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Review

Managing the manager: Gut microbes, stem cells and metabolism

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Abstract

One major discovery of the last decade in the field of metabolic diseases is that the microorganisms comprising the gut microbiota are now considered a metabolic "organ", modulating multiple functions of the host, such as intestinal immune system maturation, adiposity, cardiac metabolism, liver triglyceride storage, and brain development and behaviour. The corresponding mechanisms involve increased energy harvesting through the production by microbiota of short-chain fatty acids for use by the host, and the release of pro-inflammatory compounds, such as lipopolysaccharide (LPS), flagellin and peptidoglycan. In particular, a high-fat diet (HFD) modifies gut microbiota, resulting in an increase of plasma LPS levels known as "metabolic endotoxaemia", a major driver of the onset of metabolic diseases through a CD14-dependent mechanism. The LPS-sensitive cell types can be seen within bone marrow-derived cells (BMC), which are involved in the development of inflammation in the adipose tissue of obese and type 2 diabetic mice. Furthermore, the expression of LPS receptor/cofactor CD14 cells from the stromal vascular fraction of adipose depots can also be directly targeted by LPS to initiate precursor cell development and adiposity. Moreover, data from the literature also indicate an impact of gut microbiota on intestinal stem cells. Thus, this mini review presents the experimental evidence supporting a relationship between gut microbiota and stem cells as a new axis of metabolic homoeostasis control.

Keywords: Gut microbiota; Stem cells; Metabolic diseases; High-fat diet; Omics

1. Introduction: systemic impact of gut microbiota

The gastrointestinal tract of all animals, including humans, is inhabited by trillions of microorganisms (bacteria, archaea, fungi, viruses and protozoa), forming a complex ecosystem commonly referred to as gut microbiota. This heterogeneous population of microbes is dominated by commensal bacteria that receive nutriments from ingested food and, in turn, provide the host with molecules, such as vitamins, that the body has not evolved to synthesize. Recent advances in high-throughput molecular sequencing [1] have allowed avoiding the need for laboratory cultivation to identify bacterial species. These improvements have led to the identification of two major bacterial divisions, the *Firmicutes* and the *Bacteroidetes* which constitute up to 90% of the gut microbiota. Interestingly, a disproportion favouring *Firmicutes* has been identified as the "bacterial signature" of obesity in both humans [2] and mice [3]. In contrast, the absence of obesity is characterized by Bacteroidetes dominance in both patients [4] and mice [5] with type 2 diabetes (T2D).

The intestinal microbiota, by acting as an organ, modulate many functions of host metabolism [6], yet, the molecular factors in this regulation are still not fully identified. On the basis of a germ-free (axenic) murine model, however, some light has been shed on the mechanisms by which intestinal microbiota modulate the host metabolic processes with regard, for instance, to diet-induced obesity [7], energy metabolism [8] and intestinal physiology [9]. Furthermore, it has been shown that modifying intestinal microbiota *via* dietary treatment [10] and antibiotics [11,12] can lead to improved metabolic features, such as greater glucose tolerance and insulin sensitivity, less body weight gain

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and therefore less associated chronic low-grade inflammation. The latter in particular represents a specific feature of metabolic diseases characterized by the production of pro-inflammatory cytokines that initiate and sustain first localized and then systemic insulin resistance [13,14]. Metabolic alterations, such as obesity and gut microbiota-driven inflammation are potentially linked through a family of Toll-like receptors (TLRs) that plays a crucial role in innate immunity [15]. These membrane-bound receptors belong to the superfamily of pattern-recognition receptors (PRRs), and are distinguished by cytoplasmic PRRs, such as nucleotide-binding oligomerization domain (NOD1/2) receptors due to their cellular localization. PRRs specialize in the identification of microbe-associated molecular patterns (MAMPs), such as LPS and peptidoglycan [16].

The contribution of PRRs to gut microbiota stability and the consequent impact on glucose homoeostasis has been shown in mice lacking TLR5, the flagellin receptor [17], which present a gut dysbiosis [18]. Indeed, these mice displayed common features of the metabolic syndrome which could have been shifted into axenic mice *via* transfer of gut microbiota from TLR-5 deficient mice [18].

In addition, TLRs are highly expressed within macrophages and adipocytes, particularly TLR2 and TLR4. The latter represents, within the innate immune system, the main receptor for Gram-negative bacteria LPS, and its increased plasma levels determine the initiation of metabolic diseases [10]. In addition, TLR4-deficient mice have shown less HFD-induced obesity [19] and insulin resistance [20]. For this reason, it is now accepted that gut microbiota play a key role in inflammation-mediated metabolic diseases.

