

# Targeting the integrin $\alpha 4\beta 7$ with probiotics and nutraceuticals: a working hypothesis

## Abstract

$\alpha 4\beta 7$  integrin is critical in lymphocyte homing to the gut, a clinical relevant marker and a therapeutic target in inflammatory bowel disease (IBD). Deregulated  $\beta 7$ -mediated T lymphocytes homing was observed also in the extra-intestinal manifestations of IBD and in subjects with the irritable bowel syndrome (IBS). Nutritional interventions and/or functional foods (containing prebiotics, probiotics and/or nutraceuticals), rather than drug treatments, should be recommended in IBS. Despite dysbiosis is a common feature of both IBD and IBS, the modulation of gut microbiota and gut functional symptoms by dietary regimes, prebiotics, probiotics, symbiotics, as well as by herbal medicinal products and foods containing bioactive phytochemicals, requires future well-designed clinical trials to establish their safety and efficacy. Results from in vitro and animal models suggest a role of  $\alpha 4\beta 7$  integrin also in high-fat diet (HFD)-induced insulin resistance (IR) and atherosclerosis, as well as the potential modulation of gut homing by dietary phytochemicals and probiotics. Despite there was no significant difference in cholesterol levels between HFD fed ApoE<sup>-/-</sup> and  $\beta 7^{-/-}$ -ApoE<sup>-/-</sup> mice, the latter had a reduced the size of atherosclerotic lesions. Overall human and experimental data suggest that  $\alpha 4\beta 7$  integrin could be a target of functional foods and a useful marker in human studies, being sensitive to the complex interaction between genetic factors, microbiota and dietary habit.

**Keywords:**  $\alpha 4\beta 7$  integrin, apolipoprotein e, dietary phytochemicals, functional foods, gut-associated lymphoid tissue, gut-homing, nutraceuticals, human studies, polyphenols, prebiotics, probiotics

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**Abbreviations:** Apo E, apolipoprotein E; DC, dendritic cell; FODMAPs, fermentable oligosaccharides, disaccharides, monosaccharide and polyols; GALT, gut-associated lymphoid tissue; HFD, high-fat diet; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IR, insulin resistance; LeS, lactobacillus casei shirota; MAcCAM-1, mucosal address in cell adhesion molecule-1; PUFA, polyunsaturated fatty acids; UC, ulcerative colitis

## Introduction

The gut-homing molecule  $\alpha 4\beta 7$  integrin is a clinical relevant marker in celiac disease<sup>1</sup> cow's milk allergy,<sup>2</sup> HIV-1 infection,<sup>3,4</sup> mucosal responses to bacterial infection,<sup>5</sup> post-hematopoietic stem cell transplantation diabetes mellitus<sup>6,7</sup> and graft-versus-host disease.<sup>8-10</sup> Aberrant homing of mucosal T cells plays a role also in the extra-intestinal manifestations of inflammatory bowel disease (IBD).<sup>11</sup> In this context,  $\alpha 4\beta 7$  integrin is an emerging therapeutic target IBD.<sup>12-14</sup> Deregulated  $\beta 7$ -mediated T lymphocytes homing was observed also in patients with gastrointestinal disorders, such as irritable bowel syndrome (IBS)<sup>15-17</sup> and functional dyspepsia.<sup>18</sup> Although these conditions impair patients' quality of life, nutritional interventions and/or functional foods (containing prebiotics, probiotics and/or nutraceuticals) rather than drug treatments should be recommended.

## Prebiotics, probiotics and nutraceuticals

Dysbiosis is a common feature of both IBD and IBS,<sup>19</sup> but the therapeutic modulation of gut microbiota and symptoms by dietary regimes, prebiotics, probiotics, symbiotic, as well as by herbal medicinal products and foods containing bioactive phytochemicals, requires future well-designed clinical trials to establish their safety

