Enfermedades Inflamatorias Intestinales Crónicas

Fisiopatología

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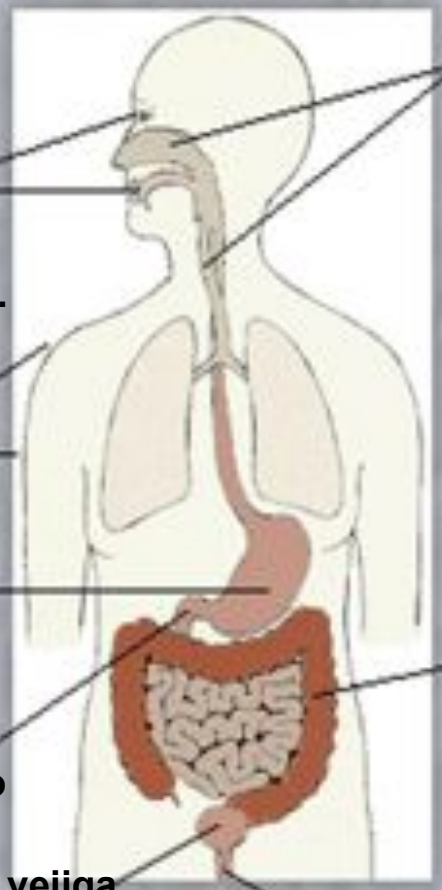
FUNCIÓN DEL SISTEMA INMUNOLÓGICO DIGESTIVO



Enzimas en saliva y lagrimas.

Moco y epitelio cilíado de la vía aérea superior.

Acido clorhídrico del estómago.

PH alcalino del duodeno

Flora intestinal.

Irrigación de la vejiga y uretra durante la micción

PH ácido de la vagina y flora vaginal.

Todos los días millones de **bacterias, virus, hongos y parásitos tratan de invadir nuestro organismo.**

Se encuentran en el aire , la comida, en la piel.

Sin embargo, **cuando lo intentan se encuentran con barreras protectoras**.

La mucosa intestinal nos protege utilizando células responsables de la respuesta inmune:macrofagos,linfocitos, granulocitos.

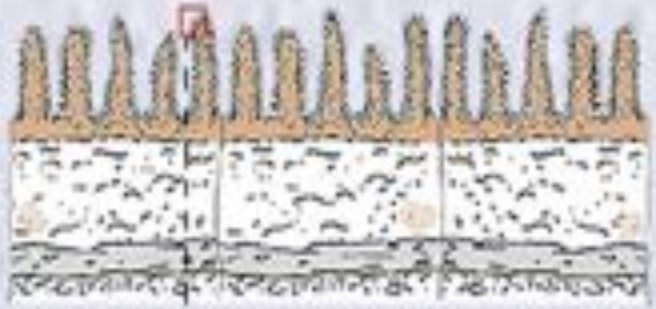
FUNCION DE DEFENSA DE LA MUCOSA DIGESTIVA

La **mayor tarea de la mucosa intestinal es la de absorber nutrientes de la luz** y al mismo tiempo **actuar como barrera de defensa**.

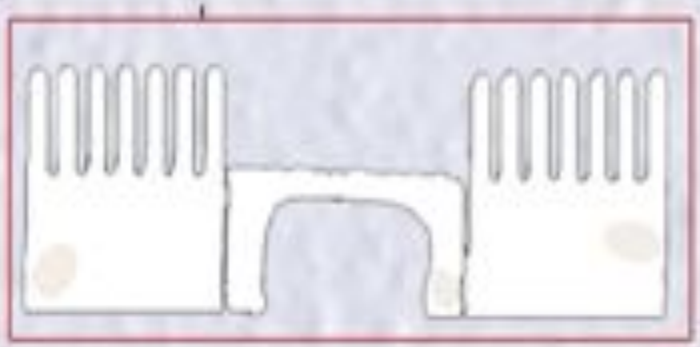
Así puede **proteger al organismo de la invasión de sustancias tóxicas y nocivas** (toxinas bacterianas, componentes alimentarios, ácidos biliares y enzimas digestivas) en el intestino.

Para lograr **un potencial defensivo eficaz ante cualquier situación, un circuito de regulación inmunológica en el cual las células M figuran preponderantemente y se desarrollan en la pared intestinal.**

Función del sistema inmuno-digestivo con Células M



Mucosa instestinal.



Células **M** del sistema digestivo.

En el epitelio intestinal hay células con numerosos micropliegues en su superficie, las células M, (células de la microvellosidad) que juegan un importante papel de defensa en contra de las bacterias, son las que derivan a las bacterias y otros antígenos hacia las células subepiteliales del sistema inmune,los macrófagos y leucocitos.

Los macrófagos absorben y procesan a los invasores y presentan a los antigenos a los linfocitos, que a su vez van a generar anticuerpos para ser utilizados ante potenciales agentes patógenos en futuras infecciones.

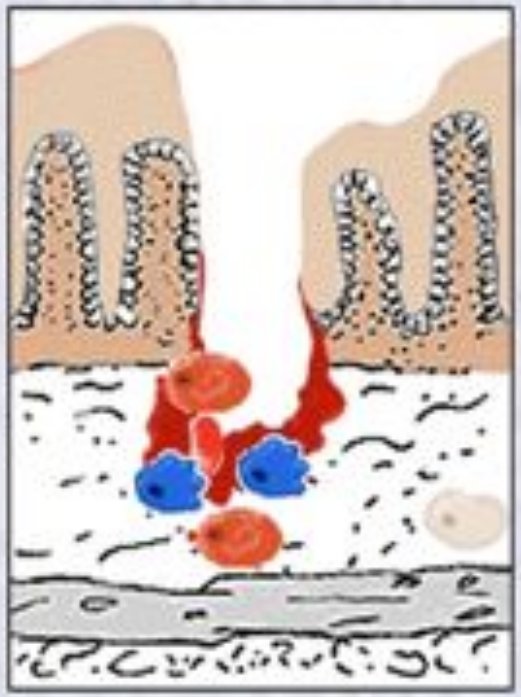
CAUSAS DE LAS INFECCIONES INTESTINALES

¿CUANDO SE DESARROLLA UNA INFECCIÓN INTESTINAL?

Cuando la barrera intestinal se daña; bacterias, virus, hongos, u otros **agentes nocivos pueden penetrar libremente la pared intestinal** y desde allí trasladarse hacia cualquier parte del cuerpo.

Los **agentes patógenos que causan diarrea** frecuentemente **poseen toxinas específicas que impiden la función del epitelio intestinal.**

MEDIADORES INFLAMATORIOS



Macrofagos (azúl) y Granulocitos (rosado) destruyen una bacteria patógena (rojo).

Los granulocitos y macrofagos activados eliminan mediadores inflamatorios que promueven la comunicación entre diferentes células inmunocompetentes.

Los macrófagos y los linfocitos T se comunican con la ayuda de mediadores y además, por contacto directo, resultando en la activación de linfocitos T.

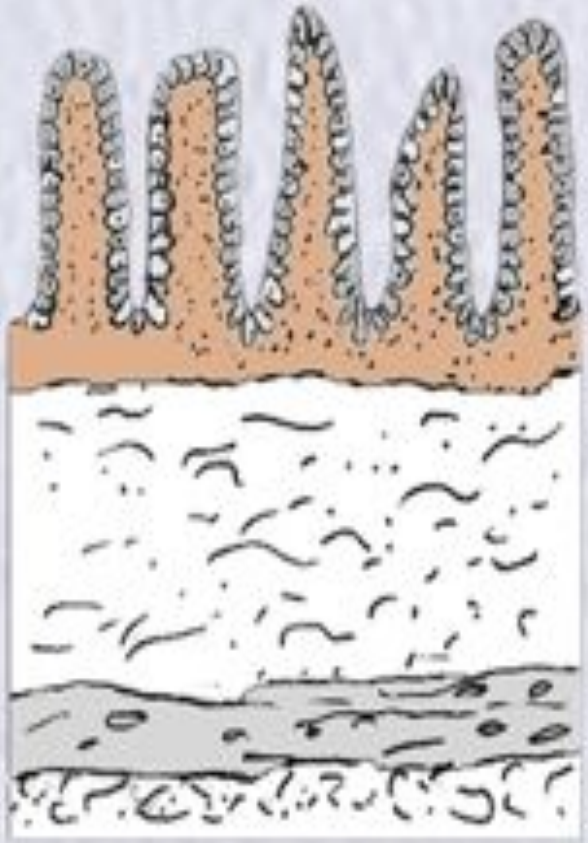
Los linfocitos T, eliminan gran cantidad de sustancias mensajeras que comienzan la reacción inmune, los linfocitos B maduran a células plasmáticas y producen muchos nuevos anticuerpos.

HIPÓTESIS DE LOS MECANISMOS INVOLUCRADOS EN LAS ENFERMEDADES INFLAMATORIAS INTESTINALES CRONICAS

Las siguientes hipótesis son el centro de discusión:

- Podrá tratarse de una infección causada por **un patógeno no identificado**
- Una **hiperreacción del sistema inmune ante bacterias habituales** del tubo digestivo y sus antígenos.
- Una **enfermedad autoagresiva** con una reacción inmune en contra de sus propios tejidos.
- Hay una **dificultad para controlar las bacterias intestinales por factores genéticos** que favorecen y contribuyen al riesgo de desarrollar inflamación intestinal.

DESARROLLO DE LAS EIIC



El primer cambio visible en la enfermedad de Crohn y la Colitis Ulcerosa es **la invasión de inmunocitos (granulocitos, macrófagos y luego linfocitos) en la mucosa intestinal.**

Durante la inflamación aguda **un número elevado de granulocitos invade la mucosa liberando radicales libres y proteasas,** así como **otros mediadores que pueden generar daño tisular directo.**

EL ROL DE LOS LINFOCITOS T y B

Granulocitos

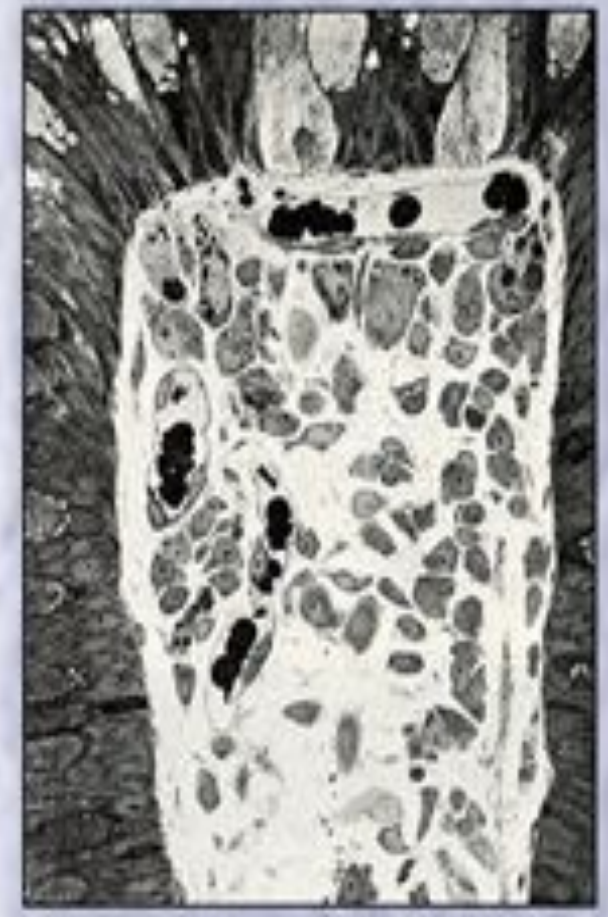
T y B linfocitos

Se observan muchos **más linfocitos de lo esperado** **considerando que algunos pocos antígenos estuviesen implicados.**

Los linfocitos **T** y **B** en la mucosa intestinal de los pacientes con EIIC están en estado **de actividad incrementada**.

Así como hay una **mayor producción de anticuerpos G (inmunoglobuline G) que puede aumentar el proceso inflamatorio e incrementar el daño tisular.**

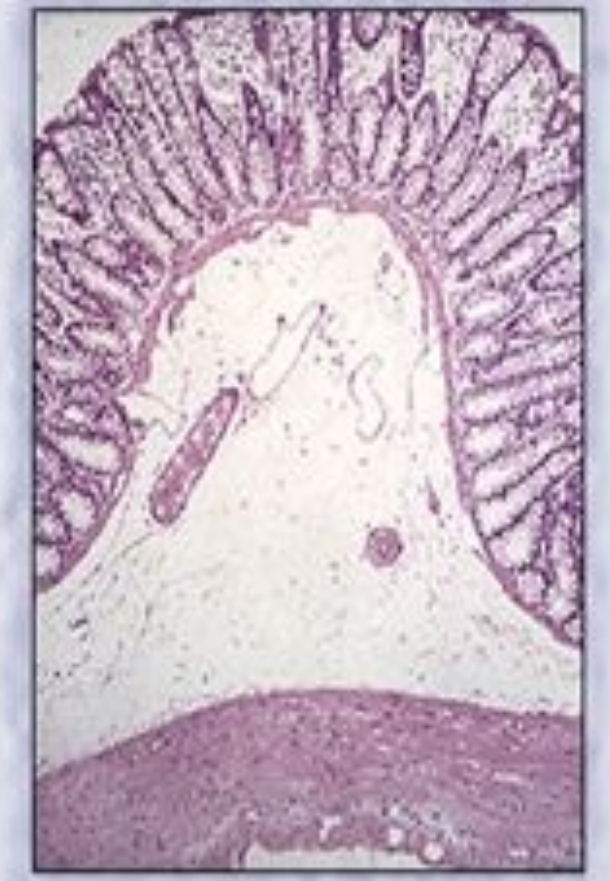
EL ROL DE LOS MACROFAGOS



En los pacientes con EIIC los **macrófagos** de la mucosa colónica muestran una **actividad aumentada** en:

- **Producción de antígenos.**
- **Fagocitosis.**
- **Producción de mediadores inflamatorios.**
- **Formación de proteasas y radicales.**

EL PAPEL DEL EPITELIO MUCOSO INTESTINAL

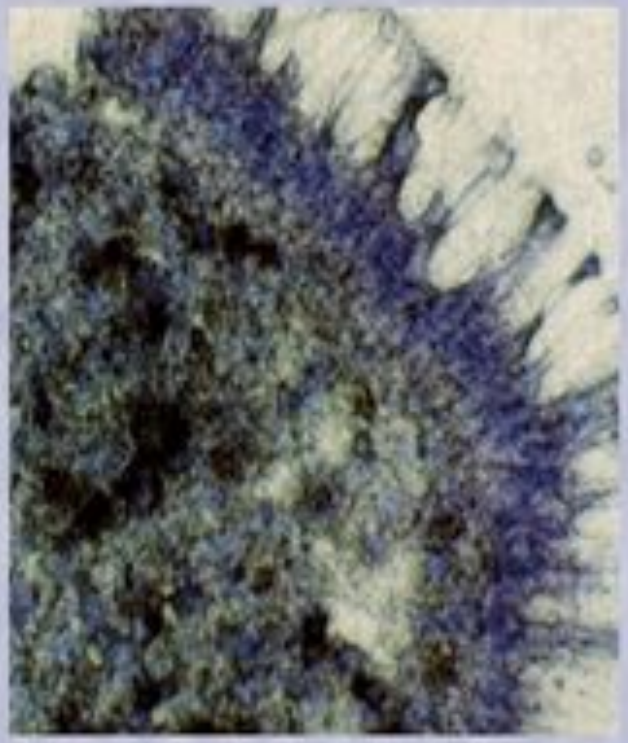


Capas colónicas

La continuidad del epitelio es crucial para la función de la mucosa intestinal.
Esto previene la invasión No controlada de bacterias, antígenos alimentarios e intraluminales.

