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Biochemical Features and Clinical Importance of Calprotectin: A Review Article

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ABSTRACT

Calprotectin (S100A8/S100A9) is a heterodimeric protein most abundant in neutrophils. It has recently gained much attention as a reasonable biomarker to monitor and diagnose inflammatory bowel diseases-IBD; more specifically, it represents Crohn's Disease-CD and Ulcerative Colitis-UC. In clinical applications, its main importance lies in being a non-invasive marker for gut inflammation, such as when expressed in conditions like CD and UC. A comprehensive understanding of the multiple functions that calprotectin plays within inflammatory responses will lead to more precise diagnostics as well as improved treatment strategies within the clinical setting. This review article provides a synthesis of recent research advances with respect to biochemical properties and functions relating to calprotectin within IBD through perspectives focused on its role both diagnostically and therapeutically. Its very complex chemical structure has attracted much interest lately in connection with related biochemical mechanisms of its synthesis. This paper further synthesizes existing research findings on calprotectin's chemical structure and production sources, highlights knowledge gaps in those areas, and suggests directions for future research.

KEYWORDS

Calprotectin, heterodimer, IBD, inflammatory response

INTRODUCTION

As a major component of neutrophils and monocytes, calprotectin participates in inflammation and therefore serves as a useful marker for inflammatory diseases within the bowel. Calprotectin is basically formed by two S100 proteins: S100A8 and S100A9. The association between these two proteins significantly contributes to stability as well as functional attributes that calprotectin manifests in any conditions relating to the gastrointestinal tract. Understanding the structural features of calprotectin, especially its binding sites and changes when it assumes different conformations under various biochemical conditions, is key to understanding its role in inflammation and disease processes. Results

described by Franzosa et al., (2018) would show an association between levels of calprotectin and metabolic shifts within the gut microbial community; those results would imply that changes in biochemical conditions may apply challenges against structural integrity and functional properties for calprotectin. This statement emphasizes how important big-picture detail on chemical structure concerning biological activity should be, particularly amid numerous conditions centered around inflammation .Calprotectin is mainly produced by neutrophils and to some lower extend by monocytes and this is why it is so important for diagnosing and monitoring inflammatory diseases. The release of calprotectin in the gut during inflammatory episodes shows that neutrophils are activated and attracted to the sites of inflammation. Production mechanisms, including genetic regulation and post-translational modifications, are important for understanding the role of calprotectin as a biomarker. The study Cheng et al., (2012) should drive an acumen to assess chemical properties that solubility and stability bring—essential for calprotectin functioning within the gastrointestinal tract. Knowing under which conditions calprotectin is released; also, how stable it is afterward can give clues about its applicability as a diagnostic tool in clinical practice.

There is a significant and fecal calprotectin correlation with metabolic and genomic compositions of patients having IBD. Findings by Franzosa et al. (2018) indicated that changes in metabolites detected in IBD are related to fecal calprotectin levels — therefore supporting its use as a non-invasive biomarker for intestinal inflammation. It appears, then, that calprotectin not only reflects the inflammatory status of the gut but also offers information on the altered biochemical activities related to gut microbiota and metabolism — thus potentiating diagnostic and therapeutic avenues. Until further reinforced by another study, Menees et al.(2015) showed through meta-analysis sensitivity as well as specificity diagnosing IBD from non-IBD individuals. This shows how important calprotectin is in medical tests when we want easy ways that do not involve cutting into the body to help avoid the need for a colonoscopy. The chemical features of calprotectin, and its part as a neutrophil cytosolic protein, help make it trustworthy as a sign of gut inflammation.

There are still several gaps in knowledge about calprotectin despite advances in understanding its biochemical properties. For example, it is known that calprotectin is raised in inflammation but the exact pathways by which it affects the gut microbiota and metabolome remain to be fully understood. Future research could involve longitudinal studies to monitor evolutions in levels of calprotectin as well as associated changes in the microbiome of IBD patients. Plus, the use of calprotectin modulation therapeutically in IBD treatment has not yet been maximally applied. Research on therapeutic implications from metal-binding aspects of calprotectin may bring brilliant ideas for new treatment strategies with inflammatory diseases. In short, important both as a biomarker and active contributor to biochemical imbalances associated with gut inflammation, more investigation into its various roles-inflammation and innate immune response will reveal how much it can be mobilized clinically and managed regarding disease.

