History of Medicine, 2023, 9(1): 1763–1768
DOI: 10.17720/2409-5834.v9.1.2023.225

The multifaceted role of Dectin-1 and Card9 in inflammatory bowel disease Iraqi patients

Alaa Saad Hasan[1*], Hazima Mossa Alabassi[2], Thamer A.A. Muhsen[3]

[1], [2], [3]Department of Biology, college of Education for pure Science (Ibn Al-Haitham), University of Baghdad, Iraq
Email: Alaasaad4458@gmail.com,

***Correspondence author:** Hussam Alabdullah (dr.surgeon2@gmail.com)

Received: 20 January 2023 **Accepted:** 15 April 2023

Citation: Hasan AS, Alabassi HM, Muhsen TAA (2023) The multifaceted role of Dectin-1 and Card9 in inflammatory bowel disease Iraqi patients. History of Medicine 9(1): 1763−1768. https://doi.org/10.17720/2409-5834.v9.1.2023.225

Abstract

The study aimed to investigate the role of Dectin-1 and Card-9 in pathogenicity of inflammatory bowel disease (IBD). This investigations involved 150 blood samples for IBD patients which divided in to two groups (50 for crohns disease CD (G2)and 50 for ulcerative colitis UC (G3)) .All a apparently (male and female) attended to) Al-Kindy hospital) in Baghdad city, department of Gastroenterology .and all of thin were diagnosis by consulters medical staff and pathologists with age range 15-65years average 40 years .in addition to 50 blood samples were collected from apparently healthy individuals as control group (G1). 10 ml were withdrawn from all participants, 5ml for the immunological study which carried by ELISA technique and 5 ml used for molecular study carried by RT-PCR. Serum was isolated than keep -20 until used m RNA were excreted The results of card9 and Dectin -1showed that, the serum concentration recorded a was highly significantly increasing level in crohns group (G2) and ulcerative colitis (G3) comparison to control group(G1) p value =0.002, 0.008 respectively also for card9 and Dectin-1. There is a non-significant in Card 9 and Dectin-1 level in the G2, G3 patients infected with Candida compared toG1, P value= 0.176 NS. 0.39 NS respectively. It has been noticed a significant Elevated Card9 andDectin-1 gene expression in patients group patients (G2) (G3) compared to (G1)p value =<0.001., <0.001** respectively Conclusion: The Dectin-1and CARD9 may has a role in the inflammatory process and might be involved in the IBD pathophysiology

The inflammatory bowel disease (IBD), Crohn's disease (CD) and ulcerative colitis (UC) are heterogenous chronic inflammatory disorders of the gastrointestinal tract (Hwyidii etal., 2014; Waly etal., 2022) Two main clinical types of IBD are recognized, namely ulcerative colitis (UC) and Crohn's disease (CD). (. Abdul-Hussein etal, 2021; Abdulamir etal., 2012.) that require long-term treatment or maintenance therapy (Jebur etal., 2018) Crohns disease (CD) is a relapsing chronic inflammatory bowel disease that can affect any part of the gastrointestinal tract, from the mouth to the anus. (Van Assche et al., 2010): Ulcerative colitis is a chronic inflammatory bowel disease (IBD); its extra gastrointestinal manifestations vary from one country to another and is a chronic inflammatory condition causing mucosal inflammation of the colon without granulomas on biopsy, affecting the rectum and a variable extent of the colon, which is characterized by a relapsing and remitting (Al-Khazraji, .2011; Dignass et al., 2012). Loss of epithelial barrier function increased colonic immune cell infiltration and upregulation of pro-inflammatory cytokines are the hallmarks of IBD. (Kanvinde., 2018). .However, the pathogenesis and etiology of UC and CD are not well-characterized, but both phenotypes are suggested to be the manifestation of complex and multifactorial processes, in which genetics, environmental influences and immunologic abnormalities may play the most important role to promote an excessive and poorly controlled mucosal inflammatory response directed against components of the luminal microflora that lead to an IBD-related tissue damage, which results from a dynamic interplay between immune and non-immune cells, in which cytokines are crucial mediators in this interplay) Ad'hiah etal., 2008). A study indicated an important role for IL1 SNPs in the pathogenesis of inflammatory bowel disease in the Iraqi Arab population. (Ad'hiah etal., 2019). Interleukin -17 pathway plays an important role in development of inflammatory bowel diseases (IBD) Muhammed etal., 2016). like that Up-regulation (IL-8, IL-12 and IP-10) and down-regulation (IL-10) of cytokines are suggested to have a role in pathogenesis of UC and CD of Iraqi IBD patients (Al-Abassi etal., 2015). Interleukine-33

