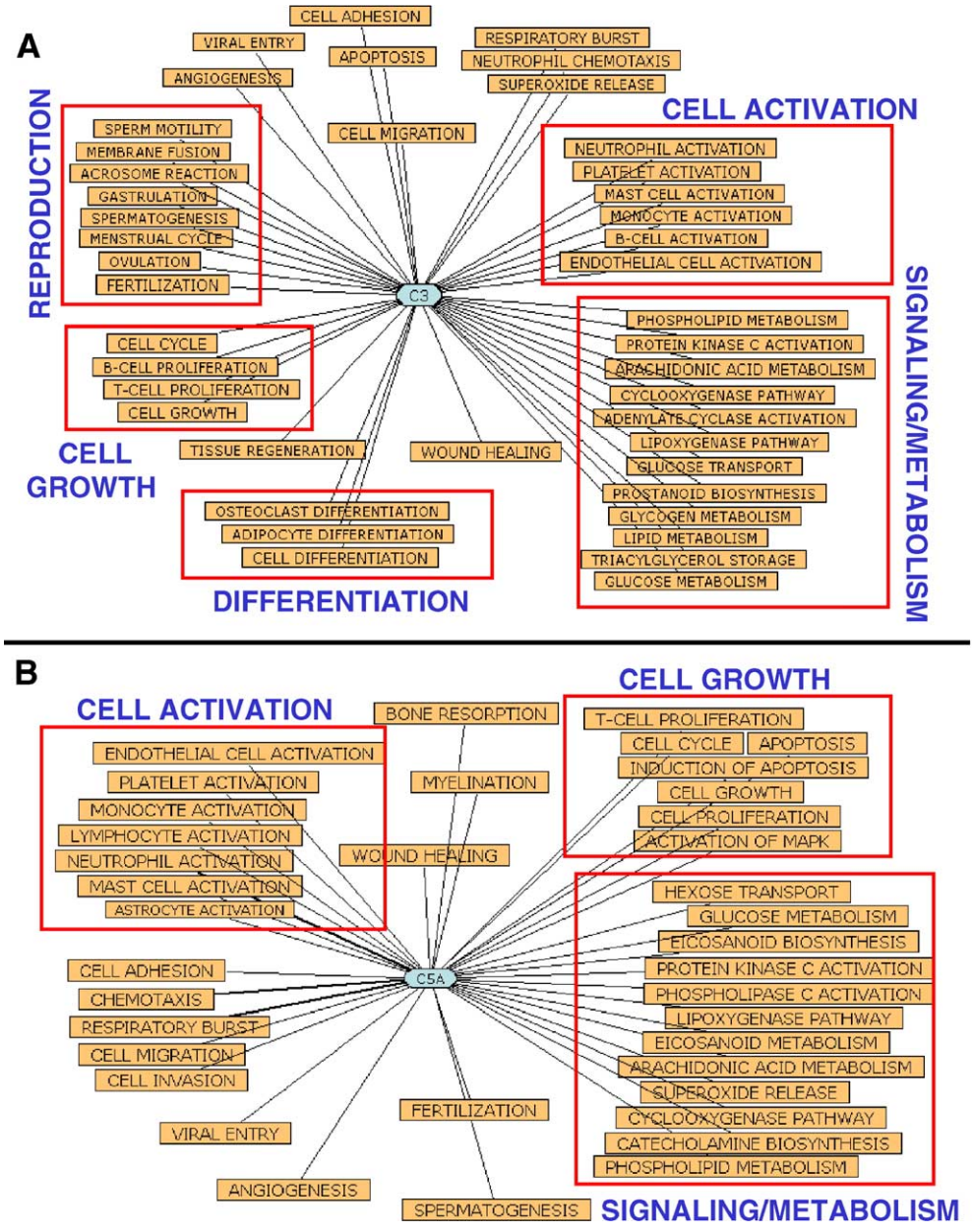

Fig. 1. 'Systems-wide', literature-based mining of complement-modulated biological processes. A global map of complement-mediated interactions integrating a wide array of GO-based biological processes was constructed using a novel systems literature analysis (SLA) platform that allows the extraction of interrelated biological terms from the databases. The multifaceted complement components C3 and C5a were used as representative targets in this pathway-specific analysis. Distinct interactions of both complement proteins with specific biological processes are discussed in the text. Panel A: SLA-based extraction of C3-pathway correlations from the entire Medline reveals a network of 87 biological processes that are modulated by C3 (the BEA-generated graph highlights the non-inflammatory system associations of C3. Panel B: Similar SLA analysis was performed for complement anaphylatoxin C5a. The figure illustrates literature-based associations of C5a with diverse biological processes ranging from inflammation and cell activation to normal development, regeneration, and cell metabolism/homeostasis. Integrated systems literature analysis was performed using the BioLab Experiment Assistant (BEA) application (http://www.biovista.com). Abbreviations: GO, Gene Ontology.

considering complement as part of a broader network of interrelated processes when designing therapeutics that target a specific complement-modulated pathway. To this end, the integration of experimental and textual information, as demonstrated in the case of C3, provides an essential platform for devising follow-up studies and a comprehensive 'systems' context for text-driven scientific discovery.

C5aR signaling and its many faces: a 'systems' overview

The complement anaphylatoxins C3a and C5a are generally considered the end products of complement activation and mediate a wide array of inflammatory responses associated with detrimental processes such as local tissue damage, phagocyte sequestration to injury sites,

Table 1
List of C3-associated biologic processes retrieved by BEA-assisted literature mining

