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REVIEW ARTICLE

Systematic Review of the Relation Between Intestinal Microbiota and Toll-Like Receptors in the Metabolic Syndrome: What Do We Know So Far?

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Abstract
Introduction: Metabolic syndrome is an emerging problem in developed countries and presents itself as a potential threat worldwide. The role of diabetes, dyslipidaemia and hepatic steatosis as pivotal components of the metabolic syndrome is well known. However, their common persistent chronic inflammation and its potential cause still elude. This systematic review aims to present evidence of the mechanisms that link the intestinal microbioma, innate immunity and metabolic syndrome.
Methods: A comprehensive research was made using PubMed database and 35 articles were selected.
Results: We found that metabolic syndrome is associated to increased levels of innate immunity receptors, namely, Toll-like receptors, both in intestine and systemically and its polymorphisms may change the risk of metabolic syndrome development. Microbioma dysbiosis is also present in metabolic syndrome, with lower prevalence of Bacteroidetes and increased prevalence of Firmicutes populations. The data suggest that the link between intestinal microbiota and Toll-like receptors can negatively endanger the metabolic homeostasis.
Conclusion: Current evidence suggests that innate immunity and intestinal microbiota may be the hidden link in the metabolic syndrome development mechanisms. In the near future, this can be the key in the development of new prophylactic and therapeutic strategies to treat metabolic syndrome patients.

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PALAVRAS-CHAVE
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Revisão Sistemática da Relação Entre a Microbiota Intestinal e os Receptores Toll-Like na Síndrome Metabólica: O Que Sabemos Atualmente?

Resumo
Introdução: A síndrome metabólica é, hoje, um problema emergente nos países desenvolvidos e apresenta-se como uma das principais ameaças médicas à escala global. O papel desempenhado pela diabetes, dislipidemia e a esteatose hepática, como componentes principais desta Síndrome é prontamente reconhecido. No entanto, a inflamação crónica persistente comum e as suas potenciais causas ainda não estão claramente definidas.
Objectivos: Esta revisão sistemática pretende apresentar evidências dos mecanismos que interligam o microbioma intestinal, a imunidade inata e a síndrome metabólica.
Métodos: Uma pesquisa sistemática foi realizada, utilizando a base de dados PubMed, tendo selecionado 35 artigos para a elaboração desta revisão.
Resultados: A síndrome metabólica está claramente associada a níveis aumentados de expressão dos receptores da imunidade inata, nomeadamente, os receptores da família Toll-like receptors, quer no tecido intestinal, quer sistemicamente, e diferentes polimorfismos parecem ser responsáveis por diferentes riscos de desenvolver esta doença. Por outro lado, a disbiose do microbioma intestinal está também presente na síndrome metabólica, com a presença de Bacteriodetes em menor prevalência e com aumento das populações de Firmicutes. Os resultados sugerem ainda que a ligação entre a microbiota intestinal e os receptores da imunidade inata possa negativamente comprometer a homeostasia metabólica, de forma semelhante à evidenciada nesta síndrome.
Conclusões: Evidência actual sugere e suporta que a imunidade inata e a microbiota intestinal possam ser a ligação pivô nos mecanismos de desenvolvimento da síndrome metabólica. Num futuro próximo, esta pode ser a chave para o desenvolvimento de novas estratégias profiláticas e terapêuticas para a síndrome metabólica.

1. Introduction

The metabolic syndrome presents itself as one as the principal chronic diseases of the developed countries and an important determinant of cardiovascular and metabolic mortality risk.[1] It is defined as a persistent pro-inflammatory state in which abnormal metabolic and physiological factors produce an increased risk of developing diabetes, obesity, dyslipidaemia and other cardiovascular risk factors.[1–3] Recent data report a consistent activation of the innate immunity through the Toll-like receptors (TLR) and its downstream signalling, suggesting not only a potential causative way, but also a possible perpetuator of its chronic immune stress to the organism.[4–6] On the other hand, new insights have revealed a pivotal role of the intestinal microbiota and its interaction with the host genetics, in the development of obesity and insulin resistance.[7–9] It has been also described in the role of intestinal microbiota, its migration and its metabolic products systemic effects, in the activation of these TLR receptors in several organs, especially the liver.[10,11]

However, in spite of this new data, the relationship, causality and the mechanisms by which the intestinal microbiota can influence the expression of several immune receptors including TLR still eludes. Also, the relationship between differential expression of TLR and the lesion of several organs presented in metabolic syndrome is poorly understood.

This systematic review aims to access the most recent data about the relevance of intestinal microbiota and TLR expression in the development of hepatic lesion and metabolic syndrome.

2. Methods

A comprehensive search was performed in PubMed and the following queries were used: [(''Metabolic Syndrome''[All Fields] AND (''microbiome''[All Fields] OR ''microbiota''[All Fields])) OR (''Metabolic Syndrome''[All Fields] AND (''Toll-like receptors''[All Fields] OR ''TLRs''[All Fields]) AND (''microbiome''[All Fields] OR ''microbiota''[All Fields]))], and [(gut microbiota[Title] OR microbiota[Title]) AND (((TLR[Title]) OR Toll like receptor[Title]) OR Innate immunity[Title])].

From the search and after duplicates were removed, 230 studies were retrieved (Fig. 1). Using inclusion and exclusion criteria, 35 articles were selected, analyzed and included in this revision (Table 1).

The principal summary measures in an outcome level were different risk ratios of developing obesity, diabetes, dyslipidaemia or metabolic syndrome in every experimental conditions used, difference in means of RNA or biochemical expression levels of markers studied and differences on histological or phenotypical assessment of major organs studied in a variety of experimental conditions. Subgroup analyses