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The role of microbiota in tissue repair and regeneration

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Abstract

A comprehensive understanding of the human body endogenous microbiota is essential for acquiring an insight into the involvement of microbiota in tissue healing and regeneration process in order to enable development of biomaterials with a better integration with human body environment. Biomaterials used for the biomedical applications are normally germ-free while the human body as the host of the biomaterials is not germ-free. The complexity and role of the body microbiota in tissue healing/regeneration have been underestimated historically. Traditionally, the studies aiming at the development of novel biomaterials had focused on the effects of environment within the target tissue, neglecting the signals generated from the microbiota and their impact on tissue regeneration. The significance of the human body microbiota in relation to metabolism, immune system and consequently tissue regeneration has been recently realised and is a growing research field. This review summarises the recent findings on the role of microbiota and mechanisms involved in tissue healing and regeneration, in particular skin, liver, bone and nervous system

re-growth and regeneration highlighting the possible potential of microbiota for development of a new generation of biomaterials

Keywords: gut microbiota; tissue regeneration; microbiome; probiotics

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1 Introduction

The human body is a giant symbiont organism composed of *Homo sapiens* and microbial cells. The diverse population of microbes in the body comes from the outside environment (Ley et al., 2006) and the microbes in the human body have a genome size larger than that of human (Shanahan, 2002). Human gut hosts a diverse range of microorganisms which fundamentally include bacteria, fungi, archaea and protozoa. These communities are collectively known as gut microbiota (Nigro and Sansonetti, 2015). The human gut is the major host for microbes followed by oral and nasal cavities, skin and urogenital tract (Turnbaugh et al., 2007). The population of gut microbiota is similar to the somatic and germ cells in the human body, representing approximately 30 trillion microbes in the intestinal tract (Ley et al., 2006, Shanahan, 2002). The beginning of the symbiosis between humans and microbiota coincides with the very same moment we enter the external world passing through the birth canal (Palmer et al., 2007). In the first few days after the birth, the first microbial community is established in the infant gut which will shape the growth

of the human body playing a part in developing organs and overcoming through crucial steps of the growth.

The gut microbiota has various metabolic activities that collectively play the role of a hidden organ. Therefore, the gut microbiota has been called a forgotten organ by O'Hara and Shanahan (O'Hara and Shanahan, 2006). Despite this general belief, the gut microbiota is far from being dormant (Walker et al., 2011); it reacts rapidly to the environment as sudden changes in diet style may reshape its community members within 24 hours from food ingestions (Wu et al., 2011). A large population of diverse microbes lives in the intestine and a single layer of epithelial cells separates the microbes' community of the intestine from the internal milieu. The mucosal surfaces of the human body, rich in glycans, act as the point of interaction for gut microbiota. Therefore, the prevention of establishing aggressive microbes towards the mucosal glycans is the primary measure to avoid dysbiosis which might lead to colon cancer, inflammatory bowel disease (IBD), obesity and many other chronical disorders (Makki et al., 2018a).

Gut microbiota has a number of roles in health and disease prevention that encompass forming a defensive barrier layer in the tract, playing an active role in vitamins K, B and D synthesis, removal of toxic carcinogens and fermentation of the nondigestible residues in the intestinal tract (O'Hara and Shanahan, 2006). In particular, the microbes can enhance the bioavailability of nutrients, reduce the infection susceptibilities, have a positive effect on the immune response and provide, in general, a protection for tissue barrier functions (Arck et al., 2010). The immune system is conventionally known as the biological defense system which protects the host from disease and infections. However, the body microbial makeup can induce a varying immune responses that can lead to tissue regeneration (Pellegatta et al., 2016). The mechanism behind the metabolic pathways of the microbiota and their influence on immune response and homeostasis of the mucosal has not yet been fully discovered. Greater understanding of the mechanism of action of this microbiota "the hidden organ" can improve the human health and result in improved therapeutic strategies. Moreover, we can nowadays visualise the shaping and control of the microbiota (Earley et al., 2018) to bear the characteristics that are beneficial for a