Inmediatamente antes y después de la exacerbación de un episodio agudo de Colitis Ulcerosa o enfermedad de Crohn se observa el daño de la mucosa intestinal que aumenta la permeabilidad a otros antígenos.

EL ROL DE LOS MEDIADORES INFLAMATORIOS



Liberación de TNFI de una célula a la mucosa colónica.

Estudios recientes destacan **la importancia de mediadores promotores de inflamación (citoquinas) para el desarrollo de exacerbaciones recurrentes y crónicas.**

En las enfermedades inflamatorias la **activación de los mediadores está significativamente aumentada.**
En forma particular los macrófagos y los mediadores son fundamentales en la regulación de la reacción inflamatoria intestinal.

Aparentemente en las **EIIC la reacción inflamatoria no se apaga por déficit de los mediadores antinflamatorios**

New insights into inflammatory bowel disease pathophysiology: paving the way for novel therapeutic targets.

Autores: Stefanelli T,Malesci A,Repici A,Vetrano S,Danese S

Curr Drug Targets 2008;9 (5):413-8.

- The exact cause and mechanisms of both IBD have yet to be completely understood, it is widely accepted that both CD and UC result from an **inappropriate immune response** that occurs in **genetically susceptible individuals** as the result of a **complex interaction** among **environmental factors**, **microbial factors**, and the **intestinal immune system**.
- In the last few years a tremendous advance in knowledge of the mechanisms underlying **intestinal inflammation in IBD** has been achieved, leading to **new therapeutic targets and novel drugs**.
- These new therapeutic weapons have been specifically designed to **selective shut down intestinal inflammation at different levels**.
- Aim of this review is to summarize the recent advances in IBD pathophysiology and the **new therapeutic targets and drugs that are changing the IBD clinical management**

Fisiopatología

- Se considera que es una **respuesta inmune inadecuada** que ocurre en **sujetos genéticamente predispuestos** derivada de la **compleja interacción** entre factores :
- **ambientales**
- **antimicrobianos**
- inmunidad intestinal

Biologics. 2009;3:77-97. Epub 2009 Jul 13.

Biologic targeting in the treatment of inflammatory bowel diseases.

Bosani M, Ardizzone S, Porro GB.University Hospital, Milan, Italy.

- Evidence indicates that a **dysregulation of mucosal immunity in the gut of IBD causes an overproduction of inflammatory cytokines and trafficking of effector leukocytes into the bowel, thus leading to an uncontrolled intestinal inflammation.**

- Under **normal situations**, the intestinal mucosa is in a state **of "controlled" inflammation** regulated by **a delicate balance of proinflammatory (tumor necrosis factor [TNF-alpha], interferon-gamma [IFN-gamma], interleukin-1 [IL-1], IL-6, IL-12 and anti-inflammatory cytokines IL-4, IL-10, IL-11).**

- The **mucosal immune system is the central effector of intestinal inflammation and injury, with cytokines playing a central role in modulating inflammation.**

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University Hospital, Milan, Italy.

- However, ongoing research continues to generate **new biologic agents targeted at specific pathogenic mechanism involved in the inflammatory process.**
- **Lymphocyte-endothelial interactions mediated by adhesion molecules are important in leukocyte migration and recruitment to sites of inflammation, and selective blockade of these adhesion molecules is a novel and promising strategy to treat Crohn's disease.**
- **Therapeutics agents to inhibit leukocyte trafficking** include natalizumab (approved for use in Crohn's disease in USA), MLN-02, and ISIS 2302.
- Other agents being investigated for the treatment of Crohn's disease include **inhibitors of T cell activation, proinflammatory cytokine receptors, Th1 polarization, growth hormone, and growth factors.**
- Agents being investigated for treatment of ulcerative colitis include many of those mentioned above. Controlled clinical trials are currently being conducted, exploring the safety and efficacy of old and new biologic agents, and the search certainly will open new and exciting perspective on the development of therapies for inflammatory bowel disease

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- **Cytokines may therefore be a logical target for inflammatory bowel disease therapy using specific cytokine inhibitors.**

- **Biotechnology agents targeted against TNF , leukocyte adhesion , Th1 polarization, T cell activation, nuclear factor-kappaB (NF-kappaB), and other miscellaneous therapies** are being evaluated as potential therapies for the treatment of inflammatory bowel disease.
- In this context, infliximab and adalimumab are currently the only biologic agents approved in Europe for the treatment of inflammatory Crohn's disease.

- Other anti-TNF biologic agents have emerged, including CDP571, certolizumab pegol, etanercept, onercept.

Dig Dis. 2009; 27(4):450-4. Epub 2009 Nov 4.

Therapeutic options to modulate barrier defects in inflammatory bowel disease.

Hering NA, Schulzke JD.
Department of General Medicine, Charité Center 10, Campus Benjamin Franklin, Berlin, Germany.

- In inflammatory bowel disease (IBD), **epithelial barrier function is impaired contributing to diarrhea by a leak flux mechanism and perpetuating inflammation by an increased luminal antigen uptake.**

  This barrier of the intestinal epithelium is composed of **the apical enterocyte membrane** and the **epithelial tight junction (TJ)** and **can be affected by TJ alterations, induction of epithelial apoptosis and appearance of gross lesions like erosions or ulcers as well as by accelerated transcytotic antigen uptake.**

- **TJ strands are reduced in Crohn's disease (CD) and strand breaks appear.**

  Several of the 24 claudins are concerned in CD as e.g. claudin-2, -5 and -8.

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- The **epithelial apoptotic rate has also been shown to be elevated** causing focal lesions.
- As far as regulation is concerned, **Th1 cytokines like TNF-alpha and interferon-gamma are important for CD,**
- while **Th2 responses are dominated by interleukin (IL)-13 and TNF-alpha in ulcerative colitis (UC) .**

  IL-13 does stimulate epithelial apoptosis as well as upregulates claudin-2 in UC.

  Together with **an IL-13-dependent restitution arrest**, this may **explain why ulcer lesions are seen already early in UC but only in advanced stages of CD.**

  Luminal antigen uptake occurs via TJ discontinuities, epithelial gross lesions and endocytotically.

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Therapeutic options to modulate barrier defects in inflammatory bowel disease.

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- Therapeutically, anti-inflammatory remedies as e.g. **TNF-alpha antibodies are most effective in improving active IBD and in parallel repairing barrier function.**
- Again, this is assumed to be **due to reduced cytokine release in active IBD**, as a result of immune cell apoptosis. However, other agents can also directly affect barrier function.
- **Glutamine is discussed as a candidate for barrier therapy** but has never been shown to have a direct barrier influence in CD, although it is an important **metabolic fuel for enterocytes** and has been shown to **preserve barrier functions** in laboratory models.
- Also, **probiotics** and **TGF-beta** and have **beneficial effects in models**, but no data exist on barrier repair in IBD.
- In contrast, **zinc has been shown to improve barrier function in CD**, although the inherent mechanisms are unknown.
- Finally, **food components can strengthen the epithelial barrier** as for example the flavonoid quercetin which has been shown to **upregulate claudin-4 within the epithelial TJ**

Gastroenterology. 2008 Feb;134(2):577-94.

Microbial influences in inflammatory bowel diseases.

Sartor RB.
Department of Medicine, Center for Gastrointestinal Biology and Disease, University of North Carolina

- The **predominantly anaerobic microbiota of the distal ileum and colon contain an extraordinarily complex variety of metabolically active bacteria and fungi that intimately interact with the host's epithelial cells and mucosal immune system.**

- **Crohn's disease, ulcerative colitis, and pouchitis are the result of continuous microbial antigenic stimulation of pathogenic immune responses as a consequence of host genetic defects in mucosal barrier function, innate bacterial killing, or immunoregulation.**

- **Altered microbial composition and function in inflammatory bowel diseases result in increased immune stimulation, epithelial dysfunction, or enhanced mucosal permeability**

Gastroenterology. 2008 Feb;134(2):577-94.

Microbial influences in inflammatory bowel diseases.

Sartor RB.
Department of Medicine, Center for Gastrointestinal Biology and Disease, University of North Carolina

- Although traditional pathogens probably are not responsible for these disorders, **increased virulence of commensal bacterial species, particularly Escherichia coli, enhance their mucosal attachment, invasion, and intracellular persistence, thereby stimulating pathogenic immune responses.**
- **Host genetic polymorphisms most likely interact with functional bacterial changes to stimulate aggressive immune responses that lead to chronic tissue injury.**
- **Identification of these host and microbial alterations in individual patients should lead to selective targeted interventions** that correct underlying abnormalities and induce sustained and predictable therapeutic responses

Altered permeability in inflammatory bowel disease: pathophysiology and clinical implications.

Autores: Mankertz J,Schulzke JD

Curr Opin Gastroenterol 2007;23 (4):379-83

- .
- PURPOSE OF REVIEW: To present the **mechanisms behind barrier disturbance in inflammatory bowel disease and their functional consequences.**

- RECENT FINDINGS: A **reduction in tight junction strands, strand breaks and alteration of tight junction protein content and composition characterize Crohn's disease**.
- **In ulcerative colitis, epithelial leaks appear early as a result of microerosions, upregulated epithelial apoptosis and tight junction protein changes with pronounced increases in claudin-2.**

- **T-helper type 1 cytokine effects** by interferon-gamma and tumour necrosis factor alpha are **important for epithelial damage in Crohn's disease**.
- **Interleukin-13 is the key effector cytokine in ulcerative colitis**, stimulating epithelial cell apoptosis, and can upregulateclaudin-2 expression.

- Together with interleukin-13-induced epithelial restitution arrest, this may explain why ulcer lesions occur in early stages of ulcerative colitis but are only observed in advanced inflammatory stages in Crohn's disease.

- .

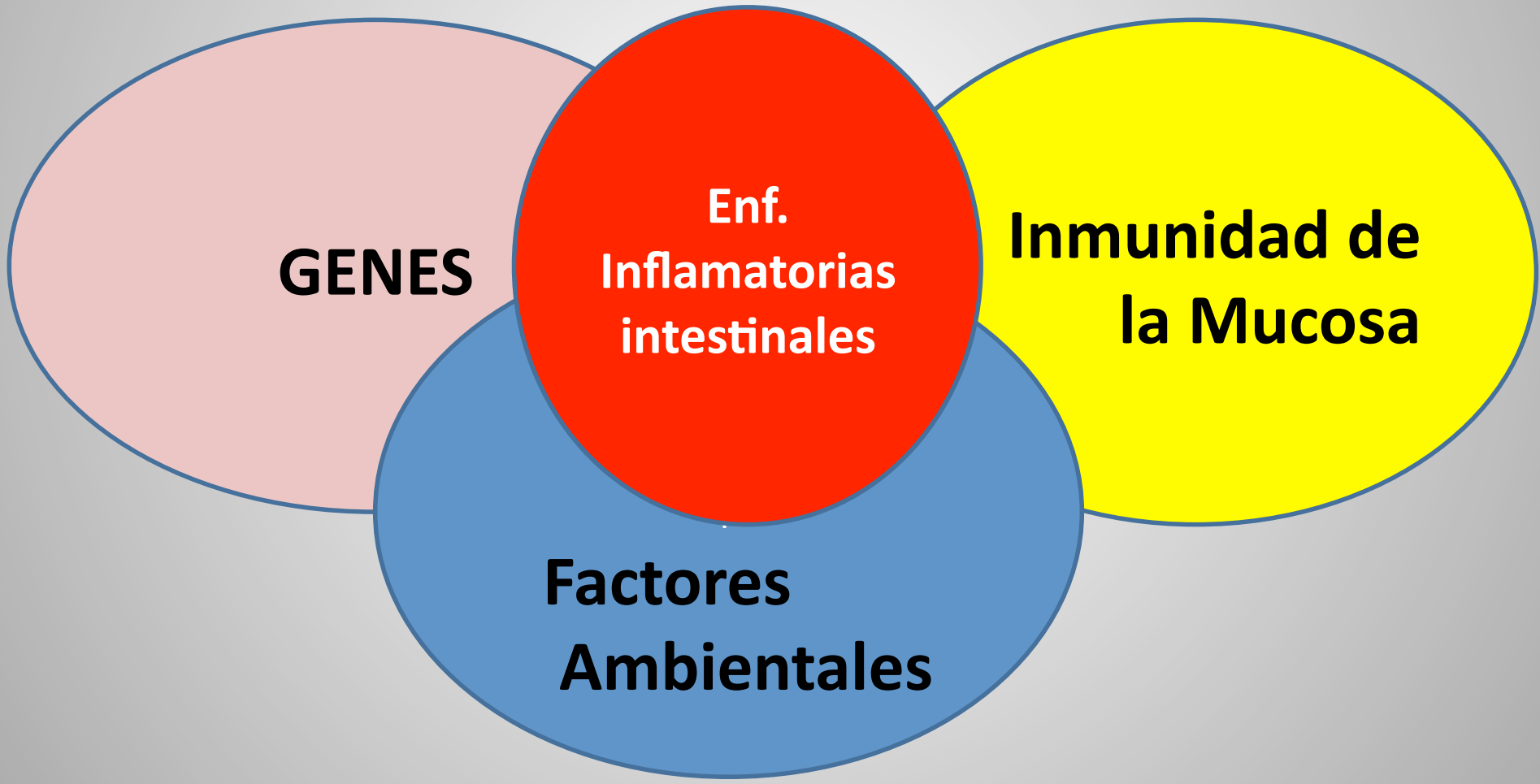
Altered permeability in inflammatory bowel disease: pathophysiology and clinical implications.