might be a crucial mediator in the pathogenesis of inflammatory bowel disease (Hwyidii etal., 2014). The TNF-a gene considered as strong candidate for immune modulator and pro inflammatory cytokine responsible for genetic susceptibility of chronic disease such as the initiation and development of (IBD). (Fadhe. and Mahood ., 2020) Epstein-Barr virus seropositivity has been detected among IBD cases, however viral infection may be associated with distinct cases and Severe cases requiring antiviral treatment(Ghazi etal., 2022).An important factor for the disease is the thickness of the The mucous membranes of intestines, particularly in the colon and rectum, as this layer is the type of food The emergence of biomarkers in subtle signs of inflammatory disease IBD, especially Crohn's disease (CD) in the early stages On other bacteria, fungi, viruses, microbes work in a secondary organ system that leads Critical biological functions of the host through functional mechanisms as it triggers an immune response against Intestinal microbiome T-helper cells T-h17 and T-h1 are involved, which are activated by microbial antigens, causing tissue injury and leading to a decreasing in the mucous membrane layer of the intestine, causing the penetration of microbes into the Intestinal tissue, which helps in the formation of more microbial antigens(Zou and Ng, 2018)

Dectin-1

Dectin-1 Dectin-1 is a primary and well-studied C-type lectin receptor (CLR) that is primarily responsible for β-glucan recognition and control of fungal infection (Taylor et al., 2007). Dectin-1 belongs to the hemITAM family and can be found in the plasma membrane of various myeloid cells,

including DCs, monocytes, and macrophages, as well as B cells. Activation of dectin-1 by fungal cell wall, β-glucans stimulates phagocytosis, to produce reactive oxygen species(ROS), and Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) -mediated cytokine secretion. In contrast to the TLR pathways, dectin-1−mediated NFκB signaling is driven by Syk recruitment and the Fungi are recognized by a number of immune receptors among which Dectin-1 has emerged as key for phagocytosis and killing by myeloid phagocytes. Dectin-1 is a C-type lectin receptor that recognizes β-1, 3-glucans found in the cell walls of nearly all fungi. Dectin-1 activates intracellular signals through CARD9 leading to

inflammatory cytokine production and induction of T helper 17 (Th17) immune responses (Cheng etal 2011)

