Investigation of the Potential Effect of Complement 5 on Transplantation Outcome by Bioinformatics Tools

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Introduction. Activation of the complement system following transplantation may result in allograft rejection. Our study aimed to evaluate the potential relationship between factors affecting kidney transplant success and complement 5 (C5) using bioinformatic tools.
Methods. GenCards and Genemania were used to provide the genetic functional information belonging to the C5 gene, and genomic browsers of STRING, UCSC, KEGG were used to reveal interactions with other genes and various pathways. MiRDB was used to specify the miRNAs that were associated with the C5 gene. The UniProt database was used to determine the tissues that expressed the C5 gene using protein-protein interactions.
Results. In the bioinformatic analyses performed, high levels of C5 gene expression were found in the naiive kidney. Twenty-five genes were found to be strongly associated with C5. Fifty-four miRNAs targeting the C5 gene were specified. The C5 gene was found to be involved in biologic processes such as complement activation (FDR = 6.46e-22), complement binding (FDR = 2.20e-06), cytolysis (FDR = 4.82e-14), regulation of complement activation (FDR = 4.08e-24), positive regulation of vascular endothelial growth factor production (FDR = 0.0430), regulation of macrophage chemotaxis (FDR = 0.0447), activation of the immune response (FDR = 1.26e-13), leukocyte-mediated immunity (FDR = 1.41e-09), innate immune response (FDR = 3.05e-09), allograft rejection (FDR = 2.40e-12), oxidative injury response (FDR = 0.00016), and trigerring of the beginning of the complement cascade (FDR = 0.0244).
Conclusions. The data obtained in this study will be used to guide future experimental investigations in the field of transplantation, and these data will give physicians with insight into allograft status following transplantation.

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Original Paper

INTRODUCTION

The complement system consists of about 40 different proteins that have activating or regulatory roles in immunologic reactions and constitute the basic molecules of the innate immune response.[1] Activating complement proteins of the complement system are involved in the beginning of three different pathways, and regulatory complement proteins may be soluble (C1-INH, C4BP, Factor H, Factor 1, clusterin, vitronectin, carboxypeptidase) or membrane-bound (CR1, CR59, CR2, CR3, DAF, MCP).[2] Most complement proteins are produced

by hepatocytes, whereas C3, which plays a key role in the complement system pathways, and C1q, which is involved in antibody-mediated rejection in transplantation, are produced in the bone marrow, lymphocytes, and macrophages.[3] Complement system proteins can activate the immune system via three pathways including the classic complement pathway, alternative complement pathway, and lectin pathway.[4]

The activation of complement activation in each pathway occurs by the way of different proteins. In all pathways, however, C5 complement protein breaks up and produces C5a and C5b following generation of C5 convertase. C5b binds to the cell membrane and triggers C6, and later, C6, C7, and C8 are activated by triggerring each other. Subsequently, C8 forms a pore-like membrane attack complex (MAC) in the cell membrane with numerous C9 proteins and causes the membrane to lose its selective permeability property, leading to a change in the cytoplasma composition.[5]

Uncontrolled entry of sodium (Na+) and water into the cell results in cell lysis.[6] The breakup of complement proteins during complement activation causes the release of anaphylatoxins such as C3a, C4a, and C5a. When these anaphylatoxins bind to specific receptors that recognize them, cytokines, chemokines, free oxygen species, free nitrogen species, prostaglandins, and vasoactive molecules may be released from relevant cells. As a result, inflammation occurs with a change in the profile of adhesion molecules expressed on cell surface and in the cell composition in the environment. Due to their impact on both the innate and adaptive immune systems, the complement systems belonging to the patient and donor are significant parameters that affect the success of renal transplantation.[7]

The procedure of dialysis performed in patients with end-stage kidney disease before transplantation has been defined as a risk factor in terms of activation of the complement system.[8] Studies have shown that the rates of C5b-9 and C3d/C3 in plasma increase by 70% throughout a dialysis session.[8] Especially in kidneys obtained from cadaver kidneys , whose hearts have stopped beating, hemodynamic imbalance and hormonal disorder occur and inflammatory responses change because of prolonged cold ischemia durations, and this may result in complement activation.[9]