Autores: Mankertz J,Schulzke JD

Curr Opin Gastroenterol 2007;23 (4):379-83

- SUMMARY: **Barrier dysfunction in inflammatory bowel disease contributes to diarrhea by a leak flux mechanism and can cause mucosal inflammation secondary to luminal antigen uptake.**
- **Barrier abnormalities, such as epithelial tight junction changes and apoptotic leaks, gross mucosal lesions, and epithelial restitution arrest are responsible for these abnormalities and are the result of immunedysregulation**.
- Studying the underlying mechanisms is important in understandingthe pathophysiology of inflammatory bowel disease and developing therapeuticstrategies

Patogenia Multifactorial



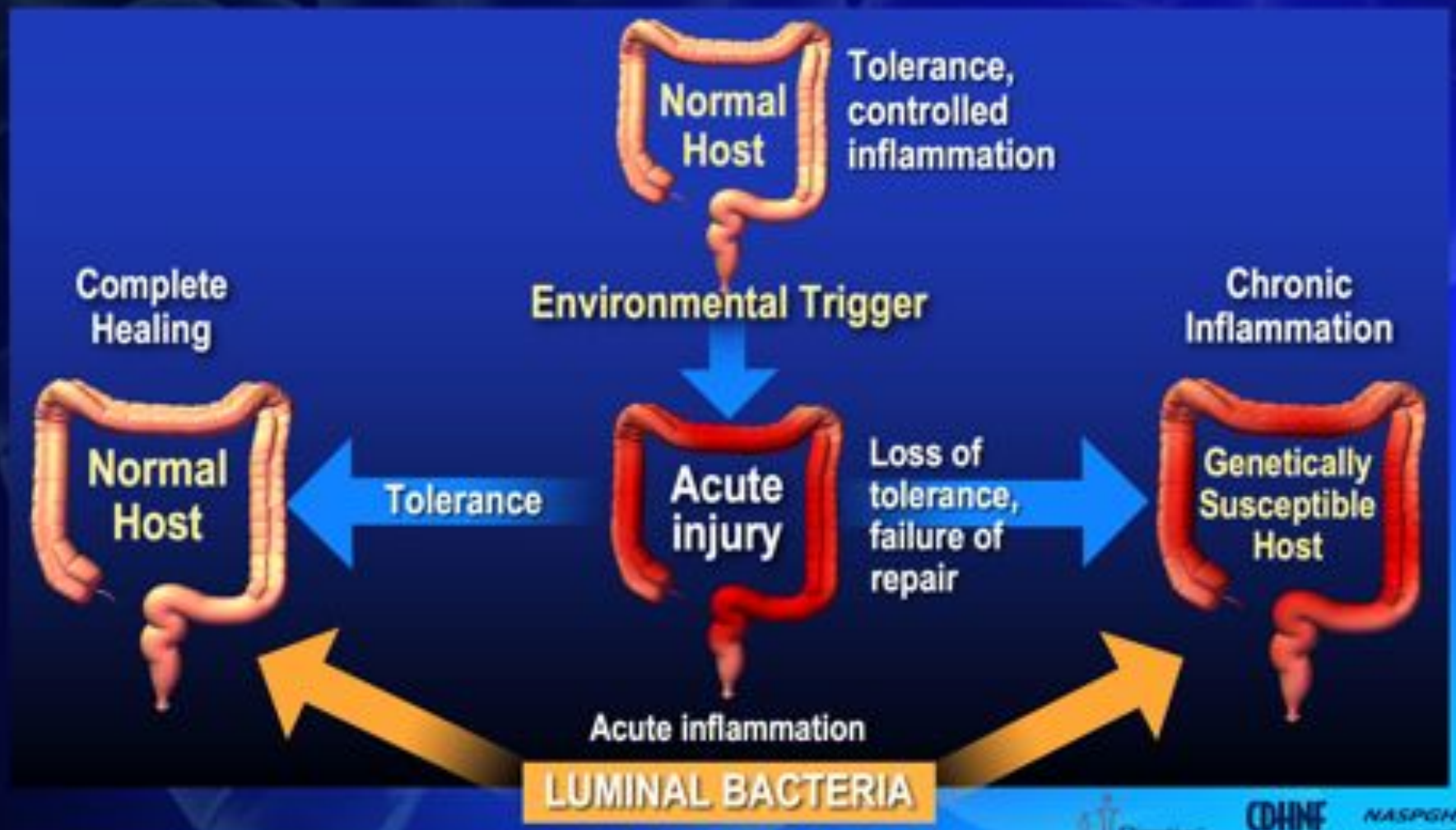
Etiología

- **Es multifactorial**

- Se cree que es una compleja interacción de **factores ambientales**, **genéticos** e **inmunológicos** la que lleva al desarrollo de EII.

- La **diferencia en los roles de éstos componentes explicaría el desarrollo de CU o EC.**

Host Response to Mucosal Injury



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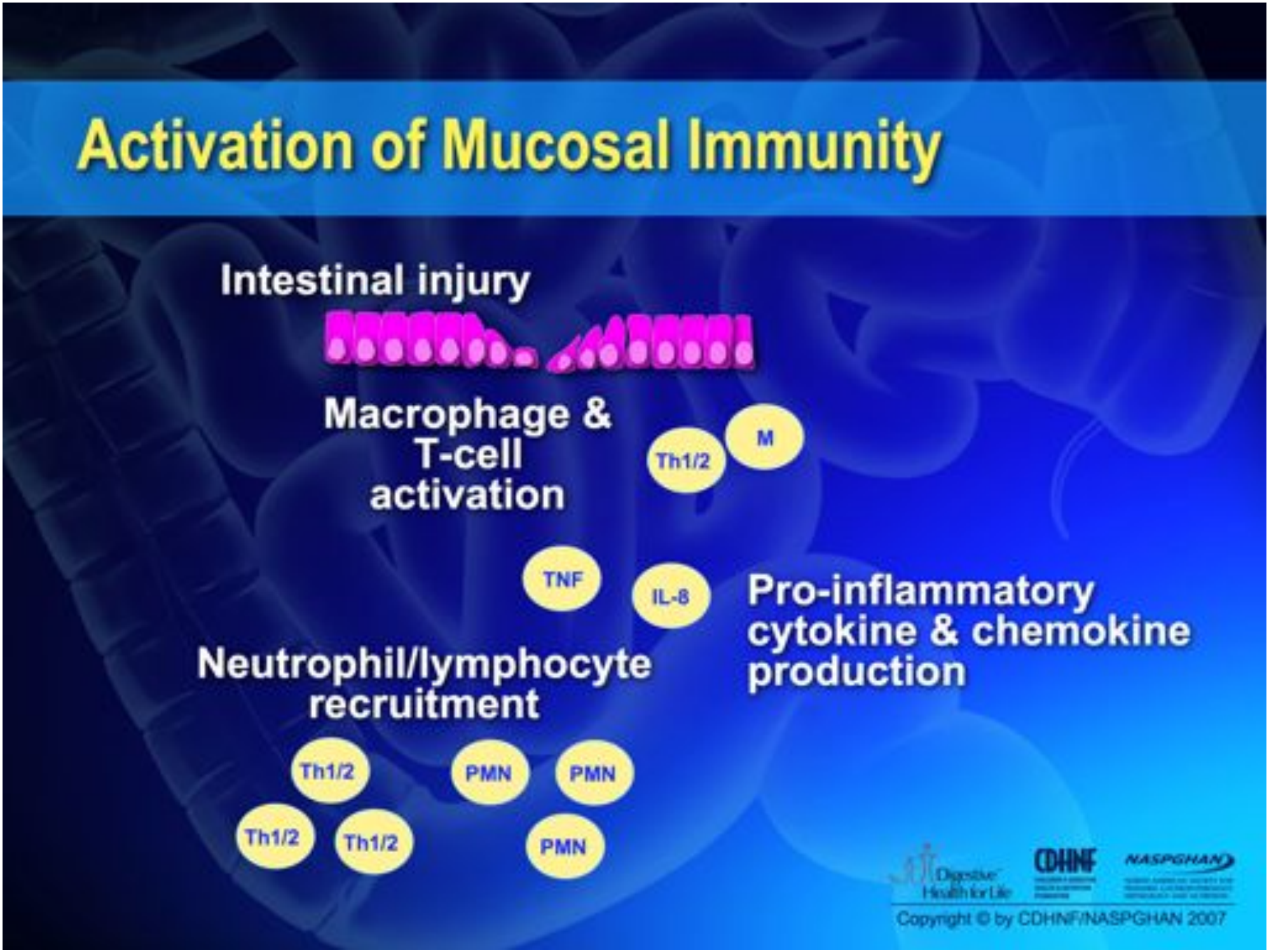
Activation of Mucosal Immunity



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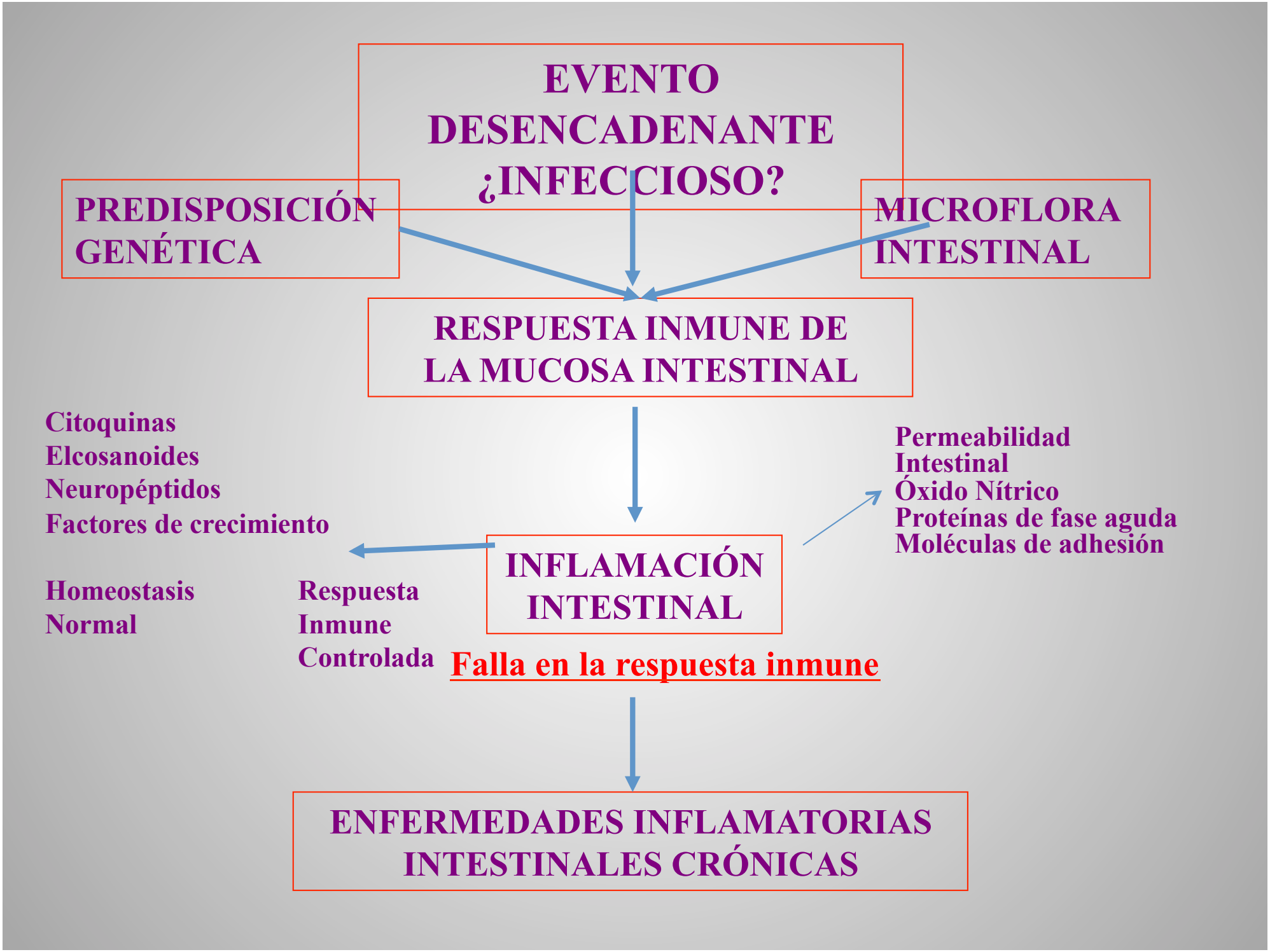
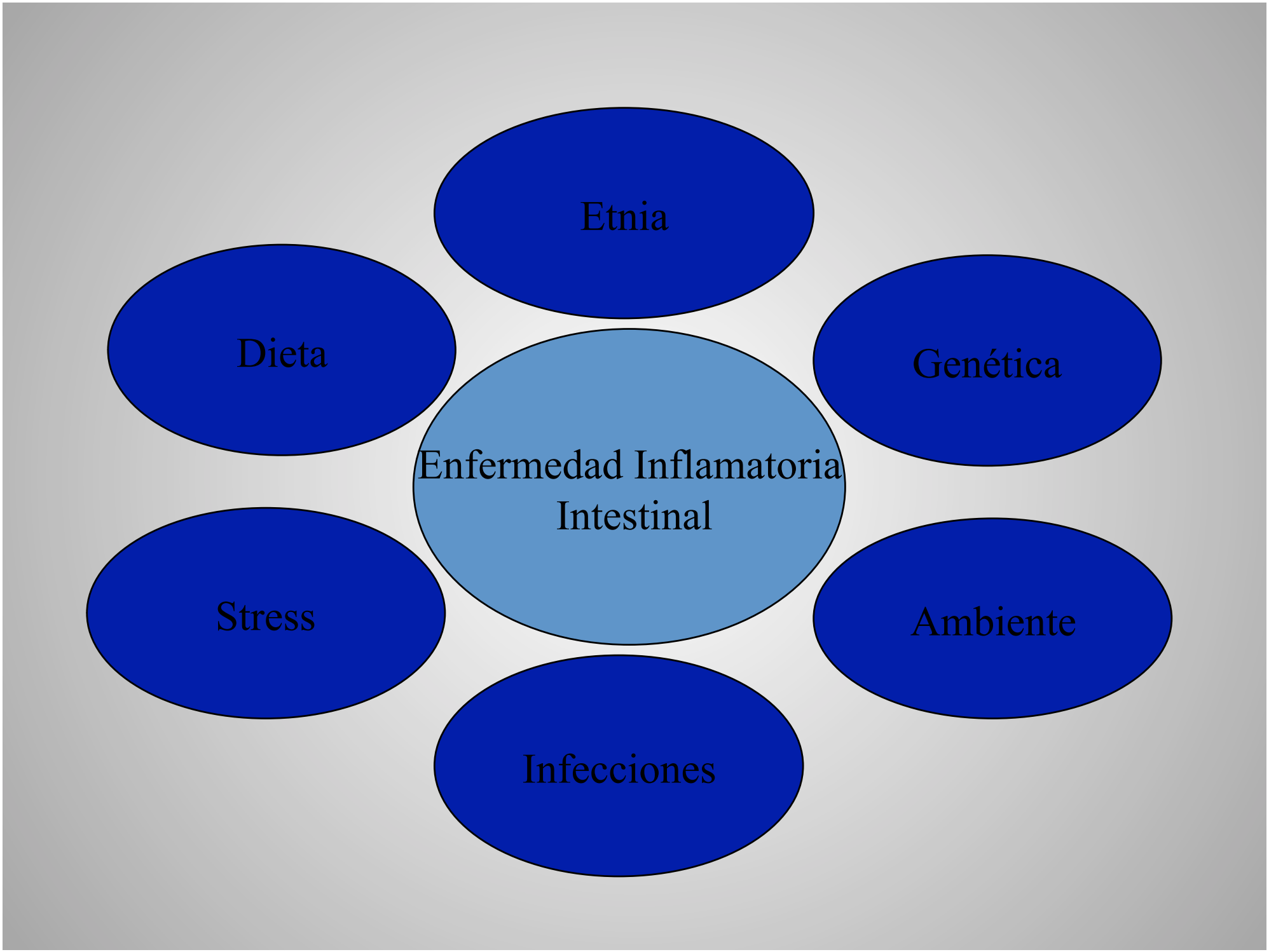