2. Gut microbiota and bone marrow-derived stem cells

One major consideration has been to identify those cells sensitive to bacterial factors and responsible for the onset of metabolic diseases. In this context, the role of TLR4 expression in bone marrow-derived stem cells (BMC) in the control of hepatic and adipose tissue insulin resistance has recently been shown in obese mice. Saberi et al. [21] demonstrated that HFD mice receiving BMC from TLR4-deficient mice became obese, with no fasting hyperinsulinaemia but with improved hepatic and adipose tissue metabolism. This clearly demonstrates that bacterial antigens can exert effects on haematopoietic (BM-derived) stem cells. Thus, bone marrow transplantation (BMT), beyond its usefulness in regenerative medicine [22], is now emerging as an important new tool in the treatment of metabolic disorders [23].

Following on from this, modulation of gut microbiota impacts on host metabolism. It has been shown that short (4-week) HFD treatment was able to increase intestinal Gram-negative-to-Gram-positive ratio by decreasing the latter bacterial count [10]. This was associated with increased plasma LPS levels, a condition referred to as "metabolic endotoxaemia", thereby, initiating insulin resistance and obesity. However, the amount of LPS and intestinal abundance of Gram-negative bacteria appears to be secondary to functionality of the gut barrier in inducing metabolic impairment. In fact, an increase in Gram-negative bacteria may also be associated with less endotoxaemia [24] and an improved phenotype [25]. In addition, the administration of Gram-negative *Akkermansia muciniphila* has recently proved beneficial against diet-induced obesity in mice [26]. The above-mentioned process was CD14-dependent, as mice lacking this gene resisted HFD-induced metabolic endotoxaemia [10]. CD14 is also involved in the modulation of inflammation-driven insulin resistance [27]. Furthermore, wild-type (WT) mice with BMC grafts from WT donor mice became insulin-resistant after HFD feeding. In contrast, WT mice with BMC grafts from CD14 knockout (KO) mice resisted such changes. Interestingly, glucose intolerance was not aggravated in CD14 KO mice with BMC grafts from HFD-fed WT mice compared to KO mice grafted with BMC from CD14 KO donor mice [27].

Modulation of host metabolism can be achieved *via* modification of gut microbiota using several strategies, such as prebiotics [28], probiotics and antibiotics [29] and, more recently, synbiotics [30] and cobiotics [31]. In addition, host metabolism can also be modulated by means of BMT, a technique often used in regenerative medicine [22,32–34]. Recently, it was reported that BMT from WT normoglycaemic mice into a T2D murine model (8-week-old db/db mice) induced normoglycaemia and loss of the obese phenotype. However, the authors emphasized that this result was strictly dependent on recipient age, as 24-week-old db/db mice displayed the same phenotype as non-transplanted db/db mice [23].

BMT has also been shown to improve hepatic and adipose tissue insulin resistance in obese mice. The authors elegantly showed that the haematopoietic cell-specific deletion of TLR4 ameliorated insulin resistance through a mechanism related to increased Akt activity and decreased JNK signaling both in liver and adipose tissue [21]. Indeed, the above-mentioned mouse models all feature a well-characterized gut microbiota dysbiosis. Thus, these data suggest a link between gut microbiota and the metabolic effects of BMT (Fig. 1).

Graft-versus-host disease (GVHD) represents a clear example that elucidates the relationship between gut microbes, BMT and metabolism. This frequent complication following allogeneic tissue transplantation can be associated with stem cell or BMC transplants, but can also be related to tissue grafts. Briefly, immune cells (white blood cells) within the implanted tissue may identify the recipient (host) as "non-self", causing the transplanted immune cells to attack the recipient's cells. Recently, Eriguchi et al. [35] showed that GVHD can induce gut microbiota dysbiosis by inhibiting Paneth cell production of α-defensins, antimicrobial molecules that play an important role in shaping gut microbial ecology [36]. The authors compared the gut microbial profiles of mice with GVHD vs control mice. The former were characterized by the expansion of otherwise rare bacteria, such as *Escherichia coli*, responsible for septicaemia. Indeed, oral administration of antibiotic polymyxin B arrested such overgrowth and improved GVHD.