Complement activation in the transplanted kidney is among the most important causes of graft injury and rejection.[9] Studies have reported that both C5a and sC5b-9 are significantly increased in plasma in brain-dead donors compared with living donors and these high sC5b-9 levels are associated with a higher rejection risk following kidney transplantation.[10-12] In brain-dead donors, C5a release in the circulation and C5aR expression in renal tubular cells increase, thus a local inflammatory response occurs.[13] In a study, in which patients who received kidney transplants from living and cadaveric donors were compared, an increase in sC5b-9 levels in the circulation was reported following transplantation only in patients who received kidney transplants from cadaver donors.[14] In a different study, it was reported that sC5b-9 levels before transplantation could be used as a clinical biomarker for delayed graft function (DGF).[15]

Our study aimed to evaluate the potential relationship between factors affecting kidney transplant success and C5 using bioinformatic tools.

MATERIAL AND METHOD

In our study, we used various bioinformatic tools for the analysis of functional information about the C5 gene, the interactions of the C5 gene with genes, proteins and pathways that may be important in rejection and kidney diseases, and miRNAs affecting the C5 gene, which are described in detail below.

Genecards

The characteristics belonging to the C5 gene were determined by using Genecards, a database that provides genomic, proteomic, transcriptomic, clinical, genetic, and functional information about all genes specified and predicted for human beings up to the present time using about 150 web databases.[16]

Genemania

The Genemania database was used to identify molecular pathways in which the C5 gene was involved, and to determine protein and genetic interactions with other genes, mutual expressions, mutual location, and protein area similarity. In the relevant database, most of the mutual expression data are obtained from the Gene Expression Omnibus (GEO), protein and gene interactions

are obtained from the primary studies found in the BioGRID and PathwayCommons databases, protein area similarities are collected from the InterPro, SMART and Pfam databases, and molecular pathways involved are collected from various source databases such as the Reactome and BioCyc via PathwayCommons.[17]

miRDB

miRNAs targeting C5 were specified using miRDB, which is a bioinformatic tool developed by analyzing thousands of miRNA-target interactions obtained from highly productive sequencing experiences.[18]

String

For demonstrating physical interactions of the C5 gene with other genes and its relationship with various pathways, highly productive laboratory experiments, genomic connection predictions, and literature search were used as a reference. Physical or functional relationships were identified inthe STRING database, which involved the predicted protein-protein interactions.[19]

KEGG

The relationship of the C5 gene with various pathways were identified by using the KEGG database, which provided information about genes' molecular reactions, interrelations and relationship networks in the issues such as metabolism, processing of genetic and environmental information, cellular processes, and diseases.[20]

UniPot

Protein-protein interactions related to the C5 gene and the tissues, in which the C5 gene was expressed, were analyzed by using the UniProt database, which included the protein sequences generated on the basis of the translations of the coding sequences (CDS) presented to the EMBL-Bank/GenBank/DDBJ nucleotide sequence sources (International Nucleotide Sequence Database Collaboration (INSDC).[21]

UCSC

The genes associated with the C5 gene were identified by using the UCSC Genome Browser, which included the data about mRNA alignments, repetetive DNA element matches, gene predictions, gene expression, and associations of genes with diseases.[22]

RESULTS

In the analysis performed in the UniProt database, it was shown that the C5 gene was highly expressed in the normal kidney (Z- score 5.1, 47 peptides) (Table 1). In the analysis performed in the KEGG database, it was found that C5 had an important role in molecular interactions that caused allograft rejection (Figure 1). In the gene-gene interaction analysis performed in the UCSC database, 25 genes, which were most strongly associated with C5, were identified. It is known that CD59, among these genes, is associated with chronic antibody-mediated rejection following renal transplantation (Figure 2). In the analysis performed in the miRDB database, 54 miRNAs targeting the C5 gene were identified, and strong evidence about the relationship of these miRNAs with C5 molecule was obtained (Table 2).