EVENTO DESENCADENANTE ¿INFECCIOSO?
PREDISPOSICIÓN GENÉTICA
MICROFLORA INTESTINAL
RESPUESTA INMUNE DE LA MUCOSA INTESTINAL
Citoquinas
Elcosanoides
Neuropéptidos
Factores de crecimiento
Permeabilidad Intestinal
Óxido Nítrico
Proteínas de fase aguda
Moléculas de adhesión
INFLAMACIÓN INTESTINAL
Homeostasis Normal
Respuesta Inmune Controlada
Falla en la respuesta inmune
ENFERMEDADES INFLAMATORIAS INTESTINALES CRÓNICAS


Etnia
Dieta
Genética
Enfermedad Inflamatoria Intestinal
Stress
Ambiente
Infecciones

Genetics of IBD

- IBD is a polygenic disease with complex genetic traits
- Affected relatives (15-20%)
- Genetic influence lower in UC than in Crohn's
- Human gene testing is looking for markers
  - Chromosomal regions of susceptibility identified by Genome-wide linkage scans 1,2,3,4,5,6,7,10,12,14,16,19 and 22

Williams, *Inflamm Bowel Dis* 2002; 8:375-81
Orholm, *Scand J Gastroenterol* 2000; 35:1075-81

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Genética de las EIIC

- Las enfermedades inflamatorias intestinales crónicas son de tipo poligénico con rasgos genéticos complejos.
- Familiares afectados : 15-20 %
- Menor influencia genética en CU que EC
- Se están buscando marcadores genéticos
- Regiones cromosómicas de susceptibilidad identificados : 1,2,3,4,5,6,7,10,12,14,16,19,22
- Williams Inflam bowel Disease 2002 8 (375-81)
- **Orholm : Scand J Gastroenterolog 2000, 84 (1075-81)**

Genetic Susceptibility

There is strong link between genetics and IBD

- Monozygotic twins studies show concordance rates of

  36 – 58 % in CD

  8 – 16 % in UC

- Dizygotic twins studies show much lower concordance rates of about 4% in both CD and UC

Russel et al, *Best Pract Res Clin Gastroenterol* 2004; 18:525-39
Tysk, *Gut* 1998; 29:990-6
Omholm, *Scand J Gastroenterol* 2000; 84:794-7

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Susceptibilidad Genética

- Hay una fuerte asociación entre la genética y las EIIC

- Hay fuerte concordancia en gemelos monozigotas
- EC : 36- 58 %
- CU : 8 – 16 %
- En cambio en los gemelos dizigóticos es del 4 % en CU y EC

- **Russel et al : Best Pract Clin Res Gastroenter 2004 18 (525-39)**
- **Tysk : GUT 1998 29 (990-6)**
- **Omholm : Scand J Gastroenterolog 2000, 84 (794-7)**

First Susceptibility Gene for Crohn's Disease NOD2/CARD15

- Attributable risk for Crohn's ~ 30 - 40 % with a higher risk in homozygotes compared with heterozygotes for the NOD2 mutation
- In adults, early onset (compared with late onset) is more associated with NOD2/CARD15
- Attributable risk in children is same as adults
- Risk by population

  Caucasian - 19.1-29%; African Americans 2.6%; Asian (Chinese, Korean, Japanese) – not detected

Hugot, *Nature* 2001; 411:599-603; Ogura, *Nature* 2001; 411:603-6
Ahmed, *Gastroenterology* 2002; 122:854-66
Chamaillard, *Clin Gastroenterol Hepatol* 2006; 4:143-51

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Genética

- Existe una fuerte asociación genética, pero no está claro el patrón de herencia.

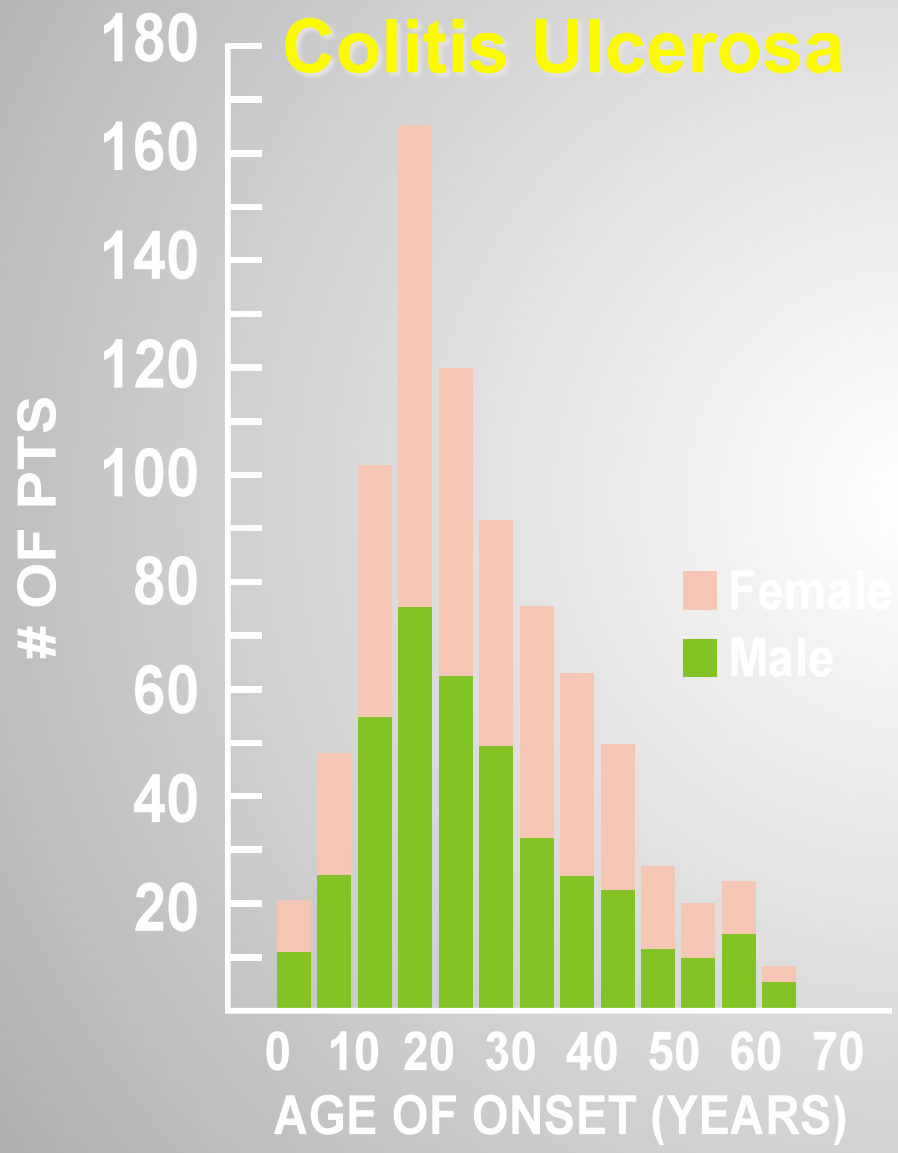
- Frecuencia de EII en parientes de primer grado se ha descrita tan alta como 40%.
-
- En la ***edad pediátrica*** se encontró que 1/3 tenía 1 ***familiar de 1º grado con EIIC***.

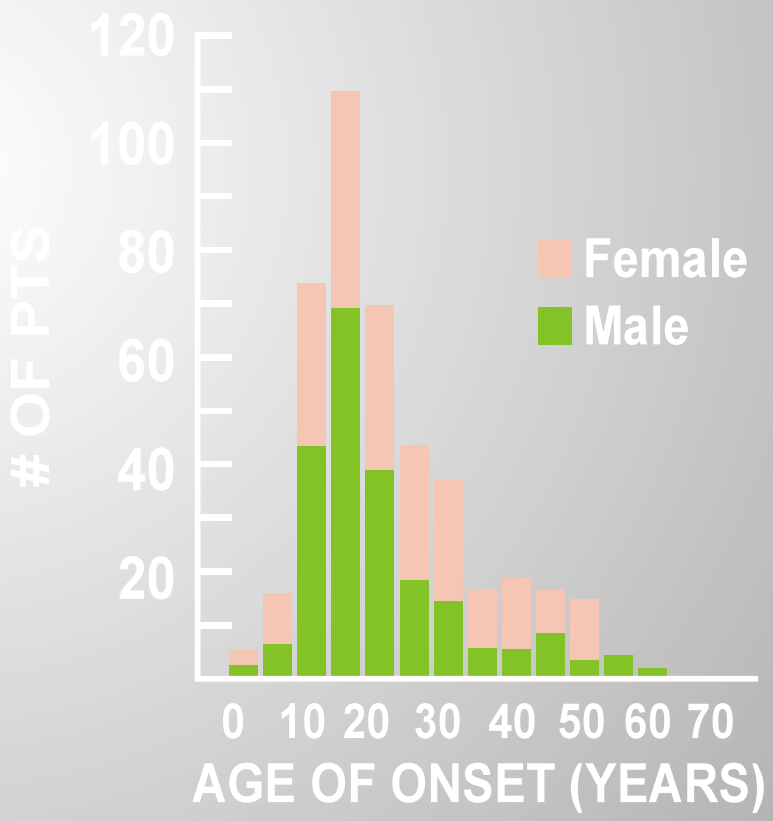
- Alta concordancia en gemelos monocigóticos para el desarrollo de EC.

INCIDENCIA DE LA ENF. DE CROHN

- La ***incidencia de la E. C. se ha incrementado*** en todos los grupos pediátricos, pero **no** hay evidencia que la edad de comienzo esté en disminución, siendo el pico entre los 10 a 20 años y sigue siendo menos frecuente en menores de 5 años.
- Los síntomas comienzan en el 20-25% durante la infancia y adolescencia.
- Incidencia es semejante entre varones y mujeres.