CARD9

CARD-9 is Caspase recruitment domain-containing protein 9 (CARD9) is a cytosolic adaptor protein in myeloid cells, which plays an important role in immunity response. CARD9 can trigger the NF-κB and MAPK signaling pathways, induce the inflammation cytokine cascade, and subsequently protect the host from microbial invasion, especially fungal infection.(. Ji etal., ., 2021). Inflammatory bowel disease (IBD) involves a dysregulated immune response to the gut microbiota. Emerging evidence has demonstrated that dysfunctions in caspase recruitment domain-containing protein 9 (CARD9) may contribute to the pathogenesis of IBD. Interestingly, an allelic series of Card9 variants have both a common predisposing and rare protective function in IBD patients (Luo etal., 2020) Innate immune cells recognize evolutionarily conserved microbial molecules through pattern recognition receptors (PRRs), such as C-type lectin receptors (CLRs) and Toll-like receptors (TLRs). These PRRs on the surface of innate cells effectively sense distinct microbial components and can trigger an inflammatory cascade in a CARD9-dependent manner. CARD9 is required for TLR pathways to activate mitogen-activated protein kinase (MAPK) and CLRs pathways to activate nuclear factor-kappaB (NF-κB). As a result, CARD9, a signaling adaptor known to regulate innate immune activation, plays a major role in the sensing of pathogenic microorganisms (Zhong etal., 2018). CARD9 loss-of-function mutations in patients have unequivocally demonstrated its importance in fungal infections, predominantly localizing to the central nervous system (CNS), subcutaneous tissues, oral mucosa, bone, and abdominal organs (. Drummond. and Lionakis2016). The species of pathogenic fungi are found to be Candida species, dark-walled molds, and yeast-like fungi (e.g., Phialophora, Aspergillus, fumigatus and Exophiala), some of them maybe cause lethal infections (. Rieber etal ., ., 2016). CARD9 was confirmed to play an essential role in the pathogenesis of inflammatory bowel diseases. CARD9, as a susceptibility factor for colitis, mainly induces the intestinal mucosal immune response and mediates gut microbiota composition and metabolism. metabolism. Interestingly, an allelic series of Card9 variants have both a common predisposing and rare protective function in IBD patients (Luo etal., 2020).

Material and Method

Subject collection

The current study included 150 participants(100 patients distributed as 50 patients with CD who were early diagnosed(G2)and 50 patients with UC also early diagnosed (G3)while the rest

(50)apparently healthy represent the control group (G1).All samples with age range (15-65)Years with average 40 years .All a apparently (male and female) attended to. the Al-Kindy hospital - in Baghdad, Department of Gastroenterology. The sample collected at period from Jan-2022 until Nov-2022.Patiants diagnosis carried out under the suppression of consultant medical staff and pathologists. All patients with other disease i.e. (any kinds of autoimmune diseases or chronic diseases) were excluded. The study has two parts (serological and molecular). blood samples were withdrawn from all participants, then serum and mRNA was isolated. ELISA was carried out to determent the serum level of Dectin-1and card-9 in all sample while RT-PCR was carried out to determine the gene expression fold for the same factors (Dectin-1and card9). For this, ELISA research kits from the Chinese company (BT LAB) were used. RT-PCR kits purchased from the American company (KAPA SYBR® FAST qPCR Master Mix (2X) Kit) were used for this purpose.

Results

Dectin-1 and card-9serum level

The result showed a significant increasing in two patients' groups (G2and G3) the Mean+S.E were ((505.02±21.76, 524.03±24.63) PG /ml in comparison to control G1was (594.91±16.71) PG/ml

p value=.0.008**but with anon significant difference between G2and G3 P value= 0.53. as shown in table (1).

Table 1: Serum levels of Dectin-1 a among three studied group.

Parameter	Patients Groups	Mean+S.E	P value
Dectin -1 (ng/L)	Control	594.91±16.71	0.008**
	Crohn's	505.02±21.76 [a]	
	Ulcerative colon	524.03±24.63 [a]	
	Between two diseases		0.53 NS

Also in regard to card-9, the result also showed a significant increasing inG2andG3 the Mean+S.E were (257.87±17.31, 237.34±7.12) PG/ml respectively in comparison to control group(G1). (202.45±5.24) PG/ml. P value =0.002** and a non-significant difference between G2and G3, P value= 0.19. as shown in table (2).

Table2: Serum levels of Card9 among three studied groups.

Parameter	Patients Groups	Mean+S.E	P value
CARD9 (ng/L)	Control	202.45±5.24	0.002**
	Crohn's	257.87±17.31 [a]	
	Ulcerative colon	237.34±7.12 [a]	
	Between two diseases		0.19 NS

a significant vs. control

Dectin-1 and card-9 serum level in infected patients with candida

The result of Dectin-1 serum level in G1 and G2 which infected with candida showed that there was no significant difference the Mean+S.E were(498.82±22.54, 523.24±28.43) PG/ml respectively compared to control (558.28±27.23) PG/ml, P value = 0.39 . .as shown in table (3).