In addition, strong genetic associations with autoimmunity, inflammation, and some syndromes

Table 1. Tissues in which the C5 gene is expressed

Experiments

Name	Source	Evidence	Confidence
Kidney	HPM	47 peptides	★★★☆☆
Liver	HPM	44 peptides	★★☆☆☆
Prostate gland	HPM	42 peptides	★★☆☆☆
Monocyte	HPM	36 peptides	★★☆☆☆
Spinal cord	HPM	35 peptides	★★☆☆☆
Heart	HPM	27 peptides	★★☆☆☆
Esophagus	HPM	26 peptides	★★☆☆☆
Right atrium	Cardiac proteome	2.1E9, 8.1E8, 1.7E9	★★☆☆☆
Left atrium	Cardiac proteome	7.9E8, 2.2E9, 1.1E9	★★☆☆☆
Liver	GNF	273 Intensity units	★★☆☆☆

Text mining

Name	Z-score	Confidence
Blood	5.1	★★★☆☆
Immune system	4.7	★★★☆☆
Blood vessel	4.3	★★★☆☆
Kidney	4.1	★★★☆☆
Heart	4.1	★★★☆☆
Lung	3.8	★★☆☆☆
Liver	3.8	★★☆☆☆
Brain	3.7	★★☆☆☆
Adult	3.7	★★☆☆☆
Blood clot	3.6	★★☆☆☆

abbreviations: HPM, Human Proteome Map; GNF, Gene Expression Atlas

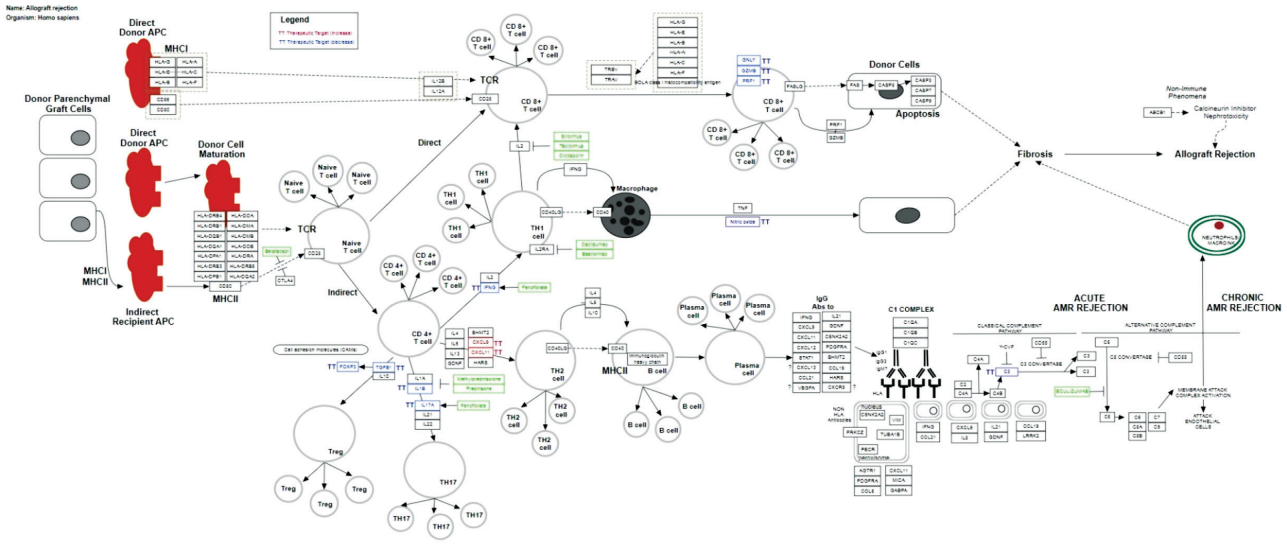

Figure 1. Molecular interactions leading to allograft rejection

were demonstrated. In the analyses performed in the STRING and UniProt databases, it was found that the C5 gene was involved in biologic processes such as complement activation (FDR = 6.46e-22), complement binding (FDR = 2.20e-06), cytolysis (FDR = 4.82e-14), regulation of complement activation (FDR = 4.08e-24), positive regulation of vascular endothelial growth factor production (FDR = 0.0430), regulation of macrophage chemotaxis (FDR = 0.0447), activation of immune response (FDR = 1.26e-13), leukocyte-mediated immunity (FDR = 1.41e-09), innate immune response (FDR = 3.05e-09), allograft rejection (FDR = 2.40e-12), oxidative injury response (FDR = 0.00016), and triggering of the beginning of the complement cascade (FDR = 0.0244) (Table 3).