INCIDENCIA POR SEXO Y EDAD





GENÉTICA

- Cromosomas 12
- Cromosomas 16
- Cromosomas 6

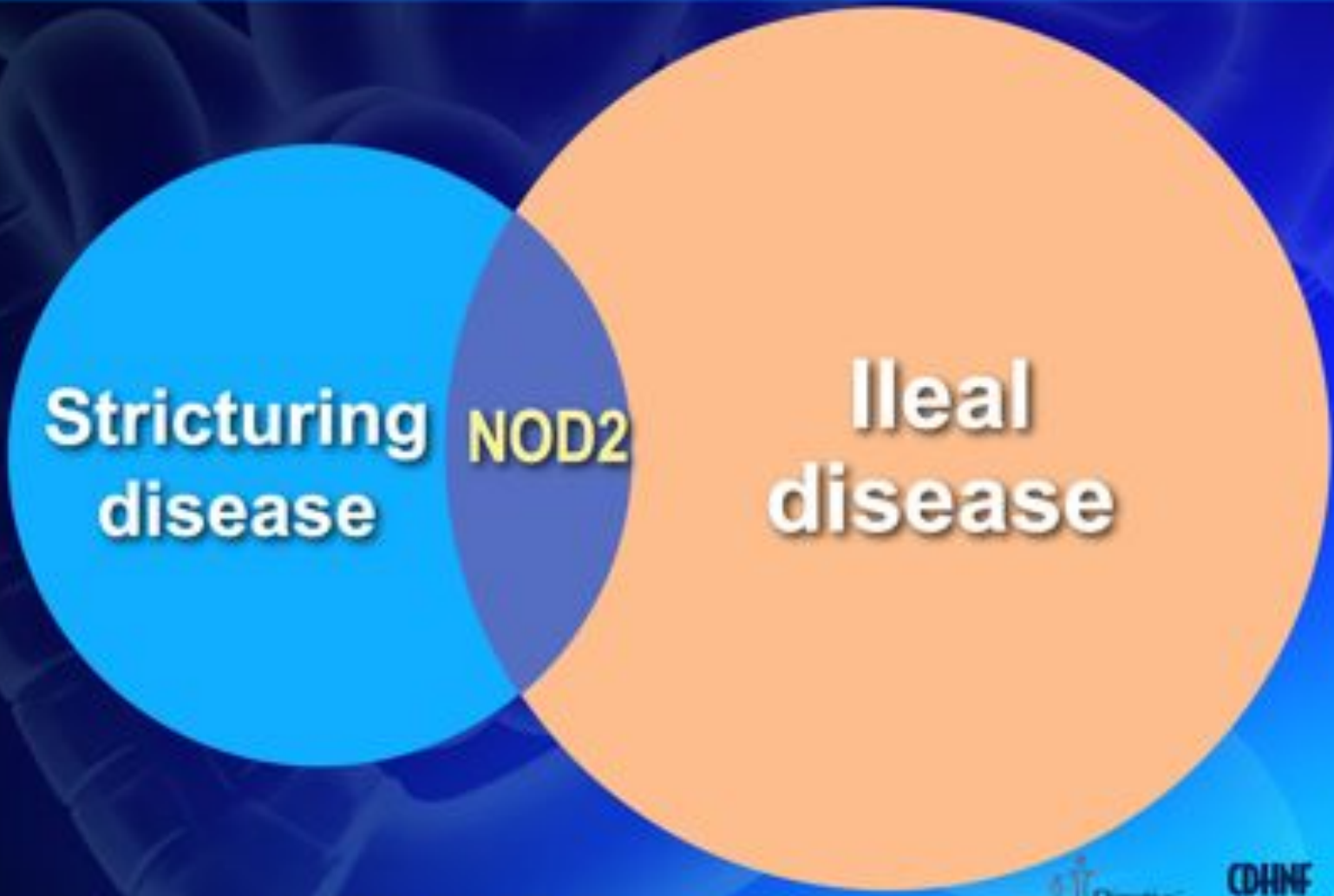
NOD12/CARD15

- Se localizan en el cromosoma 16
- Se han descrito más de 6 diferentes
- La proteína codificada por este gen tiene como rol activar el factor nuclear kappa (NF-kB), el cual es un mediador crítico de la producción de citoquinas proinflamatorias.

NOD2/CARD15

- La mutación de la molécula NOD2/CARD15 (IBD1) parece resultar en una incapacidad para activar NF en respuesta a lipopolisacáridos bacterianos.(Ogura et al.).
- Sólo 30 – 40% de pacientes con EC presentan alguna de las mutaciones descritas para NOD2/CARD15 (702W, 908R, and 1007*fs*).
- Estudios pediátricos: 30% en EC, más asociado a compromiso ileal y compromiso de peso y talla al diagnóstico.

Phenotypic Features of NOD2/CARD15



Abreu, *Gastroenterology* 2002; 123:679-88
Kugathasan, *J Clin Gastroenterol Hepatol* 2004; 2:1003-9

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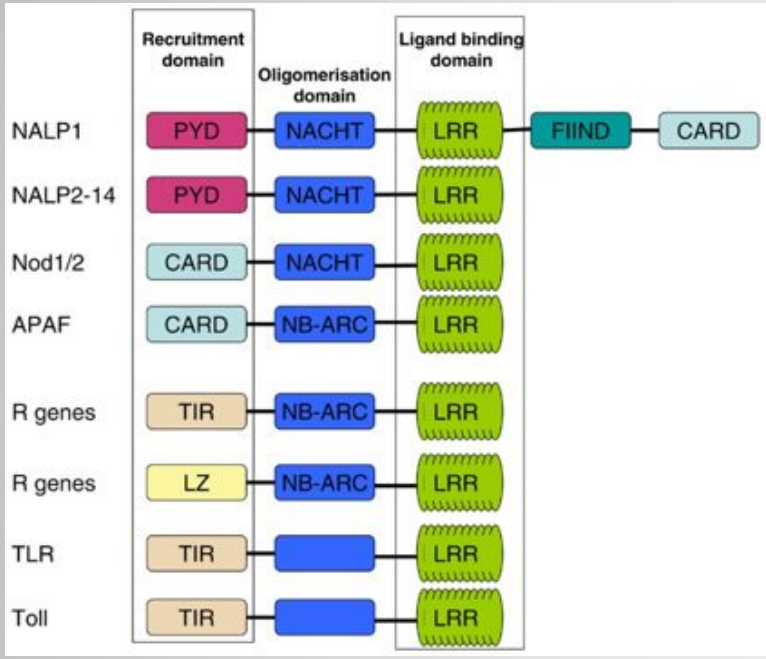
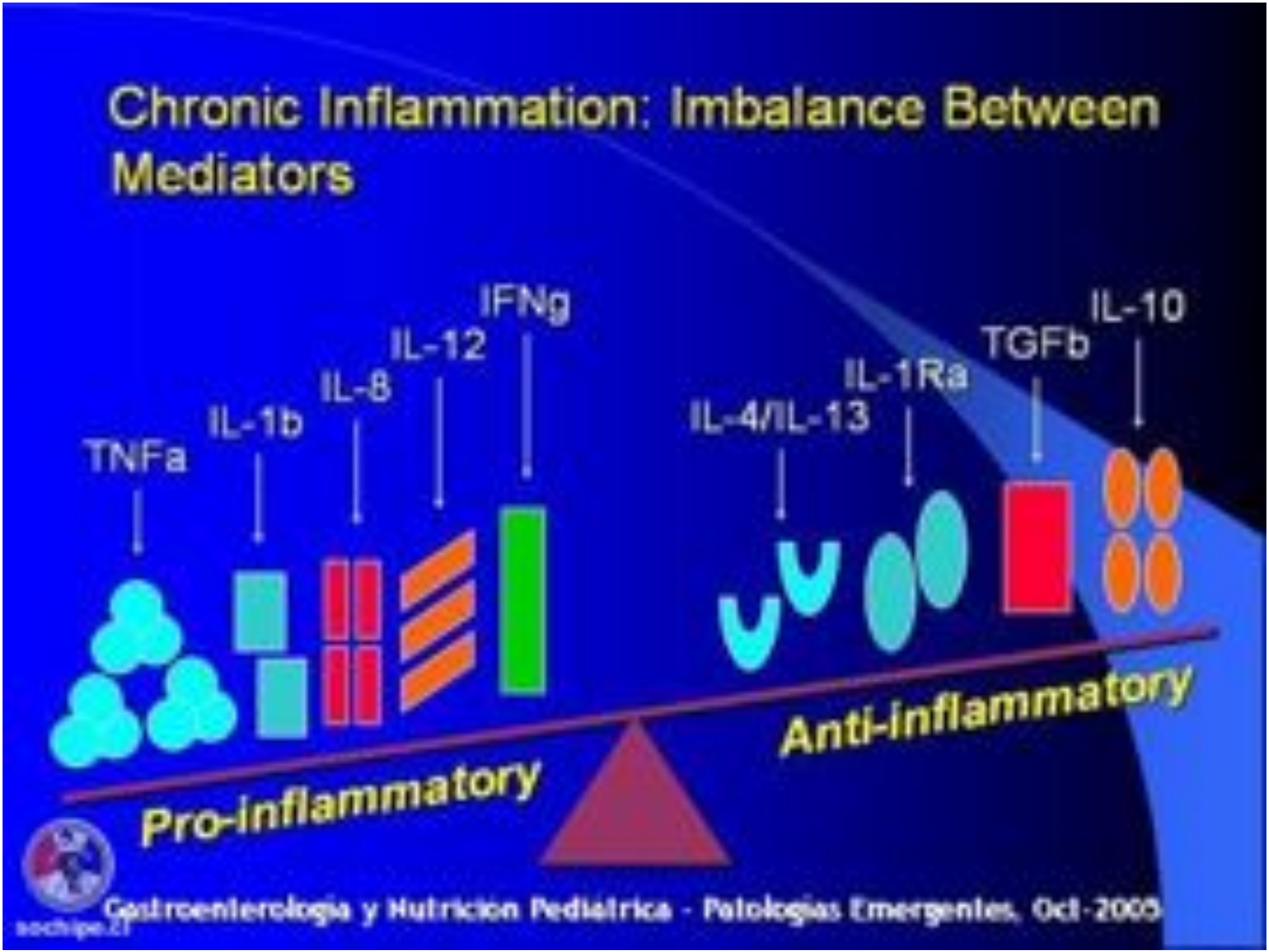
Mutaciones en genes IBD en Niños

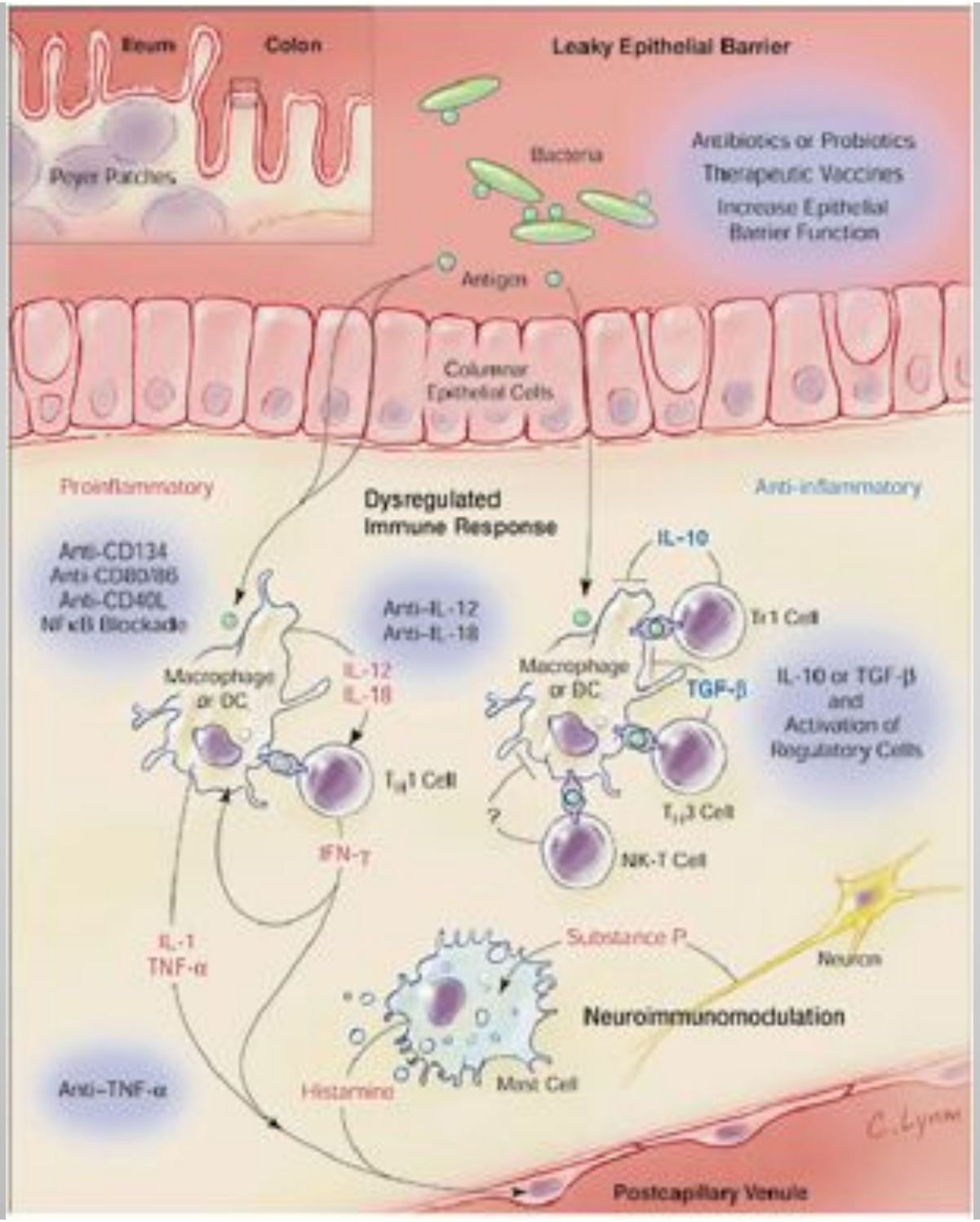


- Asociación con enfermedad fibroestenosante.
- Compromiso ileal.
- Debut precoz de la enfermedad
- Compromiso de la talla al momento del diagnóstico

FACTORES INVOLUCRADOS EN LA PATOGENIA DE LAS EIIC

- Predisposición genética
- Factores ambientales
- Agentes infecciosos
- Dieta
- Características del huésped
    - defectos inmunnológicos de la mucosa
    - alteraciones vasculares mesentéricas
    - falla en la respuesta inflamatoria


Chronic Inflammation: Imbalance Between Mediators
TNFa
IL-1b
IL-8
IL-12
IFNg
IL-4/IL-13
IL-1Ra
TGFb
IL-10
Pro-inflammatory
Anti-inflammatory
Gastroenterologia y Nutricion Pediatrica - Patologias Emergentes. Oct-2005


Ileum
Colon
Peyer Patches
Leaky Epithelial Barrier
Bacteria
Antibiotics or Probiotics
Therapeutic Vaccines
Increase Epithelial
Barrier Function
Antigen
Columnar
Epithelial Cells
Proinflammatory
Dysregulated
Immune Response
Anti-inflammatory
Anti-CD134
Anti-CD80/86
Anti-CD40L
NFκB Blockade
Anti-IL-12
Anti-IL-18
IL-10
Tr1 Cell
Macrophage
or DC
IL-12
IL-18
TGF-β
IL-10 or TGF-β
and
Activation of
Regulatory Cells
T_H1 Cell
T_H3 Cell
?
NK-T Cell
IFN-γ
IL-1
TNF-α
Substance P
Neuron
Neuroimmunomodulation
Mast Cell
Histamine
Anti-TNF-α
C. Lynn
Postcapillary Venule


“Caminante, no hay camino, se hace camino al andar” A.Machado.