Table3: Serum levels of Dectin-1 a among three groups infected with candida

Table3: Serum levels of Dectin-1 a among three groups infected with candida

Parameter	Fungi groups		Mean+S.E	P value
Dectin-1(ng/L)	Control G1	Candida	558.28±27.23	0.39 NS
	Crohn's G2	Candida	498.82±22.54	
	Ulcerative colitis G3	Candida	523.24±28.43	

Card-9 Also showed a non-significant different among the three studied groups infected with candida. The Mean+S.E were(252.23±21.55, 236.64±8.30, 197.02±9.25) PG/ml respectively P value = 0.176 . .as shown in table (4).

Table4: Serum levels of card9 among three groups infected with candida

Parameter	Fungi groups		Mean+S.E	P value
CARD9 (ng/L)	Control G1	Candida	197.02±9.25	0.176 NS
	Crohn's G2	Candida	252.23±21.55	
	Ulcerative colitis G3	Candida	236.64±8.30	

The Dectin-1 and Card-9 gene expression

The result of gene expression were in compatible with immunological study, Dectin-1 gene expression recorded a highly significant decreasing in G2and G3 as compared to G1 the Mean+S.E were (0.38±0.04 a, 0.48±0.07, 1.04±0.14) PG/ml fold respectively, P value =<0.001**and there was no significant difference between G2and G3 P value=0.46. As shown in table (5).

Table5: Gene expression of Dectin-1 among three studied groups

Gene	Patients Groups	Expression (Mean+S.E)	P value
Detectin 1	Control G1	1.04±0.14	<0.001**
	Crohn's G2	0.38±0.04 [a]	
	Ulcerative colitis G3	0.48±0.07 [a]	
	Between two diseases		0.46 NS

Card-9 showed that there is a moral gene expression in G2, while G3 recorded a slight rise in compared to G1 the Mean+S.E were (3.02±0.50 a, 1.76±0.15). PG/ml fold respectively compared to G1(1.02±0.14) PG/ml, P value =<0.001**.and there was a highly significant difference between G2 and G3 p value =0.001**. .As shown in table (6).

Table6: Gene expression of card-9among three studied groups

Parameter	Patients Groups	Mean+S.E	P value
CARD9	Control G1	1.02±0.14	<0.001**
	Crohn's G2	3.02±0.50 [a]	
	Ulcerative colitis G3	1.76±0.15	
	Between two diseases		0.001**

Discussion

Dectin-1 is the most investigated molecule, its role in the control of gut inflammation (Iliev and Leonardi., 2017). card9 induces the intestinal mucosal immune response and mediates gut microbiota composition and metabolism (Luo etal., 2020) According to evidence when opportunistic fungi are present in the intestine, absence of Dectin-1 can allow for fungal invasion of the intestinal mucosa and can be detrimental during colitis (Tang etal., 2015). The current study recorded a significant decreasing in Dectin-1 serum level while card-9 recorded a significant increasing , Also Dectin-1 recorded a non-significant decrease serum level in IBD patients who infected with candida while Card-9 recorded the increasing with a non-significany so according to this finding we can conclude that the declining in Dectin-1or deficiency in Dectin-1 .may reflect mutation in Dectin-1 gene which may lead to this decreasing especially in IBD patients or we may suppose that candida may alter then surface component to evade immune response so Dectin-1 cannot recogniz it as a result serum level decreasing or the soluble form of Dectin-1may depleted because it consumed by the candida and other pathogenic organism . This agree with (Iliev., 2017) who said the absence of Dectin-1 can allow for fungal invasion of the intestinal mucosa and can be detrimental during colitis it can lead to inability of the host to properly deal with opportunistic fungi in the gut. Thus, the ability of C. albicans to switch between different forms may be a key virulence It has also been suggested that fungal pathogens actively mask their β-glucans to avoid immune recognition by Dectin-1 (Gantner et al. 2005; Wheeler and Fink 2006). In regard to Card-9 who recorded a slight non-significant increasing serum level in spite of the non-significancy which may belong to the small sample size but still it has a rise serum level in patients with IBD, as we know Card-9consider role drive to the suggestion that Card-9 may have a specific in IBD pathogenicity. CARD9 as an intracellular adaptor molecule could activate NF−κB and/or MAPK signal pathways in macrophages and dendritic cells, leading to an inflammatory cascade against the invasive bacteria, fungi, and virus(Sheng etal., 2021). The finding of the current study(which recorded up regulation gene expression for Dectin-1and card 9suppport our hypothesis that Dectin-1 and card9were an important role in IBD pathogenesis may support our hypothesis Dectin-1and card-9recorded a significant gene expression in IBD that both of them has an important role in IBD pathogenicity .The contradictory in our result (immunological and molecular)may related to many causes