DISCUSSION

The C5 gene is localized on chromosome 9, in the region q33.2. It encodes a protein belonging to the complement system that has an important role in innate immune response. The C5 protein is composed of C5 alpha and beta chains. These chains are linked to each other with disulphide

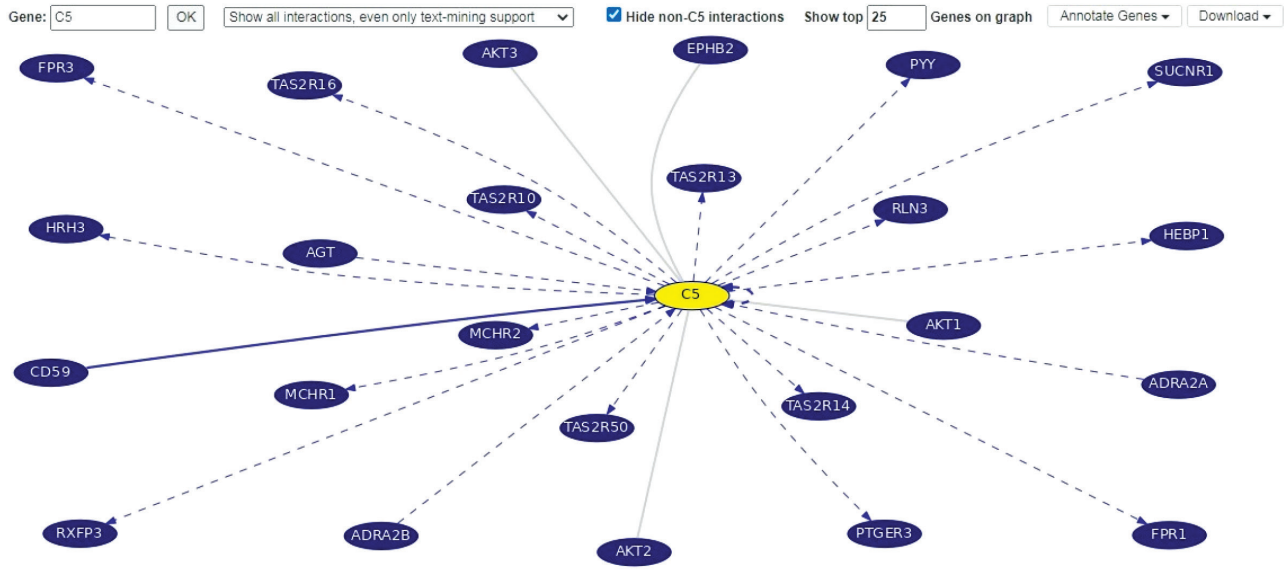

Figure 2. Genes that interact with the C5 gene

Table 2. miRNAs targeting the C5 gene

Target Detail	Target Rank	Target Score	miRNA Name	Gene Symbol	Gene Description
Details	1	94	hsa-miR-28-3p	C5	complement C5
Details	2	91	hsa-miR-205-3p	C5	complement C5
Details	3	90	hsa-miR-498-5p	C5	complement C5
Details	4	89	hsa-miR-28-577	C5	complement C5
Details	5	86	hsa-miR-6797-3p	C5	complement C5
Details	6	85	hsa-miR-4263	C5	complement C5
Details	7	83	hsa-miR-6076	C5	complement C5
Details	8	83	hsa-miR-1289	C5	complement C5
Details	9	79	hsa-miR-548e-5p	C5	complement C5
Details	10	79	hsa-miR-570-3p	C5	complement C5
Details	11	76	hsa-miR-4748	C5	complement C5
Details	12	76	hsa-miR-4716-5p	C5	complement C5
Details	13	76	hsa-miR-4464	C5	complement C5
Details	14	74	hsa-miR-1266-3p	C5	complement C5
Details	15	74	hsa-miR-3942-3p	C5	complement C5
Details	16	69	hsa-miR-4689	CS	complement C5
Details	17	68	hsa-miR-7159-5p	C5	complement C5
Details	18	67	hsa-miR-519c-3p	C5	complement C5
Details	19	67	hsa-miR-519b-3p	C5	complement C5
Details	20	67	hsa-miR-4290	C5	complement C5
Details	21	67	hsa-miR-519a-3p	C5	complement C5
Details	22	67	hsa-miR-676-5p	C5	complement C5
Details	23	65	hsa-miR-302e	C5	complement C5
Details	24	62	hea-miR-6858-5p	C5	complement C5
Details	25	61	hsa-miR-5590-3p	C5	complement C5
Details	26	61	hsa-miR-142-5p	C5	complement C5
Details	27	59	hsa-miR-1227-3p	C5	complement C5
Details	28	59	hsa-miR-33a-3p	C5	complement C5
Details	29	58	hsa-miR-3163	C5	complement C5
Details	30	58	hsa-miR-4477a	C5	complement C5
Details	31	58	hsa-miR-766-5p	C5	complement C5
Details	32	58	hsa-miR-183-5p	C5	complement C5
Details	33	57	hsa-miR-5583-3p	C5	complement C5
Details	34	57	hsa-miR-6730-5p	C5	complement C5
Details	35	56	hsa-miR-15a-3p	C5	complement C5
Details	36	55	hsa-miR-5571-5p	C5	complement C5
Details	37	54	hsa-miR-302d-3p	C5	complement C5