Gut microbiota also play a crucial role in GVHD following allogeneic BMT (A-BMT) [37]. Incompatible BMC can induce death in lethally irradiated conventional mice that develop GVHD subsequent to BMT. However, such mortality was not observed in axenic mice or in mice that had undergone a strong

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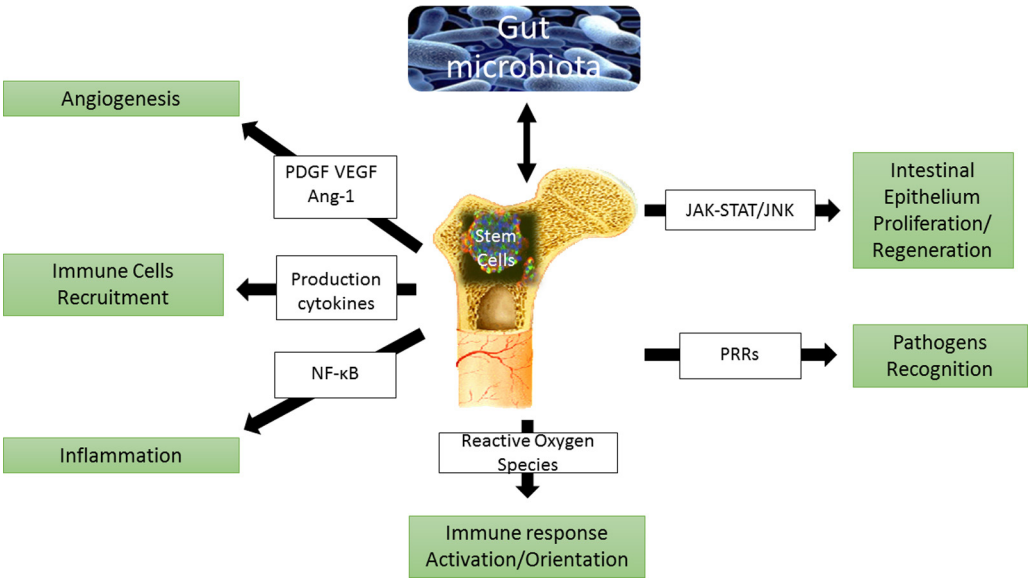

Fig. 1. Intestinal microbiota may regulate the systemic impact of stem cells. Stem cells are implicated in numerous fundamental host functions, such as angiogenesis regulation, immune cell recruitment, immune response regulation, pathogen recognition and tissue regeneration. Microbiota could communicate with stem cells and modify their pleiotropic functions [21]. In particular, lipopolysaccharides from Gram-negative bacteria may induce reactive oxygen species (ROS) production *via* tumor necrosis factor (TNF)-α. ROS, in turn, can modulate innate immune responses [51]. Thus, the interplay between microbiota and stem cells may represent a new regulatory axis for host homoeostasis. PDGF: platelet-derived growth factor; VEGF: vascular endothelial growth factor; Ang-1: angiopoietin 1; NF-κB: nuclear factor kappaB; PRRs: pattern-recognition receptors.

antibiotic treatment, suggesting that gut microbiota from A-BMT recipients can strongly influence GVHD.

As inflammation commonly develops with A-BMT, this may be the link between GVHD and metabolic diseases. Such inflammation is primarily due to T lymphocytes from the donor that may be activated by bacterial antigens in the recipient, but may also be cross-reactive with the recipient's epithelial tissue antigens [37]. GVHD-associated inflammation can, in turn, induce gut microbiota dysbiosis, which can also modulate gut inflammation severity. Jenq et al. [38] have shown that, in mice, GVHD reduced the overall diversity of gut microbes, increasing *Lactobacillales* and decreasing *Clostridiales* bacterial species. In particular, a lack of *Lactobacillales* species before BMT aggravated GVHD, whereas reintroducing the predominant species of *Lactobacillus* protected against GVHD. This pathology was also found to cause gut microbiota modification in patients to the same extent as observed in mice. Altogether, to the light of these reported results, it may be speculated that GVHD-associated gut microbiota dysbiosis could lead to metabolic diseases *via* the promotion of inflammation, thus, bringing forward a new target for improving clinical outcomes following A-BMT and its metabolic effects.

In addition, the impact of T2D on haematopoietic stem cells has clearly been shown by Ferraro et al. [39], who reported that CD34+ stem cells are trapped in the bone marrow of diabetic patients, thereby, limiting their migration into the systemic circulation after granulocyte colony-stimulating factor (GCSF) administration. Using both type 1 diabetes (streptozotocin-induced) and T2D (leptin receptor KO) murine models, they found reduced numbers of stem cells in the peripheral blood after GCSF injection due to dysfunction of the bone marrow microenvironment [39]. Given the known modifications of gut microbiota with T2D [4], this result ultimately supports a link between dysbiosis-induced metabolic alterations and weakening of BMC function.