1-ELISA technique assess the accumulative level, since patients has a fungal infection so Dectin-1and card-9 may depleted in serum

2-RT-PCR assess the instantaneous concentration, as all IBD patients has fungal infection, so there is always a demand to continuous expression for the two molecule

In spite of that there was no significant difference in Dectin-1 serum level in patients infected with candida and other fungi, still there was a slight decreasing in

Dectin-1 serum level in patients with CD patients with CD. make Abs against fungal component chitin and B-glycan(Mason ., 2012). There for Dectin-1may play a role in intestinal homeostasis and it was mediated phagocytosis and many cytokines response like TNF-α and IL-8. (Naglik etal., 2008; Plantinga etal., 2009).while CARD-9 recorded a non significant increasing serum level and as we know that CARD-9 signaling adaptor is regulate innate immune activation and play a major role in sensing pathogenic organism and mice CARD-9(-, -)phenotype were associated with defective intestinal humeral Immune response (Luo etal., 2020).So the increasing of its level this study may belong to above reasons

Conclusion

Based on the current finding Dectin-1 deficiency may allowed fungal invasion of mucosa and Card-9 may an aggressive inflammation, so, both of them may consider a good therapeutic target to stop the aggressiveness of the disorders

References

Abdulamir, A.S., Zaman, M.Z., Hafidh, R.R. and Bakar, A., 2012. The Role of Diet, Prebiotic and Probiotic in the Development and Management of Inflammatory Bowel Diseases (IBD). Inflammatory Bowel Disease-Advances in Pathogenesis and Management.

Abdul-Hussein, S.S., Ali, E.N., Alkhalidi, N.M., Zaki, N.H. and Ad'hiah, A.H., 2021. Roles of IL-17A and IL-23 in the Pathogenesis of Ulcerative Colitis and Crohn's Disease. Iraqi Journal of Science, pp.2526-2535.

Ad'hiah, A.H., Hessan, E.B. and Shahab, B.A., 2019. Interleukin-1 single nucleotide polymorphisms as risk factors for susceptibility of inflammatory bowel disease: an Iraqi Arab population-based study. Alexandria Journal of Medicine, 55(1), pp.1-6.

Ad'hiah, A. H., Jasim H. A. and Fadhil, A. M. A. (2008) HLA antigens and inflammatory bowel disease in a sample of Iraqi patients. Eastern Mediterranean Health Journal, 14: 1155-1162

Al-Abassi, H.M., Nazal, M.F., Ad'hiah, A.H., Mushe'al, K.I., Mubarak, I.H., Alqaisy, I.A., Saadi, A.W. and Kadhim, S.S., 2015. Serum profile of cytokines in Iraqi inflammatory bowel disease patients. Mustansiriya Medical Journal, 14(2), p.11.

Al-Khazraji, K.A., 2011. Descriptive study of Extragastrointestinal Manifestations of Ulcerative Colitis and their relation to disease activity in 100 Iraqi patients. Journal of the Faculty of Medicine Baghdad, 53(1), pp.24-28.