C3-associated biologic processes (retrieved by BEA analysis)	BEA co-occurrences/link	Key references
Acrosome reaction	1	[19]
Adenylate cyclase activation	1	[32]
Adipocyte differentiation	1	[21]
Aging	8	[33]
Angiogenesis	1	[34]
Antigen presentation	6	[35]
Antigen processing	5	[35]
Apoptosis	7	[36]
Arachidonic acid metabolism	2	[37]
B-cell activation	3	[38]
B-cell proliferation	1	[39]
Cell adhesion	11	[40]
Cell cycle	3	[11]
Cell death	17	[36]
Cell growth	10	[39]
Cell migration	5	[14]
Cyclooxygenase pathway	1	[41]
Endothelial cell activation	3	[42]
Eosinophil chemotaxis	2	[43]
Fertilization	4	[19]
Fibrinolysis	4	[44]
Gastrulation	1	[45]
Glucose homeostasis	1	[46]
Glucose metabolism	5	[46]
Glucose transport	3	[47]
Glycogen metabolism	1	[48]
Isotype switching	3	[49]
Lactation	3	[50]
Lipid metabolism	1	[51]
Lipoxygenase pathway	1	[41]
Lymphocyte activation	2	[52]
Lymphocyte proliferation	5	[39]
Macrophage activation	9	[53]
Mast cell activation	1	[54]
Membrane fusion	1	[19]
Menstrual cycle	2	[55]
Mitosis	1	[56]
Monocyte activation	5	[53]
Muscle contraction	3	[57]
Neutrophil activation	6	[53]
Neutrophil chemotaxis	3	[58]
Osteoclast differentiation	1	[17]
Ovulation	1	[55]
Phospholipid metabolism	1	[59]
Platelet activation	12	[60]
Prostanoid biosynthesis	1	[61]
Protein kinase C activation	1	[62]
Respiratory burst	7	[63]
Sperm motility	3	[64]
Spermatogenesis	1	[65]
Superoxide release	1	[66]
T-cell proliferation	3	[67]
Tissue regeneration	1	[13]
Triacylglycerol storage	1	[68]
Tropism	2	[69]
Vasoconstriction	1	[70]
Viral entry	1	[16]
Wound healing	2	[71]

and the onset of severe inflammatory syndromes that lead to organ failure [23]. Recent studies, however, have pointed to novel functions of these anaphylatoxic peptides that do not correlate with such proinflammatory effects. Indeed, C5a and its G-protein-coupled transmembrane receptor, C5aR/CD88, have been linked to several biologic processes that affect normal organ development, early differentiation of various cell lineages, and protection of cells from apoptotic death [13,24]. Moreover, several reports discuss the molecular mechanisms and multiple intracellular effectors that participate in these C5aR-dependent signaling cascades [25].