The knowledge gaps about calprotectin are wide. Though it is recognized more and more as a biomarker, there remains an opportunity for longitudinal studies that validate the added value of monitoring calprotectin in terms of patient outcomes. Jukic et al., (2021) also gave an indication that integration with other biomarkers could enhance predictive value and bring to light the role of calprotectin in the inflammatory mechanism of IBD. Further research should also be directed toward assessing the therapeutic potential of calprotectin, as more is known about its status as a useful biomarker than its biological activities concerning immune response investigation.

Biochemical features of Calprotectin

Calprotectin, high in amounts with S100A8 and S100A9 subunits, is a calcium and zinc binding heterodimeric protein complex found mostly in neutrophils and monocytes. It accounts for up to 60% of the cytosolic protein content of neutrophils and is released upon activation during inflammatory responses (Föll et al., 2004). When it binds calcium, calprotectin undergoes conformational changes that increase its attractive affinity for transition metals like zinc, manganese, iron etc., thereby playing a role in nutritional immunology by withholding these metals from the invading microbes (Nakashige et al., 2015; Zygiel & Nolan, 2018). The metal-chelating action takes place through specific coordination sites at the interface between heterodimers required for antimicrobial activity as well (Damo et al., 2013). Calprotectin is pro-inflammatory; it

interacts with receptors such as Toll-like receptor 4 (TLR4) and receptor for advanced glycation end-products (RAGE) to amplify innate immune responses. Its bioactivity is modulated by pH and Ca++ concentrations, which mediate metal binding and structural stability (Hayden et al., 2013). In the clinic, calprotectin is a strong biomarker for inflammatory diseases, such as IBD, rheumatoid arthritis, and sepsis because it is stable in biofluids and proteolytically resistant. Inflammatory diseases are accompanied by protease activation; therefore, these two characteristics enhance the value of calprotectin as a biomarker Kristensen et al., 2017; Ayling & Kok, 2018). Further improvements have recently been made to its detection through biosensor technologies that bring calprotectin closer to being useful for point-of-care diagnostics (Thomas et al., 2023).

Calprotectin as a Biomarker for Gut Inflammation

Calprotectin is put not only as an IBD marker but as a marker of profound biochemical changes within the gut environment. It behooves the integration of calprotectin measurement with metabolomic and metagenomic analyses, which is set forth by Franzosa et al., 2018 to better fathom the etiopathogenesis and evolution of IBD. This integrated approach might drive further steps in personalized treatment development wherein clinicians would be empowered to adjust interventions based on an individual's biochemical profile. Findings show that fecal calprotectin levels are significantly associated with metabolomic and metagenomic profiles for patients having IBD. It was shown by Franzosa et al., 2018 that disturbed metabolite features in IBD correspond to fecal calprotectin levels thus emphasizing its role a non-invasive biomarker for gut inflammation. This finding implies that gut on calprotectin not only reflects gut inflammatory status but also offers 'vision' into related biochemical changes concerning gut microbiota and metabolism; hence it is key in diagnostics and therapeutics. In another boost for calprotectin as a diagnostic tool, Menees et al. (2015) provided a meta-analysis showing its sensitivity and specificity in separating IBD from non-IBD conditions. This underscores the importance of calprotectin in clinical practice where non-invasive methods are preferred to reduce the need for invasive procedures such as colonoscopy.The biochemical properties of calprotectin, neutrophil cytosolic protein,