3. Gut microbiota and intestinal stem cells: a putative mechanism for glycaemic control?

That gut physiology is strongly affected by gut microbiota composition can be considered logical because of anatomical contiguity. Nevertheless, the relationship between the host and the trillions of microbes inhabiting the gastrointestinal tract of animals goes beyond simple anatomical positioning. In fact, gut microbiota modification *via* prebiotics has proved capable of modifying the differentiation of precursor cells into enteroendocrine cells in the proximal colon of rats [40]. This demonstrates that gut microbes can affect gut epithelial cell turnover. Indeed, gut epithelium renewal is controlled by the proliferation activity of epithelial intestinal stem cells lying at the base of the so-called crypts [41], epithelial invaginations around the intestinal villi.

Recently, the group led by P.J. Sansonetti discovered the presence of strictly aerobic bacteria in the caecal and colonic crypts of mice by combining multiple techniques, such as laser capture microdissection (LCM), DNA amplification targeting the V5–V6 hypervariable regions of the 16S rRNA bacterial gene, and 454 sequencing [1]. They also validated, by fluorescence in situ hybridization (FISH), the most representative genera found, using genus-specific probes. The so-called "crypt-specific core microbiota" (CSCM) were dominated by *Acinetobacter* species, strictly aerobic Gram-negative bacteria belonging to the *Proteobacteria* phylum. Interestingly, *Acinetobacter* has also been identified in other animal models, such

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as the invertebrate fruit fly *Drosophila melanogaster* [42]. This discovery was not new in terms of concept, as crypt microbiota had already been found in patients with inflammatory bowel diseases and colitis, although the precise bacterial species remained unidentified [43]. However, the presence of bacteria in such close proximity to active tissues, such as intestinal epithelium can be interpreted as a mechanism that has evolved to exploit, *via* TLRs [44], signals from the microbiota to trigger regeneration of gut epithelium.

In line with the above findings, *D. melanogaster* has also recently emerged as another powerful animal model (other than mice) that can help to elucidate the relationship between gut microbiota and the host. Indeed, these flies harbour a simple bacterial ecosystem comprising up to 20 species, with three or four dominant ones [42]. Gut microbes are known promoters of maturation of the gut immune system and also favour the acquisition of a tighter intestinal barrier [45]. In particular, intestinal microbes can interfere with the functions of intestinal stem cells [46]. Buchon et al. [47] showed a reduction in the number of mitotic stem cells in the intestine of axenic flies. Conversely, colonization by an indigenous microflora was able to reverse this phenotype, showing that the gut microbiota can affect gut epithelium renewal capacity in these flies.

These results highlight the importance of a healthy gut microbiota for maintenance of gut physiology, such as the function of the barrier against external stimuli. Animal models characterized by gut microbiota dysbiosis also display a leaky gut with increased permeability [3,48]. This condition can, in turn, induce translocation of bacterial antigens, such as LPS, thus, initiating and sustaining chronic low-grade inflammation leading to metabolic disorders [10,13,14].

This suggests that the impact of gut microbes on intestinal stem cells may be a prelude to more complex changes at the level of the gut. The concomitant *in loco* inflammation can, in turn, be responsible for the impairment of insulin-signalling to a systemic extent, leading to altered glucose homeostasis.

4. Conclusion

The more our understanding of the complexity of gut microbiota develops, the deeper the link between host physiology and gut microbes appears. This inner relationship is not only related to and present in the intestine, but also extends to a systemic level. Indeed, modulation of gut microbiota has been shown to affect a wide range of host physiological functions [1,49,50]. In particular, intestinal microbes not only shape host metabolism *via* their targeting of metabolically active organs, but they also have an impact on stem cells. This capacity is extremely meaningful, as this specific compartment of cells is essential for crucial physiological functions, such as renewing adult tissues and maintaining the normal turnover of regenerative organs, such as blood circulation, skin and intestines.

In the light of the data reported here, it appears mandatory to pay more attention to the body's vast ecosystem of gut microbes and its adaptive measures in response to both physiological and pathological conditions. This will definitively push for a better understanding and managing of the molecular mechanisms adopted by our gut symbionts to share life with their human hosts.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.diabet.2013.12.004.

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