However, to date, there has been no attempt to evaluate and integrate these diverse functions of C5a within a ‘systems’ context that will allow the rational planning of genome-wide studies and facilitate the integrative interpretation of its functions and the design of effective C5a-based therapeutics.

Employing a systems-wide literature analysis approach similar to the one discussed above, we were able to reconstruct the complex network of interacting pathways that converges at C5aR stimulation. This was achieved by mining the literature for text-based co-occurrences between C5aR (the C5a receptor) and a wide array of GO-based biologic processes. Through the retrieval of documents that support the co-occurrence of C5aR with diverse biologic processes (as listed in Gene Ontology), we demonstrate that complement and in particular, C5aR stimulation, participates in a broad spectrum of more than 75 biologic processes (Fig. 1, panel B; also, Table 2).

Those C5a-modulated processes that do not strictly relate to immunologic functions were the focus of our analysis. BEA-assisted text mining through the entire Medline database resulted in the retrieval of correlations for processes such as cell activation, regulation of cell cycle and proliferation, as well as various aspects of cell metabolism and intracellular signal transduction (see Fig. 1, panel B). Interestingly, our text-mining survey revealed a putative link between C5a and the biological process of angiogenesis. Thus far, the potential involvement of complement in angiogenic processes has remained elusive to the broader research community. A closer inspection of the literature that supported this BEA-generated link provides validity to the concept that C5a may modulate processes that are associated with the manifestation of an angiogenic phenotype. Indeed, through our literature analysis, we retrieved studies that have demonstrated a synergistic effect of C5a in PMN-endothelial cell adhesion and transendothelial migration stimulated by several angiogenic factors, such as VEGF and bFGF [26]. Further supporting a role for C5a in the angiogenic process, a high-throughput cDNA screening of human umbilical vein endothelial cells (HUVECs) has revealed that C5a stimulation causes significant downregulation of several genes that regulate angiogenesis at the endothelium interface [27]. The literature-based retrieval of such scarce reports linking C5a to angiogenesis underscores the benefit of integrating a

Table 2
List of C5a-associated biologic processes retrieved by BEA-assisted literature mining

C5a-associated biologic processes (retrieved by BEA analysis)	BEA co-occurrences/link	Key references
Activation of MAPK	1	[72]
Angiogenesis	3	[27]
Apoptosis	20	[73]
Arachidonic acid metabolism	14	[74]
Astrocyte activation	1	[75]
Basophil activation	9	[76]
Blood coagulation	6	[77]
Bone remodeling	1	[78]
Bone resorption	2	[79]
Catecholamine biosynthesis	1	[80]
Cell adhesion	26	[81]
Cell cycle	2	[82]
Cell differentiation	5	[83]
Cell growth	6	[84]
Cell invasion	1	[85]
Cell migration	19	[72]
Cyclooxygenase pathway	3	[86]
Eicosanoid biosynthesis	1	[20]
Endocytosis	5	[87]
Endothelial cell activation	2	[27]
Eosinophil chemotaxis	16	[88]
Exocytosis	32	[89]
Fertilization	1	[90]
Fibrinolysis	9	[91]
Glucose metabolism	1	[20]
Glycolysis	6	[92]
Hexose transport	2	[93]
Hyperphosphorylation	2	[94]
Lipid metabolism	2	[86]
Lipoxygenase pathway	4	[86]
Lymphocyte activation	2	[95]
Lymphocyte chemotaxis	3	[96]
Lymphocyte proliferation	5	[84]
Macrophage activation	5	[97]
Macrophage chemotaxis	4	[57]
Macrophage differentiation	1	[98]
Mast cell activation	7	[99]
Microtubule polymerization	1	[100]
Monocyte activation	3	[97]
Myelination	1	[101]
Neutrophil activation	63	[73]
Neutrophil chemotaxis	97	[23]
Phospholipase C activation	2	[102]
Phospholipid metabolism	2	[103]
Platelet activation	18	[77]
Protein kinase C activation	3	[24]
Regulation of actin polymerization	1	[104]
Respiratory burst	58	[105]
Smooth muscle contraction	15	[106]
Spermatogenesis	1	[107]
Superoxide release	12	[105]
T-cell proliferation	2	[84]
Vasoconstriction	17	[106]
Vasodilation	6	[106]
Viral entry	1	[108]
Wound healing	5	[109]