Curr Opin Clin Nutr Metab Care. **2006** May;9(3):314-8. Links

Enteral feeding in inflammatory bowel disease.

Griffiths AM.
Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada.

PURPOSE OF REVIEW: Treatment algorithms for inflammatory bowel disease are changing rapidly. **Increased and earlier use of immunomodulatory drugs and availability of biologic agents have reduced dependence on corticosteroids and made mucosal healing a realistic goal. It is timely to debate the role of enteral nutrition in this evolving therapeutic armamentarium for Crohn's disease,** and to examine the mechanisms of its anti-inflammatory effects in light of current understanding of disease pathogenesis.

- RECENT FINDINGS: Clinical studies have suggested that **response to enteral nutrition is associated with decreased mucosal inflammation in Crohn's disease,** that **isolated Crohn's colitis is less responsive** and that exclusive enteral nutrition is required.

Curr Opin Clin Nutr Metab Care. **2006** May;9(3):314-8. Links

Enteral feeding in inflammatory bowel disease.

Griffiths AM.
Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada.

- Basic research has demonstrated that **lipids in the intestinal lumen can alter signalling of the mucosal immune system by intestinal epithelial cells.**
- **Exclusive enteral nutrition is associated with alteration of enteric microflora.**

- SUMMARY: **Enteral nutrition is an efficacious treatment of active inflammation involving the ileum; recent-onset disease may be particularly responsive.**
- **The significance of effects on enteric flora deserves further exploration in view of the importance of microbes to disease pathogenesis**

Aliment Pharmacol Ther. **2008** Sep 15;28(6):724-33.

Sustained modulation of intestinal bacteria by exclusive enteral nutrition used to treat children with Crohn's disease.

Leach ST, Mitchell HM, Eng WR, Zhang L, Day AS.
School of Women's and Children's Health, University of New South Wales, NSW, Australia.

- BACKGROUND:

  The use of **exclusive enteral nutrition to treat paediatric Crohn's disease** (CD) is widely accepted, although **the precise mechanism(s) of action remains speculative**.

- AIM:
- To investigate the **changes to key intestinal bacterial groups** of Eubacteria, Bacteroides, Clostridium coccoides, Clostridium leptum and Bifidobacteria, during and **after exclusive enteral nutrition treatment for CD in paediatric patients and correlate these changes to disease activity and intestinal inflammation.**

-

Aliment Pharmacol Ther. **2008** Sep 15;28(6):724-33.

Sustained modulation of intestinal bacteria by exclusive enteral nutrition used to treat children with Crohn's disease.

Leach ST, Mitchell HM, Eng WR, Zhang L, Day AS.
School of Women's and Children's Health, University of New South Wales, NSW, Australia

- METHODS: Stool was collected from **six children at diagnosis of CD, during exclusive enteral nutrition and 4 months post-therapy, and from seven healthy control children.**

- The **diversity of bacteria** was assessed by polymerase chain reaction-denaturing gradient gel electrophoresis with changes to bacterial diversity measured by Bray-Curtis similarity, intestinal inflammation assessed by faecal S100A12 and the **disease activity assessed by PCDAI.**

Aliment Pharmacol Ther. **2008** Sep 15;28(6):724-33.

Sustained modulation of intestinal bacteria by exclusive enteral nutrition used to treat children with Crohn's disease.

Leach ST, Mitchell HM, Eng WR, Zhang L, Day AS.
School of Women's and Children's Health, University of New South Wales, NSW, Australia.

- RESULTS:
- A **significantly greater change in intestinal bacterial composition was seen with exclusive enteral nutrition treatment** compared with controls.
- Further, the intestinal bacteria remained altered 4 months following exclusive enteral nutrition completion.
- **Changes in the composition of Bacteroides were associated with reduced disease activity and inflammation.**

Aliment Pharmacol Ther. **2008** Sep 15;28(6):724-33.

Sustained modulation of intestinal bacteria by exclusive enteral nutrition used to treat children with Crohn's disease.

Leach ST, Mitchell HM, Eng WR, Zhang L, Day AS.
School of Women's and Children's Health, University of New South Wales, NSW, Australia

- CONCLUSIONS:
- **Exclusive enteral nutrition reduces bacterial diversity and initiates a sustained modulation of all predominant intestinal bacterial groups.**
- **Exclusive enteral nutrition may reduce inflammation through modulating intestinal Bacteroides species.**
- **The implications of these results for exclusive enteral nutrition therapy and CD pathogenesis should now be the subject of further investigation.**

Enteral nutrition should be used to induce remission in childhood Crohn's disease.

Heuschkel R.
Department of Paediatric Gastroenterology, Hepatology and Nutrition, Addenbrookes Hospital, Cambridge University Hospital,

- BACKGROUND: **Exclusive enteral nutrition has been used over many years as a therapy to try and achieve a remission in adults and children presenting with acute Crohn's disease. Despite its reported efficacy at achieving clinical responses in excess of 80% in some case series, it has not been taken up widely as a first-line therapy.**
- This is, at least in part, **due to the lack of a large prospective randomised study.**
- METHODS: The literature is replete with small case series and anecdotal reports from units who use this therapy. Recent literature is reviewed on efficacy, application, composition and potential mechanisms of action of this therapy.
  RESULTS: Although the evidence base remains quite limited, further data are available that **suggest a clear benefit of exclusive enteral nutrition as an efficacious alternative to steroid therapy at inducing a clinical remission in Crohn's disease.**
- .

Dig Dis. 2009;27(3):297-305.

Enteral nutrition should be used to induce remission in childhood Crohn's disease.

Heuschkel R.
Department of Paediatric Gastroenterology, Hepatology and Nutrition, Addenbrookes Hospital, Cambridge University Hospital,

- Certain sub-groups are likely to benefit more, with **potential benefits on growth making it particularly useful in adolescents and growing young adults.**

- **Given the lack of side effects compared to the alternative of steroid therapy,** along with the clear nutritional benefits of this therapy, it remains an obvious choice for patients presenting with Crohn's disease and a degree of malnutrition.

- CONCLUSIONS: **This therapy should remain a first-line therapy for children and adults presenting with mild to moderate Crohn's disease**

Dig Dis. 2009;27(3):297-305

Guidelines for the management of growth failure in childhood inflammatory bowel disease.

Heuschkel R, Salvestrini C, Beattie RM, Hildebrand H, Walters T, Griffiths A.
Royal Free Hampstead NHS Trust, Centre for Paediatric Gastroenterology, Hampstead, London, UK

- Around 1 in 4 patients with inflammatory bowel disease (IBD) present in childhood, the majority around the time of their pubertal growth spurt. This presents challenges over and above those of managing IBD in adults as this period is a time of dramatic psychological and physical transition for a child.
- **Growth and nutrition are key priorities in the management of adolescents and young adults with IBD.** Growth failure in IBD is characterized by delayed skeletal maturation and a delayed onset of puberty, and is best described in terms of height-for-age standard deviation score (Z score) or by variations in growth velocity over a period of 3-4 months.
- Growth failure is common at presentation in Crohn's disease (CD), but less common in ulcerative colitis (UC). **The etiology of growth failure is multifactorial.**

Inflamm Bowel Dis. 2008 Jun;14(6):839-49.

Guidelines for the management of growth failure in childhood inflammatory bowel disease.

Heuschkel R, Salvestrini C, Beattie RM, Hildebrand H, Walters T, Griffiths A.
Royal Free Hampstead NHS Trust, Centre for Paediatric Gastroenterology, Hampstead, London, UK.

- Principal determinants, however, include **the inflammatory process per se, with proinflammatory cytokines** (e.g., IL-1beta, IL-6) being directly implicated.
- Furthermore, **poor nutrition and the consequences of prolonged corticosteroid use also contribute to the significant reduction in final adult height of almost 1 in 5 children**. Initially a prompt, where possible steroid-free, induction of remission is indicated.
- The ideal is then to **sustain a relapse-free remission until growth is complete**, which is often not until early adulthood. These goals can often **be achieved with a combination of exclusive enteral nutrition (EEN) and early use of immunosuppressants.**

Inflamm Bowel Dis. 2008 Jun;14(6):839-49

Guidelines for the management of growth failure in childhood inflammatory bowel disease.

Heuschkel R, Salvestrini C, Beattie RM, Hildebrand H, Walters T, Griffiths A.
Royal Free Hampstead NHS Trust, Centre for Paediatric Gastroenterology, Hampstead, London, UK.

- The advent of potent and efficacious biological agents considerably improves the range of growth-sparing interventions available to children around puberty, although well-timed surgery remains another highly effective means of achieving remission and significant catch-up growth.

- We carried out a systematic review of publications to identify the best available evidence for managing growth failure in children with IBD. Despite the paucity of high-quality publications, sufficient data were available in the literature to allow practical, evidence-based where possible, management guidelines to be formulated.

Inflamm Bowel Dis. 2008 Jun;14(6):839-49

Guidelines for the management of growth failure in childhood inflammatory bowel disease.

Heuschkel R, Salvestrini C, Beattie RM, Hildebrand H, Walters T, Griffiths A.
Royal Free Hampstead NHS Trust, Centre for Paediatric Gastroenterology, Hampstead, London, UK.

- Although there **is clear evidence that exclusive enteral nutrition achieves mucosal healing, its effect on growth has only been assessed at 6 months.**
- **In contrast to corticosteroids, EEN has no negative effect on growth.**
- **Corticosteroids remain the key therapy responsible for medication-induced growth impairment,** although the use of budesonide in selected patients may minimize the steroid effect on dividing growth plates.

Guidelines for the management of growth failure in childhood inflammatory bowel disease.

Heuschkel R, Salvestrini C, Beattie RM, Hildebrand H, Walters T, Griffiths A.
Royal Free Hampstead NHS Trust, Centre for Paediatric Gastroenterology, Hampstead, London, UK.

- **Immunosuppressants have become a mainstay of treatment in children with IBD, and are being used earlier in the disease course than ever before. However, there are currently no long-term data reporting better growth outcome if these agents are introduced very soon after diagnosis.**
-
- In comparison, **recent data from a large prospective trial of infliximab in children with moderate to severe CD suggested significant catch-up growth during the first year of regular infusions.**
-
- **The only other intervention that has documented clear catch-up growth has been surgical resection.**

Inflamm Bowel Dis. 2008 Jun;14(6):839-49

Guidelines for the management of growth failure in childhood inflammatory bowel disease.

Heuschkel R, Salvestrini C, Beattie RM, Hildebrand H, Walters T, Griffiths A.
Royal Free Hampstead NHS Trust, Centre for Paediatric Gastroenterology, Hampstead, London, UK.

- Resection of localized CD, in otherwise treatment-resistant children, early in the disease process achieves clear catch-up growth within the next 6 months. There are **no data available that growth hormone improves final adult height in children with CD.**
- In conjunction with expert endocrinological support, pubertal delay, more common in boys, may be treated with parenteral testosterone if causing significant psychological problems.
- The optimal management of children and adolescents requires a **multidisciplinary approach frequently available within the pediatric healthcare setting. Dedicated dietetic support, along with nurse-specialist, child psychologist, and with closely linked medical and surgical care will likely achieve the best possible start for children facing a lifetime of chronic gut disease**

Nutritional status and nutritional therapy in inflammatory bowel diseases.

Hartman C, Eliakim R, Shamir R.

Institute of Gastroenterology, Nutrition, and Liver Disease, Schneider Children's Medical Center of Israel, 14 Kaplan Street, Petach-Tikva 49202, Israel.

- Underweight and specific nutrient deficiencies are frequent in adult patients with inflammatory bowel disease (IBD). In addition, a significant number of children with IBD, especially Crohn's disease (CD) have impaired linear growth.
- Nutrition has an important role in the management of IBD. In adults with CD, enteral nutrition (EN) is effective in inducing clinical remission of IBD, although it is less efficient than corticosteroids. Exclusive EN is an established primary therapy for pediatric CD.
- Limited data suggests that EN is as efficient as corticosteroids for induction of remission.
- Additional advantages of nutritional therapy are control of inflammation, mucosal healing, positive benefits to growth and overall nutritional status with minimal adverse effects.

World J Gastroenterol. 2009 Jun 7;15(21):2570-8

Nutritional status and nutritional therapy in inflammatory bowel diseases.

Hartman C, Eliakim R, Shamir R.
Institute of Gastroenterology, Nutrition, and Liver Disease, Schneider Children's Medical Center of Israel, 14 Kaplan Street, Petach-Tikva 49202, Israel.

- The available evidence suggests that supplementary EN may be effective also for maintenance of remission in CD. More studies are needed to confirm these findings. However, EN supplementation could be considered as an alternative or as an adjunct to maintenance drug therapy in CD.
-
- EN does not have a primary therapeutic role in ulcerative colitis. Specific compositions of enteral diets-elemental diets or diets containing specific components-were not shown to have any advantage over standard polymeric diets and their place in the treatment of CD or UC need further evaluation.

- Recent theories suggest that diet may be implicated in the etiology of IBD, however there are no proven dietary approaches to reduce the risk of developing IBD.

- **World J Gastroenterol. 2009 Jun 7;15(21):2570-8**

Gracias por su atención.