Cheng, S.C., van de Veerdonk, F.L., Lenardon, M., Stoffels, M., Plantinga, T., Smeekens, S., Rizzetto, L., Mukaremera, L., Preechasuth, K., Cavalieri, D. and Kanneganti, T.D., 2011. The dectin-1/inflammasome pathway is responsible for the induction of protective T-helper 17 responses that discriminate between yeasts and hyphae of Candida albicans. Journal of leukocyte biology, 90(2), pp.357-366.

Dignass, A., Lindsay, J.O., Sturm, A., Windsor, A., Colombel, J.F., Allez, M., D'Haens, G., D'Hoore, A., Mantzaris, G., Novacek, G. and Öresland, T., 2012. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. Journal of Crohn's and Colitis, 6(10), pp.991-1030.

Drummond, R.A. and Lionakis, M.S., 2016. Mechanistic insights into the role of C-type lectin receptor/CARD9 signaling in human antifungal immunity. Frontiers in cellular and infection microbiology, 6, p.39

Fadhe, I. and Mahood, W.S., 2020. Genotyping of Tumor Necrosis Factor-? in Inflammatory Bowel Iraqi Patients. Indian Journal of Forensic Medicine & Toxicology, 14(2), pp.526-532.

Ghazi, H.F., Alubaidi, G.T. and Fahad, H.M., 2022. SERO-PREVALENCE OF EPSTEIN-BARR VIRUS IN IRAQI INFLAMMATORY BOWEL DISEASE. Wiad Lek, 75(8), p.2.

Hwyidii, R.R., Abbas, A.A. and AL-Khazraji, K.A., 2014. The Role of Interleukine-33 in Inflammatory Bowel Disease. Al-Kindy College Medical Journal, 10(2), pp.14-18.

Jebur, N.J., Kadhim, D.J. and Firhan, N.M., 2018. Belief about Medications among Sample of Iraqi Patients with Inflammatory Bowel Disease. Iraqi Journal of Pharmaceutical Sciences (P-ISSN 1683-3597 E-ISSN 2521-3512), pp.32-41.

Ji, C., Yang, Z., Zhong, X. and Xia, J., 2021. The role and mechanism of CARD9 gene polymorphism in diseases. biomedical journal, 44(5), pp.560-566.

Kanvinde, S., Chhonker, Y.S., Ahmad, R., Yu, F., Sleightholm, R., Tang, W., Jaramillo, L., Chen, Y., Sheinin, Y., Li, J. and Murry, D.J., 2018. Pharmacokinetics and efficacy of orally administered polymeric chloroquine as macromolecular drug in the treatment of inflammatory bowel disease. Acta biomaterialia, 82, pp.158-170.

Liu, X., Jiang, B., Hao, H. and Liu, Z., 2022. CARD9 Signaling, Inflammation, and Diseases. Frontiers in Immunology, 13, p.880879. Lloyd-Price, J., Arze, C., Ananthakrishnan, A.N., Schirmer, M., Avila-Pacheco, J., Poon, T.W., Andrews, E., Ajami, N.J., Bonham, K.S., Brislawn, C.J. and Casero, D., 2019. Multi-omics of the gut microbial ecosystem in inflammatory bowel diseases. Nature, 569(7758), pp.655-662.

Luo, P., Yang, Z., Chen, B. and Zhong, X., 2020. The multifaceted role of CARD9 in inflammatory bowel disease. Journal of cellular and molecular medicine, 24(1), pp.34-39.

Luo, P., Yang, Z., Chen, B. and Zhong, X., 2020. The multifaceted role of CARD9 in inflammatory bowel disease. Journal of cellular and molecular medicine, 24(1), pp.34-39

Mason, K.L., Erb Downward, J.R., Falkowski, N.R., Young, V.B., Kao, J.Y. and Huffnagle, G.B., 2012. Interplay between the gastric bacterial microbiota and Candida albicans during postantibiotic recolonization and gastritis. Infection and immunity, 80(1), pp.150-158.