literature-mining approach into a global and 'systems-wide' consideration of complement.

This network of interacting pathways produced through literature mining visualizes in the most emphatic way the dynamic 'systems' character of complement and exemplifies the enormous versatility of function that characterizes several complement components, such as C5a.

To further elucidate the gene regulatory networks that are recruited in these C5a-modulated biologic processes, we went on to perform a second round of text-mining analysis and identified literature-based interconnections of C5aR (the C5a receptor) with other gene products. As shown in Fig. 2 (panel A), C5aR associates with a large number of intracellular effectors, membrane receptors, and immune mediators (e.g., cytokines, chemokines) and is also found to physically interact with novel ligands that affect cytoskeletal movement and actin sequestration during cell migration (e.g., Wiskott–Aldrich syndrome protein—WASP) [28]. Among the downstream C5aR effectors that were retrieved in our analysis, several transcription factors appeared to be linked to C5aR stimulation. Text mining of MEDLINE documents produced links between C5aR and transcription factors such as c-*jun*, c-*fos*, NF-6B and the cAMP-responsive element binding protein CREB (Fig. 2). Although the interaction of C5a with signaling pathways that lead to AP-1 (C-JUN/FOS) and NF-kB transcactivation is well-documented in several models of inflammation [29], very little is known about the mechanism by which C5a affects CREB activation and the potential implications of a C5aR/cAMP/CREB pathway 'crosstalk' in normal physiology or disease. CREB is a nuclear protein with pleiotropic functions that has been mainly associated with neuronal plasticity and survival and has also been implicated in learning and memory. Recent evidence has suggested that CREB signaling is also involved in glucose homeostasis and regulates growth-factor-dependent cell growth and survival [30]. The literature supporting the link between C5aR and CREB in our mining analysis points to a study that documents the C5a-dependent expression of CREB in human mesangial cells [31]. This study, however, does not expand on the possible implications of such an interaction. Given that both C5a and CREB have been recently shown to regulate glucose metabolism [20], but no direct evidence exists linking both molecules to this process, it would be interesting to speculate on a potential interaction of C5aR with CREB-dependent signaling effectors during glucose metabolism. The retrieval of such a bibliographic link through text-mining represents an example of how systems literature analysis can provide a platform for hypothesis-driven discovery and the design of follow-up studies to validate a putative link which is based on literature-derived correlations of two independent biological entities (such as C5aR and CREB).

Most of the gene correlations for C5aR that resulted through text mining of the Medline database have been validated through experimental approaches that have used a cross-disciplinary arsenal of techniques ranging from