Details	38	54	hsa-miR-302b-3p	C5	complement C5
Details	39	54	hsa-miR-302c-3p	C5	complement C5
Details	40	54	hsa-miR-302a-3p	C5	complement C5
Details	41	53	hsa-miR-6813-3p	C5	complement C5
Details	42	52	hsa-miR-3666	C5	complement C5
Details	43	52	hsa-miR-301b-3p	CS	complement C5
Details	44	52	hsa-miR-19b-3p	C5	complement C5
Details	45	52	hsa-miR-301a-3p	C5	complement C5
Details	46	52	hsa-miR-4295	C5	complement C5
Details	47	52	hsa-miR-130a-3p	C5	complement C5
Details	48	52	hsa-miR-19a-3p	C5	complement C5
Details	49	52	hsa-miR-130b-3p	C5	complement C5
Details	50	52	hsa-miR-454-3p	C5	complement C5
Details	51	51	hsa-miR-580-5p	C5	complement C5
Details	52	51	hsa-miR-765	C5	complement C5
Details	53	51	hsa-miR-4534	C5	complement C5
Details	54	50	hsa-miR-543	C5	complement C5

Table 3. Biologic processes in which the C5 gene is involved

Biological Process (Gene Ontology)				
GO-term	**Description**	**Count in network**	**Strength**	**False discovery rate**
GO:0006957	Complement activation, alternative pathway	7 of 13	2.98	3.00e-16
GO:0006958	Complement activation, classical pathway	8 of 38	2.57	2.57e-16
60:0019835	Cytolysis	7 of 34	2.56	4.82e-14
00:0030449	Regulation of complement activation	11 of 56	2.54	4.08e-24
60:0006956	Complement activation	9 of 54	2.47	4.77e-18
Molecular Function (Gene Ontology)				
G0:0001848	Complement binding	4 of 21	2.53	2.20e-06

bonds. Degradation of the alpha chain by the convertase enzyme during complement activation results in generation of C5a and C5b. C5a is an anaphylatoxin with strong chemotactic activity, and C5b is a subunit of MAC.[23] Previous studies have reported that C3a and C5a are associated with various inflammatory and autoimmune diseases including renal allograft rejection and renal ischemia/reperfusion injury.[24-29] It has been reported that expression of C3a, C5a, and their receptors in the kidney is significantly associated with the activity and severity of kidney injury.[30] In addition, other research have showed that the level of donor-specific antibody developing after transplantation is especially associated with activation of the complement system and might ultimately cause antibody-mediated rejection.[31,32]