Potential Future Applications of Genomics

- Individualizing therapy based on genetic subsets
  - Genetic subsets predict response to treatment
  - Optimize medications to avoid toxicity and enhance response
- Identifying high risk subjects
  - Screen siblings and offspring
  - Preventative therapy tailored by genetic abnormality

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Other Genes Involved in IBD

- OCTN – organic cation transporter gene located on 5q31, mutations at this loci affect the ability of the transporters to pump xenobiotics and amino acids
- DLG5 – membrane scaffold protein located on 10q23, mutations impart the ability to maintain epithelial polarity

Both genes important in epithelial permeability and disruption may facilitate exposure to bacterial products

Peltekova, *Nat Gen* 2004; 36:471-5;
Stoll, *Nat Gen* 2004; 36:476-80;
Babusukumar, *Am J Gastroenterol* 2006; 101:1354-61

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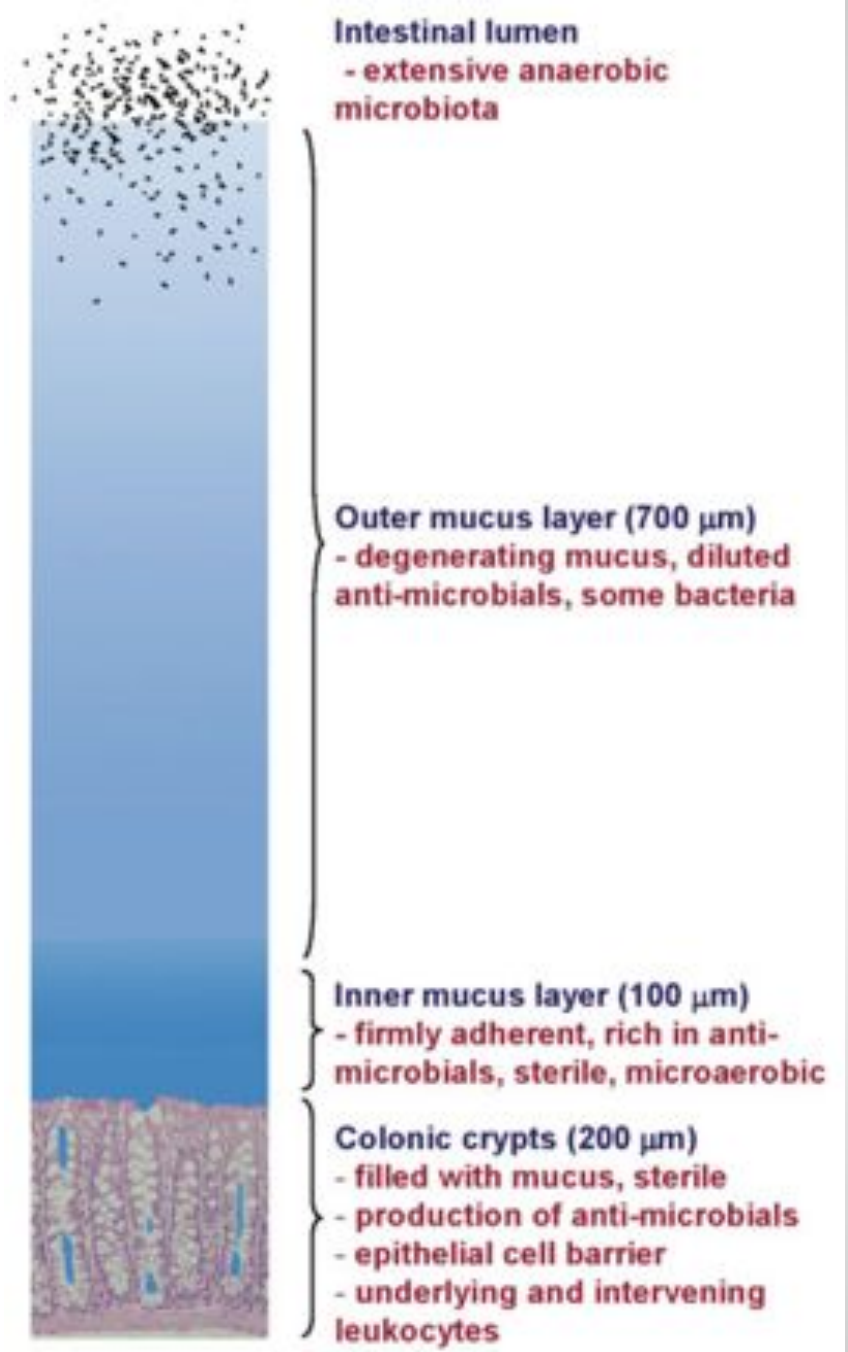


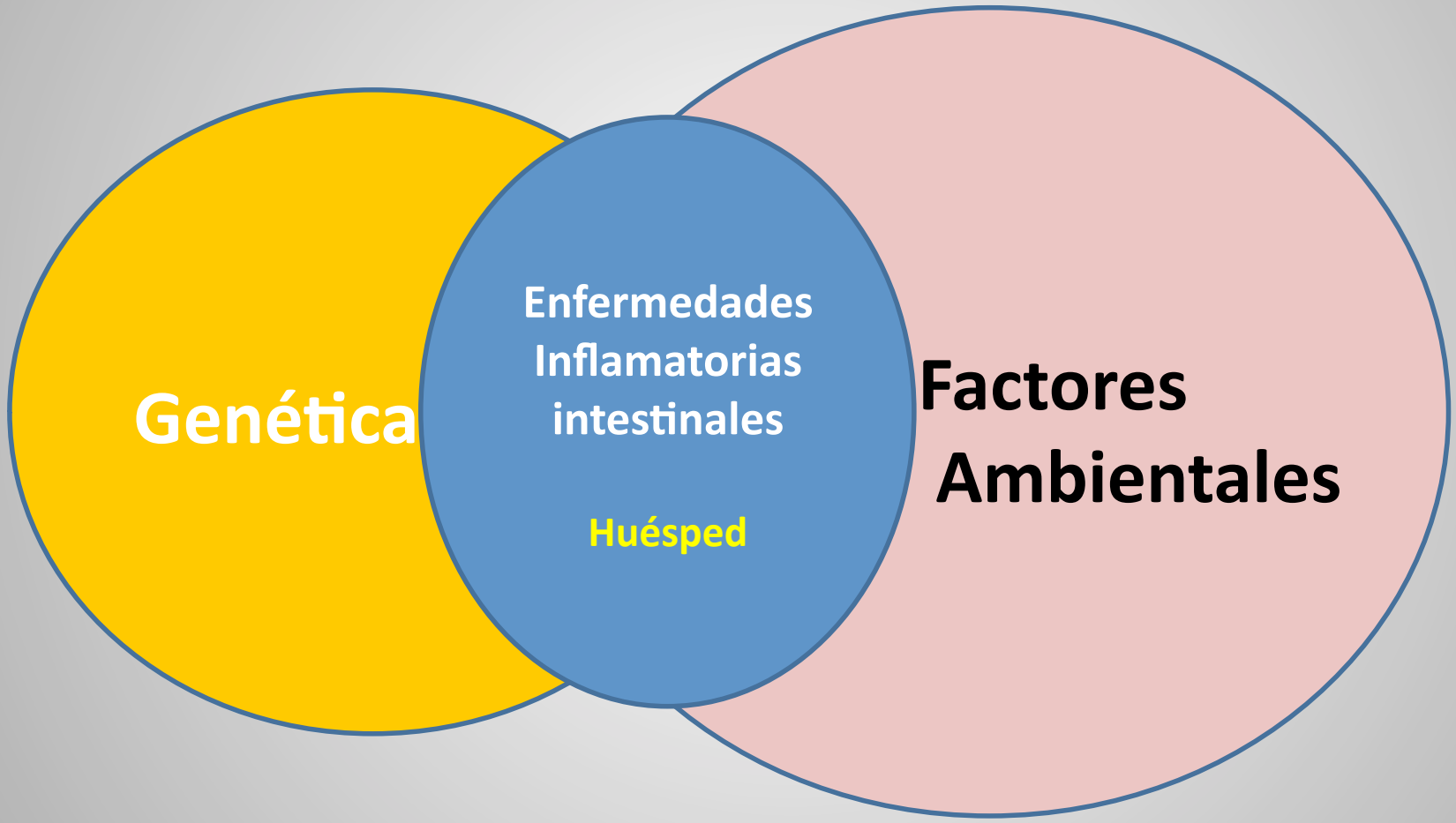
Inflamm Bowel Dis • Volume 15, Number 1, January 2009

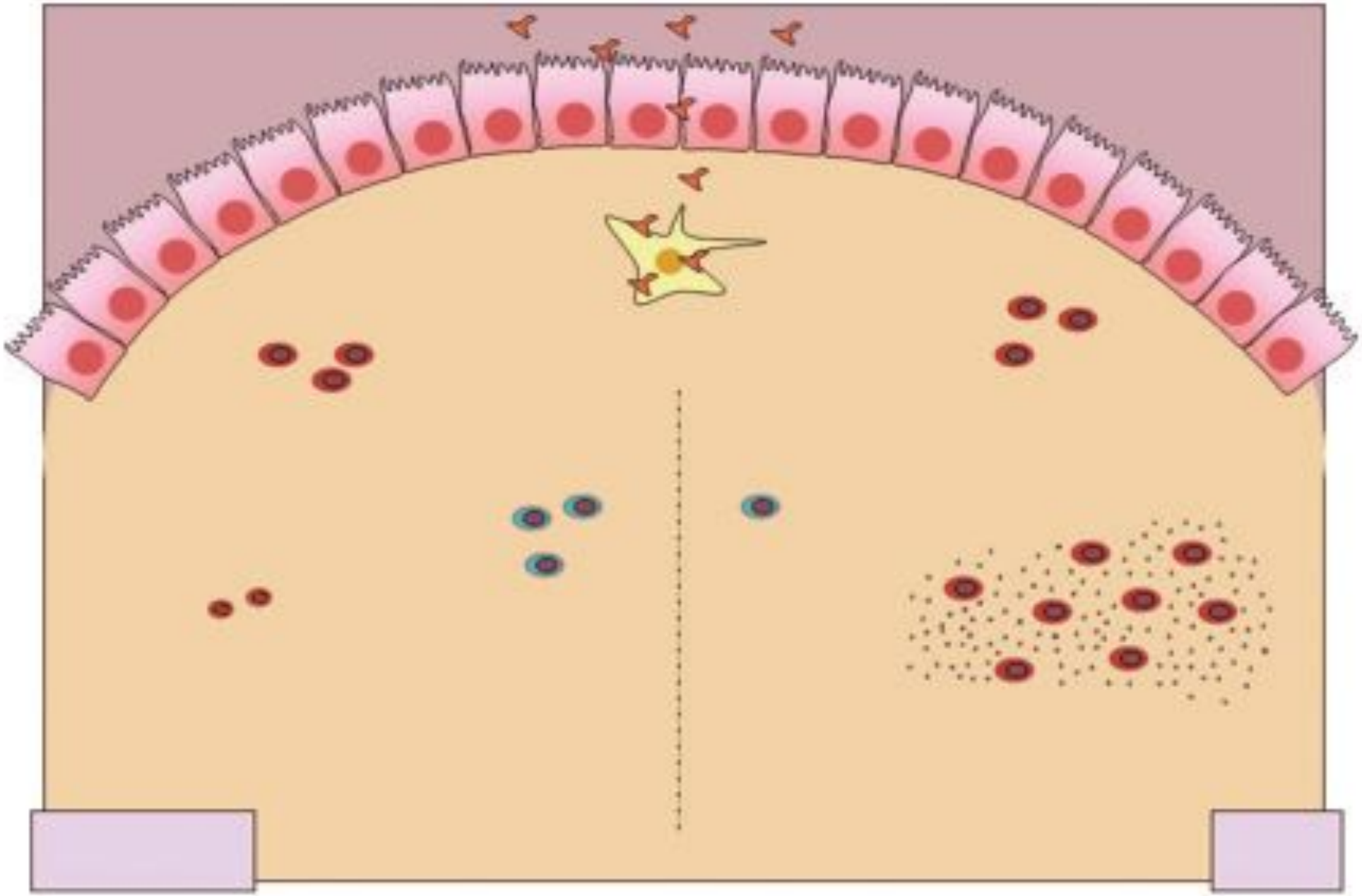
TABLE 1. Molecular Elements of the Intestinal Mucus Barrier Relevant to Barrier Function

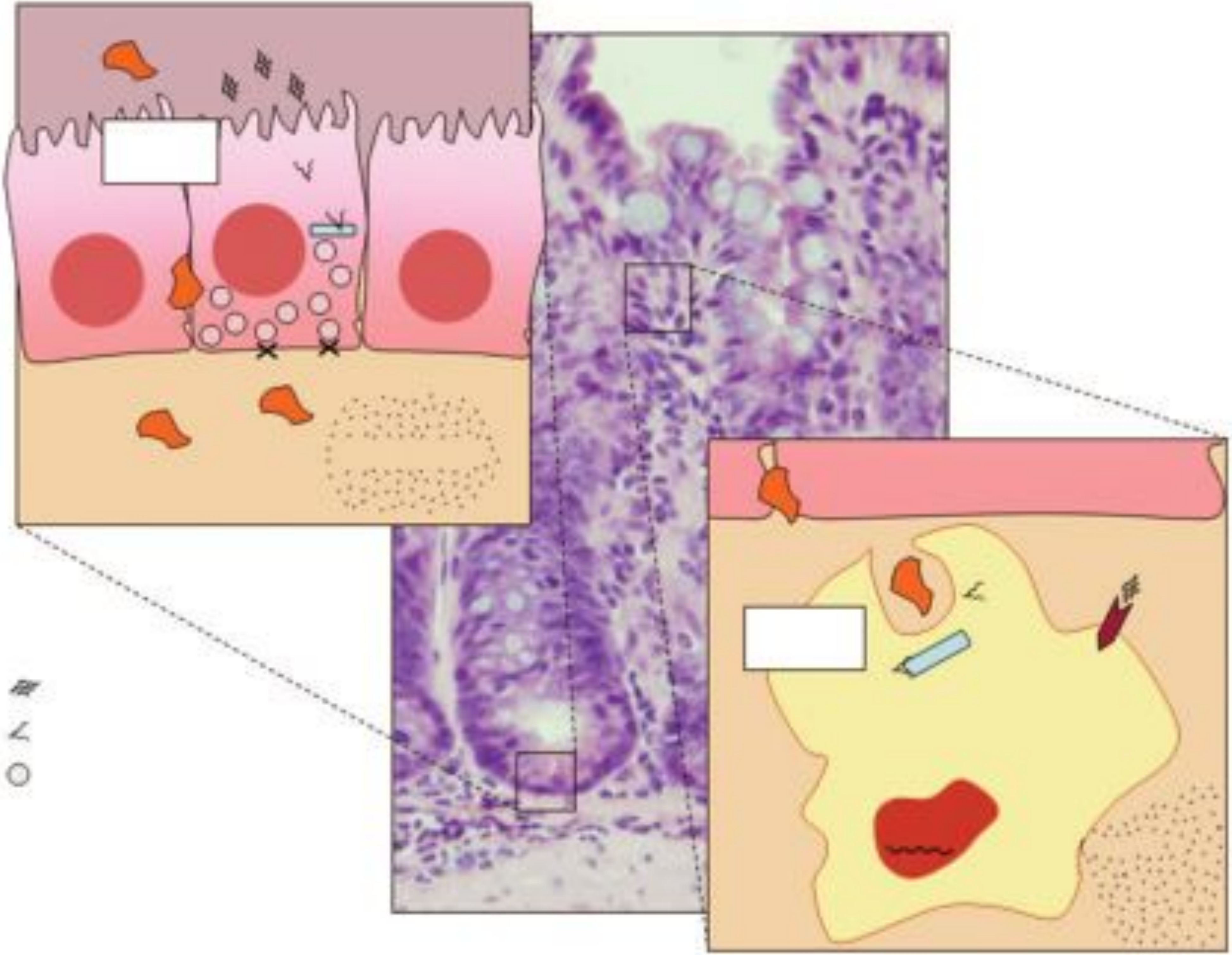
Component	Source	Regulation	Function
Mucin (MUC2)	Goblet cells, Paneth cells	Constitutive. ↑ TLR ligands, inflammatory cytokines, growth factors, lipid mediators, hormones, neural stimulus	Major macromolecular component of hydrophili hydrated mucus: physical barrier, hydration, lubrication, retention of antimicrobial molecules
Immunoglobulins (sIgA, IgG, IgM) Secretory component (SC) and FcRn	B lymphocytes, epithelial cells (SC and FcRn)	Constitutive. Regulated by antigen presenting cells, helper T cells and epithelial cells.	Antimicrobial: opsonization of microbes, blocking microbial penetration of mucus SC and FcRn facilitate transport across epithelium Glycosylated SC protects Fc region of IgA dimer in external environment.
Trefoil peptides (ITF/ TFF3)	Goblet cells	Constitutive. Regulation not well understood.	Co-secreted with MUC2, possible modulator of mucin polymerization, stimulator of wound repair.
Antimicrobial peptides (defensins, cathelicidins, lysozyme, PLAP2)	Paneth cells, enterocytes	Constitutive. TLR and NOD ligands, cholinergic stimuli.	Peptides with direct antimicrobial activity.
Phospholipids	Enterocytes	Not known	Hydrophobic element of mucus probably interdispersed in striated layers with hydrated mucus: lubrication and barrier function
Lectins (RegIIIγ, collectins)	Paneth cells, enterocytes	Constitutive and regulated by TLR ligands (e.g,. RegIII expression is lost in MyD88$^{-/-}$ mice)	Direct antimicrobial activity.
Antimicrobial protease inhibitors (SLPI, elafin)	Epithelial cells, leukocytes	Constitutive and increased by inflammation.	Some direct antimicrobial activity.