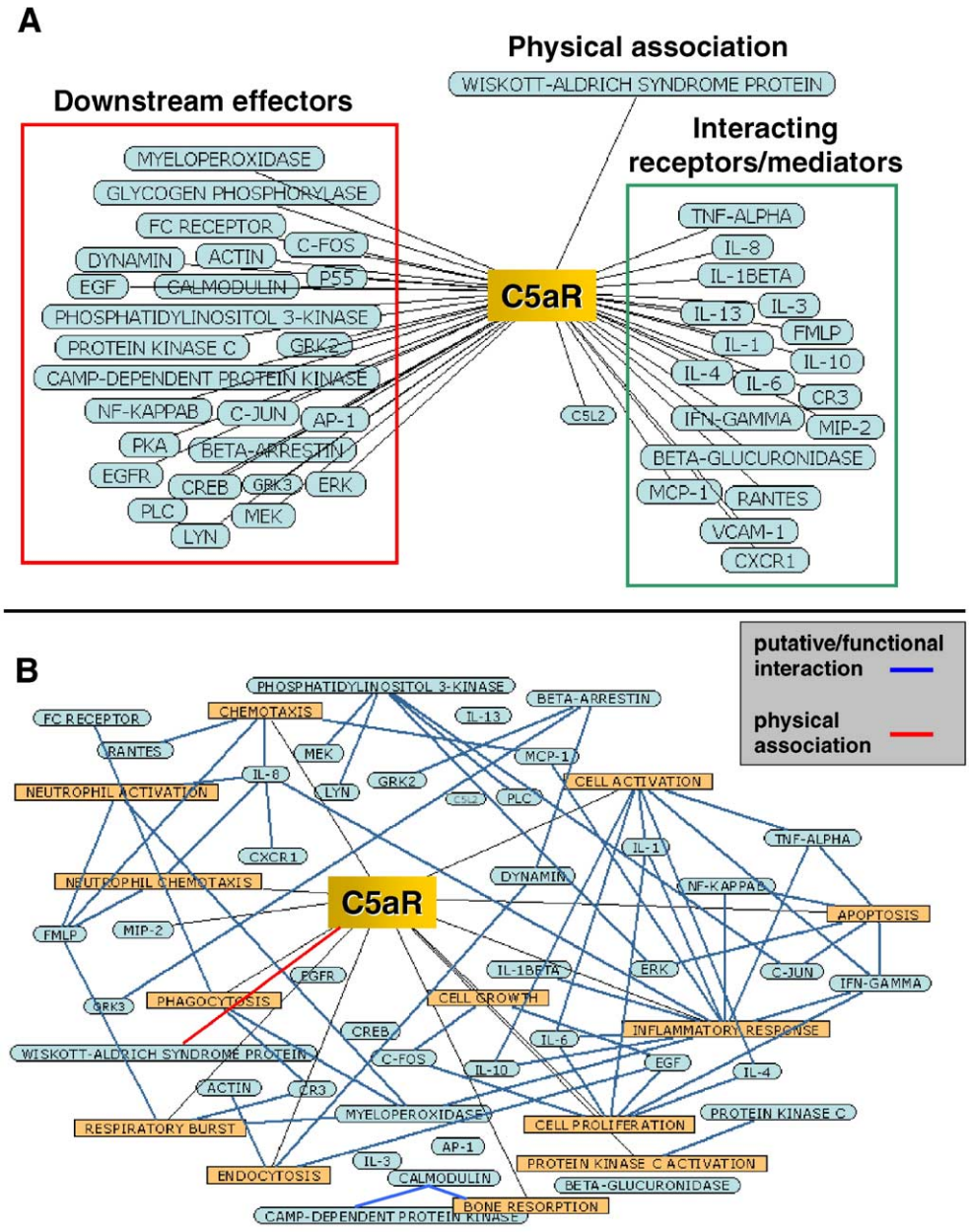

Fig. 2. Systems literature analysis (SLA) supports a 'global role' for C5aR stimulation in intercepting multiple signaling pathways: Interaction of C5aR-dependent signaling with a wide array of surface-expressed immune modulators and intracellular effectors is supported by the retrieval of text-based 'co-occurrences' between C5aR and various gene products in the scientific literature (MEDLINE). Panel A illustrates the network of literature-based links that were identified between C5aR and GO-annotated gene products, as these were visualized using Biovista's integrated SLA application (BEA). Panel B: Schematic representation of the global network of interactions that are modulated by C5aR. Interconnections between genes and pathways were generated through literature mining and were visualized using the BEA application. SLA-generated links that denote an indirect or putative interaction with C5aR are marked in black color, while links that indicate a physical association with C5aR are marked red. Abbreviations: GO, Gene Ontology. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

structural–biochemical studies and high-throughput screening strategies (such as yeast two-hybrid studies) to in vivo and ex vivo experiments.