In a study conducted by Farrar *et al.*, it was reported that C3a and C5a produced systemically or locally could lead to allograft rejection by incresing antigen presentation and T cell response.[33] Eculizumab is a monoclonal antibody that prevents decomposition of C5, a complement sytem protein, into its proinflammatory components, and studies have shown that eculizumab treatment reduces the incidence of acute antibody-mediated rejection in sensitized kidney transplant recipients.[34] In a study conducted by Cernoch *et al.*, higher levels of C3, CD55, CD59, CFH, CFI, and C1-INH expression were shown in the grafts of the patients who had chronic antibody-mediated rejection.[35] In our study, a strong relationship was found between C5 and CD59 in the bioinformatic analysis performed for gene-gene interaction.

The literature includes abundant evidence indicating that miRNA expressions in grafts or in serum, plasma, and urine samples of kidney transplant recipients are significant markers for monitoring the response in terms of rejection and the development of chronic allograft nephropathy, following kidney transplantation. However, there are limited data demonstrating their functions in molecular pathways in allograft pathologies.[36]

In a study, in which expression profiles of miRNAs were compared in kidney transplant recipients, who had chronic antibody-mediated rejection and healthy graft function, miR-142-5p was reported to be increased in biopsies obtained from patients with antibody-mediated rejection (AMR) and in an experimental model of chronic AMR. In the same study, it was shown that miR-142-5p was not expressed in peripheral blood mononuclear cells in patients with kidney failure, suggesting that excessive expression in chronic AMR was a result of immunologic disorders rather than renal dysfunction.[37] In another study, which investigated microRNAs that could predict renal allograft status, it was shown that miR-142-5p was expressed excessively in biopsies with allograft rejection.[38] We also found that miR-142-5p was strongly associated with C5 expression in the bioinformatic analysis performed to identify C5-associated miRNAs. In addition, various clinical studies in the literature showed that miR-302b and miR-302c, which were shown to have a strong relationship with C5 in our study, played a key role in lung transplantation,[39] miR-19a and miR-33a played a key role in liver transplantation,[40] miR-28-3p played a key role in bone marrow transplantation,[42] and miR-142-5p played a key role in renal transplantation.[38] These studies suggest that miRNAs may be promising for early diagnosis of organ rejection in the clinical setting. Experimental studies aiming to demonstrate the effect of the relationship between miRNAs and C5 in various organ transplantations on allograft status after transplantation, would potentially contribute to the literature.

CONCLUSIONS

The complement system of the patient and the candidate donor has significant impact on transplantation success, especially in solid organ transplantations. C5 protein is an important complement protein that has significant roles in the terminal stage in complement activation. Factors such as dialysis sessions performed in patients with end-stage kidney disease, donor-specific antibodies, and donor type plan (cadaveric or living donor), affect allograft survival after kidney transplantation. In our study, other genes, proteins, and pathways that are in interaction with the C5 gene, which is important in complement response, miRNAs, and expression profiles were analyzed by using bioinformatic analysis. The data obtained are guiding for future experimental studies. Supporting these data with experimental studies will provide foresight for physicians about allograft status following transplantation, give way to the development of biomarkers for the probability of rejection, guide physicians about immunosuppressive treatment to be administered, and contribute to the literature by providing data that will enable a much longer survival for allografts.

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None declared.

DISCLOSURE STATEMENT

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

The authors accept responsibility for all content of this manuscript and approve its submission.

AUTHOR CONTRIBUTIONS

Working Concept/Design—Oguz SR, Kivanc D,, Senturk HS, Data Collection- Kivanc D,, Senturk HS, Gurer EE; Data Analysis/Interpretation- Oguz RS, Sentuk HS, Karadeniz S, Ozdilli K.; Manuscript Draft- Oguz RS, Kivanc D,, Senturk HS.,; Critical Review of Content- - Senturk HS, Ozdilli K, Karadeniz S.; Final Approval and Responsibility- Oguz SR, Kivanc D,, Ozdilli K, Karadeniz S, Gurer EE, Senturk HS; Material and Technical Support- Ozdilli K, Karadeniz S, Gurer EE.; Supervision- Ozdiili K, Karadeniz S, Senturk HS.

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