Mohammed, A.K., Al-Qadhi, H.I., Alkhalidi, N.M. and Fawzi, H.A., 2020. Effectiveness of Infliximab and Adalimumab in Iraqi patients with ulcerative colitis–Real-World Data. Journal of Advanced Pharmacy Education & Research| Apr–Jun, 100(2), p.47.

Muhammed, H.J., Mohsun, N.N. and Al-Kaisi, A.A., 2016. Effect of IL-17 Single Nucleotide Polymorphisms Gene on the Risk of Developing Colorectal Cancer in Iraqi Patients. Iraqi journal of biotechnology, 15(2).

Naglik, J.R., Fidel Jr, P.L. and Odds, F.C., 2008. Animal models of mucosal Candida infection. FEMS microbiology letters, 283(2), pp.129-139

. Plantinga, T.S., van der Velden, W.J., Ferwerda, B., van Spriel, A.B., Adema, G., Feuth, T., Donnelly, J.P., Brown, G.D., Kullberg, B.J., Blijlevens, N.M. and Netea, M.G., 2009. Early stop polymorphism in human DECTIN-1 is associated with increased candida colonization in hematopoietic stem cell transplant recipients. Clinical Infectious Diseases, 49(5), pp.724-732.

Rieber, N., Gazendam, R.P., Freeman, A.F., Hsu, A.P., Collar, A.L., Sugui, J.A., Drummond, R.A., Rongkavilit, C., Hoffman, K., Henderson, C. and Clark, L., 2016. Extrapulmonary Aspergillus infection in patients with CARD9 deficiency. JCI insight, 1(17).

Rogler, G. and Vavricka, S., 2015. Exposome in IBD: recent insights in environmental factors that influence the onset and course of IBD. Inflammatory bowel diseases, 21(2), pp.400-408.

Seelig, M.S., 1966. Mechanisms by which antibiotics increase the incidence and severity of candidiasis and alter the immunological defenses. Bacteriological reviews, 30(2), pp.442-459.

Taylor PR, Brown GD, Reid DM, Willment JA, Martinez-Pomares L, et al. The beta-glucan receptor, dectin-1, is predominantly expressed on the, surface of cells of the monocyte/macrophage and neutrophil lineages. Journal of Immunology. 2002;169:3876–3882.

Taylor, P.R., Tsoni, S.V., Willment, J.A., Dennehy, K.M., Rosas, M., Findon, H., Haynes, K., Steele, C., Botto, M., Gordon, S. and Brown, G.D., 2007. Dectin-1 is required for β-glucan recognition and control of fungal infection. Nature immunology, 8(1), pp.31-38.

Underhill, D.M. and Braun, J., 2022. Fungal microbiome in inflammatory bowel disease: a critical assessment. The Journal of Clinical Investigation, 132(5).

Van Assche, G., Dignass, A., Panes, J., Beaugerie, L., Karagiannis, J., Allez, M., Ochsenkühn, T., Orchard, T., Rogler, G., Louis, E. and Kupcinskas, L., 2010. The second European evidence-based consensus on the diagnosis and management of Crohn's disease: definitions and diagnosis. Journal of Crohn's and Colitis, 4(1), pp.7-27.

Waly, A.H.T., Barraj, A.H. and Alrikabi, M.H., 2022. Estimation of Calprotectin, IL-17, and IL-23 levels in the Blood of Iraqi Patients with Crohn's Disease. The Egyptian Journal of Hospital Medicine, 88(1), pp.3699-3702.

Zhong, X., Chen, B., Yang, L. and Yang, Z., 2018. Molecular and physiological roles of the adaptor protein CARD9 in immunity. Cell death & disease, 9(2), p.52.

Zhou, G.G.D., Song, D., Choi, C.E., Pasuto, A., Sun, Q.C. and Dai, D.F., 2018. Surge impact behavior of granular flows: effects of water content. Landslides, 15, pp.695