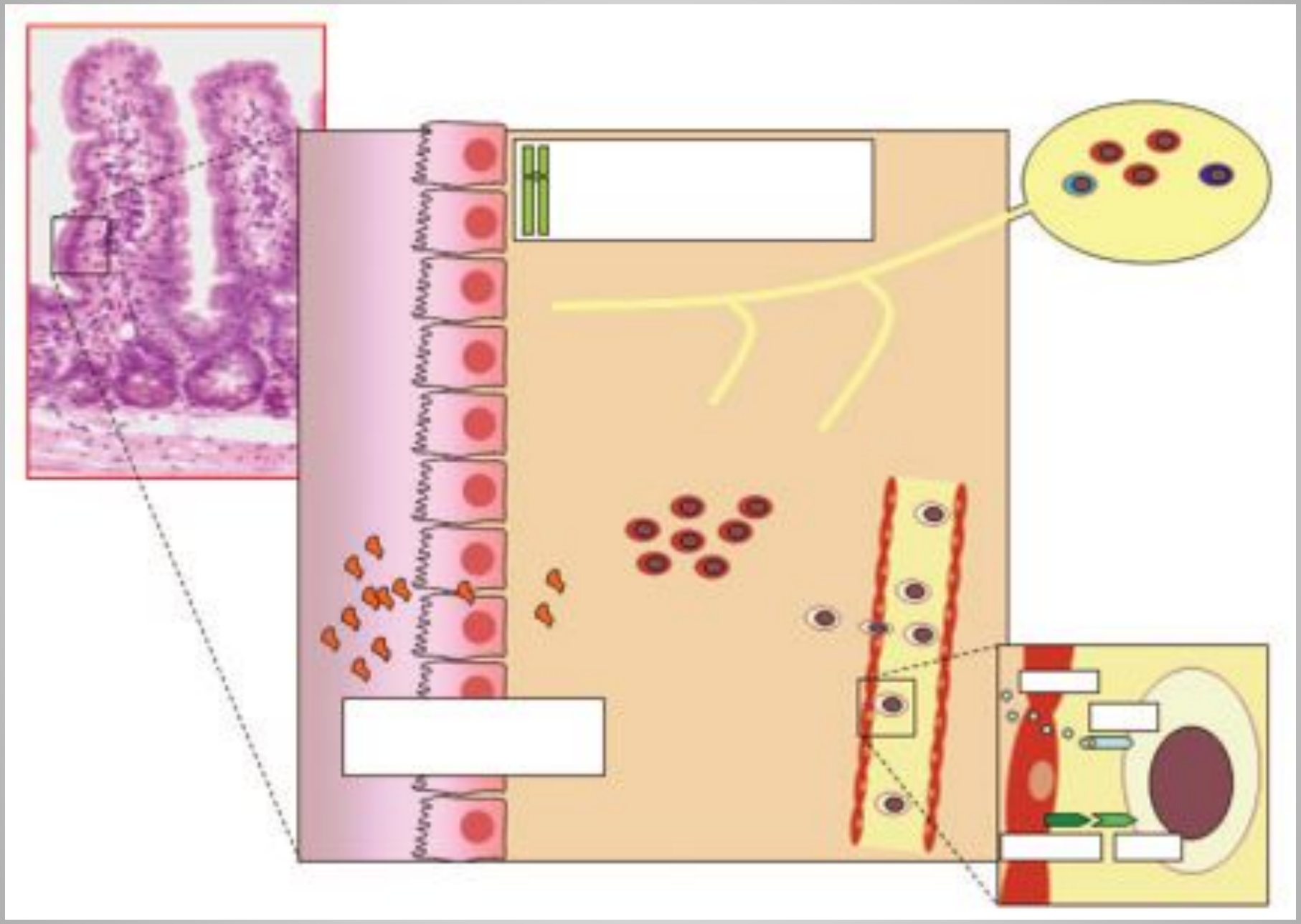
- Lactancia materna
- Tabaco
- Tipo de Actividad
- Nivel Educacional
- Clima
- Stress
- Hábitos de Alimentación
- Infecciones

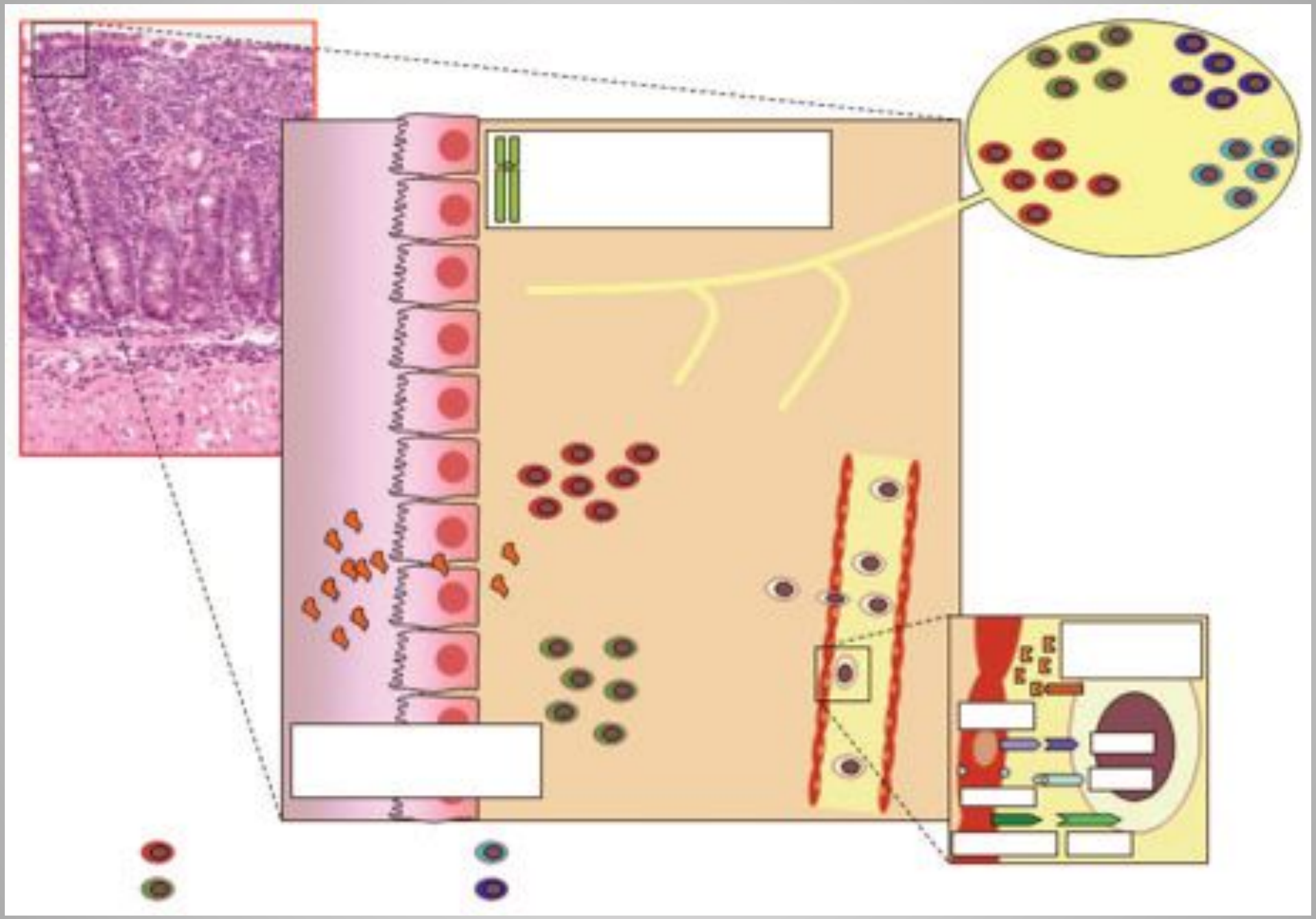
Que causa las Enfermedades Inflamatorias Intestinales ??



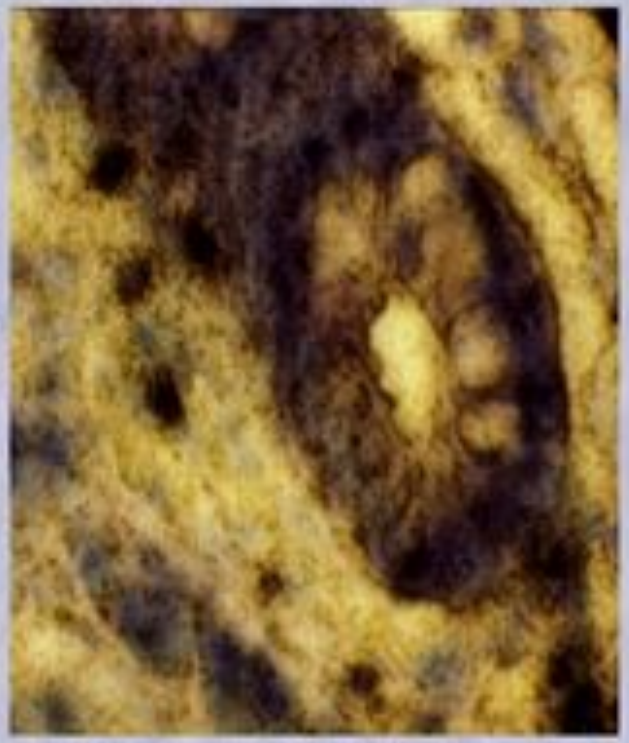








SUSTANCIAS MENSAJERAS



Liberación de Interleuquina 10b En el colon de un paciente con enfermedad de Crohn.

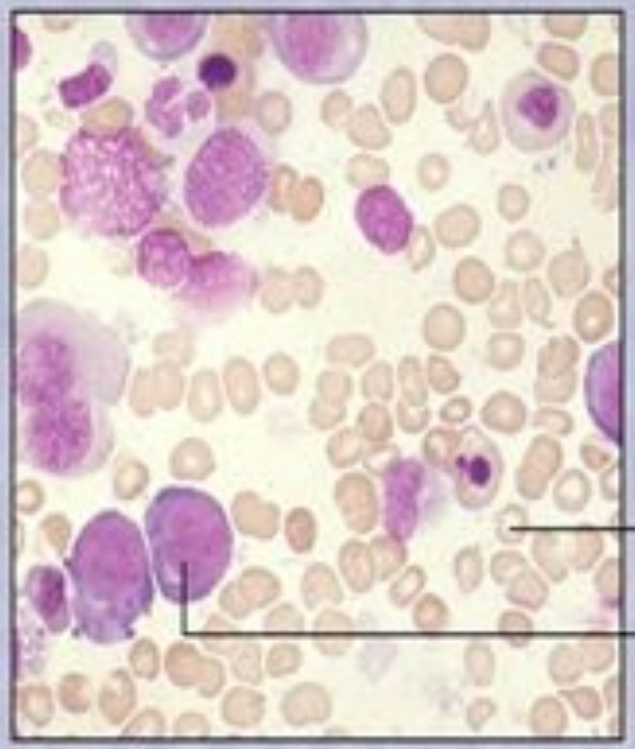
Las **citoquinas** (**sustancias mensajeras**) son producidas y liberadas por una variedad de células.

Llevan a cabo un sinnúmero de tareas en el sistema inmune.

Como mediadores intercelulares regulan la **activación de células**.

Las **citoquinas** se subdividen en **linfoquinas , interleuquinas, monoquinas y factores de crecimiento.**

LIBERACIÓN DE LEUCOCITOS



Los leucocitos (macrófagos y granulocitos) son estimulados por las bacterias y sus productos y estos metabólitos **comienzan a atacar a los invasores.**