In a further attempt to visualize these gene correlations within a unified network of C5a-dependent biologic pathways, we employed systems literature analysis, and used a text-mining platform to retrieve multiple interconnections that 'bridge' the identified genes, the C5a-associated biologic pathways, and C5aR. A graphical representation of this highly interactive gene regulatory network is shown in Fig. 2 (panel B). It is of particular note that some of the genes identified as interacting with C5aR (see panel A) remained 'orphan' (without a corresponding 'co-occurrence' link) when analyzed for potential association with the selected biological processes. This observation may be attributed partly to a 'terminology ambiguity' that

escapes the selected parameters of our 'mining' query or, may represent potential gene targets for the design of appropriate 'wet' experiments that will test the existence of a putative link and promote the generation of hypothesis-driven discovery.

For example, our mining analysis for gene–gene interconnections retrieved a co-occurrence link between C5aR and the Epidermal Growth Factor receptor (EGFR) pathway (Fig. 2, panel A). Indeed, this link is supported by relevant literature according to which C5aR and EGFR signaling cascades converge to common downstream intracellular effectors in endothelial cells [25]. However, in our second round of literature analysis, EGFR failed to produce any links to the biological processes that associate with C5aR stimulation (Fig. 2, panel B). This observation indicates that EGFR may represent a novel molecular target that modulates C5a-dependent cellular processes. Such an association remains putative and further studies are needed to investigate a potential EGFR/C5aR 'crosstalk' and define its biological implications.

Undoubtedly, the literature-based discovery of an array of 77 biological processes that engage in direct or indirect interaction with C5a and its receptor, C5aR, constitutes the first report that profiles COMPLEMENT-mediated interactions in a global and 'systems'-driven manner. Furthermore, this study illustrates the advantage of using a bioinformatics platform such as SLA to manage and integrate a knowledge domain that constantly increases in size through the generation of more experimental data and the reciprocal accumulation of more scientific articles in the databases. Thus, systems literature analysis serves as an essential supplement to high-throughput gene and protein analysis, providing at the same time a comprehensive context for biological interpretation and text-based correlation that can potentially lead to knowledge discovery.

Conclusions—perspectives

Biomedical research has entered a new era that fosters the consideration of integrated biological systems, gradually displacing the investigation of single pathways and isolated gene products. Biological processes are now more often analyzed as a unified network of interacting pathways, and cross-disciplinary experimental platforms are employed in an effort to characterize the dynamics and constituents of any given system. In this respect, innate immunity is being drastically re-assessed in a 'systems biology' context. Complement represents such an innate immune system that has been shown to engage in diverse and until recently unrelated biologic processes and cell regulatory networks. The inherent complexity of complement biology lies within its numerous components and the diverse interactions that are formed with other biological systems.

In an effort to provide a global map of these complement-modulated interactions and establish an integrative 'systems' platform for literature-based discovery, we have performed a systematic analysis of complement associations using a novel text-mining platform that treats the biomedical literature as an integrated system of interrelated biologic entities. Our findings indicate that complement proteins engage in complex and dynamic biological networks consisting of both inflammatory and non-inflammatory processes. Moreover, pivotal complement components, such as C3 and the anaphylatoxin C5a, appear to be linked with a wide array of intracellular signal transduction pathways that affect cell homeostasis, activation, and proliferation. Although this 'systems' overview of complement is based on an integrated survey of the expanding literature, it strongly points our attention to putative interactions and gene regulatory networks that call for further elucidation by relevant genome and/or proteome-wide studies.

It is our conviction that biomedical discovery will be spearheaded in the next decade by combinatorial and cross-disciplinary approaches that will address basic biological networks in a global and integrated manner. In conclusion, the rational 'mining' of biomolecular and textual databases will essentially complement these experimental strategies and enable scientists to form an integrative context for hypothesis-driven scientific discovery.

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