and efficacy.<sup>20-26</sup> Whereas the role of fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) in eliciting IBS requires further investigations,<sup>27</sup> a diet low FODMAPs is increasingly recommended for patients with IBD.<sup>28</sup> FODMAPs are found in many vegetables and fruits,<sup>29</sup> rich food-sources of polyphenols. Despite the suggested prebiotics, anti-inflammatory, anti-oxidant and immuno-modulatory activities of polyphenols, potential adverse effects due to their interaction with the phase I, II and III metabolizing/transport system must be taken into account.<sup>30</sup> Also food-drug interactions with statins are a commonly overlooked aspect.<sup>31</sup> In this context, the cross-talk between the Gut-Associated Lymphoid Tissue (GALT) and microbiota has a role also in metabolic syndrome.<sup>32</sup> Both in vitro and in vivo studies suggest that many interactions could occur among probiotics, prebiotics, omega 3 polyunsaturated fatty acids ( $\omega$ -3 PUFA) and polyphenols from dietary or non-dietary sources in the GALT.<sup>33</sup> Prebiotics,  $\omega$ -3 PUFA and polyphenols affect the colonic microflora.<sup>33</sup> The latter converts polyphenols into metabolites with different activities that could directly interact with immune cells in the GALT.<sup>33</sup> Despite the evidence of the mutual cooperation among prebiotics,  $\omega$ -3 PUFA and polyphenols in the prevention of metabolic syndrome, suggesting that Mediterranean diet is a natural multiple supplement.<sup>33</sup> studies in mice and human subjects indicate that the Apolipoprotein E (ApoE) 3 genotype, which has high frequency in the Mediterranean area, may significantly benefit from dietary flavonoids and  $\omega$ -3 PUFA.<sup>34</sup> On the contrary, the apoE4 genotype, the most important genetic risk factors for age-dependent chronic diseases showing high frequency in Northern Europe, is associated with higher circulating vitamin D levels.<sup>34</sup>

The role of vitamin D and A in the induction of homing properties in T cells is well known.<sup>35</sup> Results from animal models suggest a primary role of  $\alpha 4\beta 7$  in high-fat diet (HFD)-induced insulin resistance (IR)<sup>36</sup> and atherosclerosis.<sup>37</sup> HFD-induced IR was lower in  $\beta 7$  integrin-deficient mice ( $\beta 7^{-/-}$ ) versus control wild-type C57BL/6 mice.<sup>36</sup>  $\alpha 4\beta 7$  and its ligand mucosal addressin cell adhesion molecule-1 (MAdCAM-1) were up-regulated in HFD-induced atherosclerotic lesions in the ApoE $^{-/-}$  mouse model of atherosclerosis.<sup>37</sup> The increase in plaque area in HFD fed ApoE $^{-/-}$  aortas occurs in parallel with an increase in peripheral blood lymphocyte  $\alpha 4\beta 7$  integrin expression.<sup>37</sup> The genetic deletion of  $\beta 7$  integrin reduced the size of the HFD-induced atherosclerotic lesions in ApoE $^{-/-}$  mice, despite there was no significant difference in cholesterol levels between HFD fed ApoE $^{-/-}$  and  $\beta 7^{-/-}$  ApoE $^{-/-}$  mice.<sup>37</sup> Also intestinal bacteria influence the development of atherosclerotic in ApoE $^{-/-}$  mice.<sup>38</sup>

A high cholesterol diet, but not a low cholesterol diet, induced atherosclerotic aortic plaques ApoE $^{-/-}$  mice.<sup>38</sup> However, a diet low in cholesterol induced atherosclerotic plaques in ApoE $^{-/-}$  mice in germ-free conditions.<sup>38</sup> Differential immuno-modulatory effects of probiotic strain *Lactobacillus casei* Shirota (LcS) on human dendritic cell (DC) from healthy controls and active in ulcerative colitis (UC) patients have been reported.<sup>39</sup> LcS treated DC from healthy subjects induced  $\beta 7$  on T cells and enhanced DC ability to induce transforming growth factor- $\beta$  production by T cells, but had no effects on UC-DC.<sup>39</sup>

On the other hand, *in vitro* experiments indicate that the unsaponifiable fraction of extra virgin olive oil is able to reduce the expression of integrin  $\alpha 4\beta 7$  on T lymphocytes from peripheral blood of patients with IBD,<sup>40</sup> suggesting a potential modulation of gut homing by dietary phytochemicals.

## Conclusion

Overall human and experimental data suggest that  $\alpha 4\beta 7$  integrin could be a target of functional foods and a useful marker in human studies, being sensitive to the complex interaction between genetic factors, microbiota and dietary habits.

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## Conflict of interest

There is no conflict of interests regarding the publication of this paper.

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