reliability_integer_of:intestinal_inflammation

The STRIDE recommendations defined therapeutic targets for management of IBD with clinical response, endoscopic healing, and normalisation of inflammatory markers including calprotectin. This guides treatment strategies to be individualized based on calprotectin levels as an indicator of disease activity and response to treatment(Turner et al., 2020). Therefore, the inclusion of calibrations for providers in the healthcare field allows better tailoring and hence more effective therapies that lead to improved patient outcomes related to IBD. Menees et al.(2015) also shared reliability on useful calprotectins as biomarkers regarding activities as diseases and responses by treatments concerning maladies like those resulting from Crohn's disease or ulcerative colitis. Their meta-analysis highlights inflammation-based objective measurement provided by calprotectin to direct therapeutic decisions toward individualized treatment options; that means a change in therapy would have a more positive effect on quality of life if it was implemented in time Ander et al. (2019) emphasize the high sensitivity and specificity of calprotectin in the differentiation of IBD from non-inflammatory conditions, e.g., irritable bowel syndrome (IBS). In this respect, it not only aids diagnostic differentiation but also lowers the need for invasive procedures such as a colonoscopy. The proposed algorithm for interpreting the levels of calprotectin may streamline clinical decision-making and elicit better patient care in inflammatory conditions.

The capacity of calprotectin to be used in monitoring disease activity has been underlined by its validation as a marker for both the diagnosis and monitoring of IBD. In another report, Mosli et al. (2015) provide evidence through a systematic review that calprotectin is quite efficient in positive patients concerning symptomatic endoscopic activity; thus, it can be used non-invasively to guide clinical management decisions. Thus, regular monitoring of calprotectin levels should enable an informed adjustment of treatment that will ensure optimal management for IBD. Jukic et al. (2021) present information on the multifactorial participation of calprotectin in the pathogenesis of IBD by pointing out its interaction with the IL-17/IL-23 axis; this unveils not only important clinical applications for calprotectin but also potential uses in research aimed at further understanding the basic mechanisms underlying IBD pathogenesis. In line with these thoughts, by extending such pathways, more targeted therapeutic approaches

and better management strategies could be possible for IBD.

Role of Calprotectin in Inflammatory Processes

Apart from being used as a biomarker, calprotectin has been described as a rheostat of mucosal inflammation. Batiha et al. (2020) highlighted the biological functions of the subunits of calprotectin, S100A8 and S100A9 which control inflammatory responses in different organ systems. This unveils even more complex participations for calprotectin in the modulation of immune responses and provokes thoughts that its biochemical properties may find applicability in patient-specific therapies for IBD. In addition to its previously mentioned roles, one antimicrobial function of calprotectin is also considerable. Jukic et al., 2021 detailed one mechanism: sequestration of essential metals required for bacterial proliferation such as iron and manganese; by this means, it participates not only in inflammation but also in microbial protection, placing calprotectin at an important position with dual functions in the innate immune response! The last provides an important biochemical aspect on calprotectin that may need much closer probing particularly regarding its interactions with certain microbial adversaries. Role of calprotectin extends to specific infections. Infections caused by Clostridium difficile were discussed by Waugh et al., who believed that calprotectin significantly influences the immune response to CDI through antimicrobial effects, which means that biochemical features of calprotectin are not only management-related in IBD but rather have some more general implications concerning gut health and the immune response to infections. Moreover, characterization of calprotectin in neutrophil extracellular traps further clarifies its antimicrobial function: Jukic et al. claimed that calprotectin contributes to bactericidal features of NETs; therefore, it is highlighted regarding its importance in defense mechanisms within innate immunity. This link between calprotectin and NETs opens new paths for looking into its part in different inflammatory and infectious diseases. A Recently published article showed that calprotectin is high in patients with bone break, which is one of the main inflammatory conditions in the body (Amshawee et al., 2025).

CONCLUSION

In principle, calprotectin is of great clinical value as an inflammatory responsive biomarker particularly when placed within the IBD context. The fact that it can be used as a marker for between inflammatory and non-inflammatory conditions, as well as for monitoring disease activity, further underlines its importance in clinical practice. Long-term implications studies integration with other biomarkers and exploration of its potential therapeutic target aspects are what is needed further. Filling these knowledge gaps will help advance the management of inflammatory diseases to benefit patient outcomes. The chemical composition and the area of production of calprotectin are instrumental in its function as an IBD biomarker. Though fairly well understood regarding its implications in gut inflammation, further research is needed to investigate its structural dynamics and regulatory mechanisms because filling these two gaps would lead to better diagnostic tools and treatment approaches for managing inflammatory diseases.

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