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REVIEW ARTICLE

# Angiopoietins in inflammation and their implication in the development of inflammatory bowel disease. A review

**Pablo M. Linares***, **María Chaparro**, **Javier P. Gisbert**

*Gastroenterology Unit, Hospital Universitario de La Princesa and Instituto de Investigación Sanitaria Princesa (IP), Madrid, Spain*
*Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Spain*

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**Abstract**

*Background:* Angiopoietins are essential angiogenic mediators. Since inflammatory bowel disease (IBD) involves inflammation, ulceration and regeneration of the intestinal mucosa, the angiopoietin system has been proposed as a factor to maintain pathological angiogenesis during the development of the IBD.
*Aim:* To review the potential role of angiopoietins in the inflammation driven by angiogenesis during the course of the IBD.
*Methods:* Publications were identified by PubMed searches using the following key words: angiopoietin; Tie-2 receptor; angiogenesis; inflammatory bowel disease and inflammation, in various combinations.
*Results:* Angiopoietin-1 acts as a regulator of blood vessel maturation and has anti-inflammatory properties, whereas angiopoietin-2 marks the onset of angiogenesis and is required for normal formation of lymph vessels. Both angiopoietins make use of their angiogenic regulatory effects via the angiopoietin tyrosine-kinase receptor (Tie-2). While angiogenesis has been shown to promote and sustain many events of inflammation, the involvement of the angiopoietin system in IBD has been reported in few studies. It is not clear whether the angiopoietins' role in the development of intestinal inflammation is due to an imbalance in the levels of these proteins or this system exerts its pro-angiogenic properties through a different mechanism during the close-loop relationship between angiogenesis and inflammation.

*Abbreviations:* IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; Ang-1, angiopoietin-1; Ang-2, angiopoietin-2; Tie-2, angiopoietin tyrosine-kinase receptor; VEGF, vascular endothelial growth factor; EC, endothelial cell; VSMCs, vascular smooth muscle cells

* Corresponding author at: C Rio Águeda, 6, 28023 Madrid. Spain. Tel.: +34 667365335.
*E-mail address:* pablus@hotmail.com (P.M. Linares).


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*Conclusions:* Angiopoietins have key functions in the angiogenic process, and their abnormal activation might depend on their surrounding inflamed environment. The determination of these angiogenic factors in serum and tissue could be useful for monitoring IBD progression.


**Contents**



## 1. Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder that encompasses two different clinical entities: Crohn's disease (CD) and ulcerative colitis (UC) [1,2]. CD may affect any part of the gut from the mouth to the anus, though it is usually located in the terminal ileum and colon. It is characterized by macroscopic affectation and segmental distribution along the gut. On the other hand, UC affects the mucosa of the colon with variable extension from the rectum to the cecum on a continuous basis.

The etiology of CD and UC remains unclear, but it is characterized by inflammation located in the gut due to an altered immune response. Genetic and environmental factors in the development of both diseases are known to be involved [3,4].

During the clinical course of both conditions, flare-ups in activity, characterized by an increase and exacerbation of inflammation, alternate with remission periods. The number, frequency and severity of these flares are unpredictable. Recent investigations have been conducted to elucidate the etiology of these diseases and the factors that might influence their evolution.

For instance, IBD is associated with extensive tissue injury and lymphatic remodeling caused by tissue edema, inflammatory cell infiltrates, numerical or functional alteration of ertain subpopulations of immune cells, loss of epithelial integrity and increased angiogenesis. These features, together with the release of cytokines in the intestinal mucosa, might contribute to the pathogenesis and development of IBD by triggering diverse molecular mechanisms [5–7]. Recently, scientific evidence suggests that vascular development, particularly lymphangiogenesis and angiogenesis, could play a main role as a cause of IBD tissue injury and not simply an epiphenomenon ascribed to inflammation [5,8–10].

## 2. Methods

Bibliographical searches were performed in PubMed from the earliest records to February 2012 using the following key words (all fields): (angiopoietin OR Tie-2 receptor OR angiogenesis) AND (inflammatory bowel disease OR inflammation). The references from the articles selected for the study were also examined in search of articles meeting the inclusion criteria. Relevant abstracts and other material from meetings were investigated. Studies on angiopoietin function in other diseases were included if relevant information was reported.

### 2.1. Angiogenesis

Blood vessels originate through two processes called vasculogenesis and angiogenesis. Vasculogenesis starts in the embryonic period from multipotent progenitor cells, while in angiogenesis the vascular networks are created from the pre-existing ones. Physiological angiogenesis takes place during processes like the menstrual cycle, embryonic development, tissue repair and bone growth.[11,12] Angiogenesis is considered to be activated primarily by hypoxia [7,13]. Afterwards, the basal membrane is degraded by metalloproteases and endothelial cells (ECs) proliferate, triggered by the released integrins and adhesion molecules. Finally, pericyte recruitment stabilizes the newly-formed vessels. Upon stabilization and structuring of the new microvessel network, the balance between proangiogenic and antiangiogenic factors in physiological angiogenesis returns to the baseline levels and the