specific individual, like selecting microbial population specific for tissue healing or regeneration after a surgery or to prevent a disease. One major factor influencing the composition of microbiota is the influx of dietary components specifically those named glycans (Koropatkin et al., 2012b). Most of the animal- and plant-derived glycans are not digested by human enzymes. Thus, their digestion depends on microbial gut which uses these glycans to establish stable communities (Makki et al., 2018b). The Hippocratic motto "Let the food be thy medicine and let the medicine be thy food" has never been so contemporary like before. The characterisation of human gut microbiota has become an emerging field (Turnbaugh et al., 2007). Recent interdisciplinary findings are in support of organ communications. There are evidences and information that indicate the functional relationship between the gut microbiota, brain and tissue growth. The abnormal changes in the balance of microbial community, such as infections, can negatively affect the axis of the gut and other tissues (Beraza and Trautwein, 2008, Bercik et al., 2009). For example, *Helicobacter pylori* infection in mice has shown alteration in the gastric emptying and its mechanosensitivity (Bercik et al., 2009). Therefore, gut microbiota has a wide

range of contribution to metabolites, hormones, immune and nervous systems. The details of these effects are gradually revealing (Shanahan, 1999, Romijn et al., 2008, Beraza and Trautwein, 2008, Dinan and Cryan, 2017).

Tissue engineering and biomaterial development are based on the use of germ-free models. In some cases, such as skin tissue, which harbour various bacteria, sterile biomaterials do not represent the environment of the human body. There are several good review articles which highlight the importance of gut bacteria in human health, however, this review aims to provide an overview of the role of the body endogenous microbes in promotion of tissue healing and regeneration for their possible applications in the field of biomaterials. Furthermore, it highlights recent studies on the establishment of beneficial microbes' community based on glycans and the relationship between the microbiome and healing and regeneration of various host tissues. We will also discuss the significance of immune system activation and physicochemical changes due to microbiota activities on tissue regeneration, healing and growth. This review lays emphasis on the importance of

gut microbiota–tissue regeneration interaction with both external tissues (e.g. skin) and internal organs (e.g. liver and skeletal system).

2 Local effects of endogenous or probiotic bacteria on the skin tissue healing and regeneration

Human skin is one of the major microbiota sites, with every square centimetre of it containing about one billion bacteria (Grice et al., 2008). *Actinobacteria*, *Proteobacteria*, *Firmicutes* and *Bacteroidetes* are the four main bacteria phyla found on the human skin (Grice, 2014). Characteristics of the host, age and the anatomical area affect the composition of microbiota (Grice, 2014) and each individual has a unique microbiota (Grice et al., 2008, The Human Microbiome Project, 2012, Costello et al., 2009, Grice et al., 2009). The bacteria residing on the skin produce substances that affect the growth and behaviour of the neighbouring microbes and are considered as the first line of defence against pathogens (Gallo and Nakatsuji, 2011). *Staphylococcus epidermidis* is the predominant bacteria on the human

epithelia while *Propionibacterium acnes* is mostly found in sebaceous follicles. The successful colonisation of bacterial is the result of a commensal or mutualistic lifestyle. The ability of some skin bacteria such as *S. epidermidis* to produce antimicrobials or the ability of *P. acnes* to produce short chain fatty acids can silence the pathogenic properties of *S. aureus (Christensen and Bruggemann, 2014)*. For more comprehensive account on the mechanisms involved in the effects of bacteria and wound healing, the reader is referred to a recent review paper (Johnson et al., 2018).

The skin microbes modulate the release of innate factors such as interleukin 1α and antimicrobial peptides (AMPs), which are synthesised by sebocytes and keratinocytes (Chen et al., 2018). It should be noted that skin bacteria could act in synergy or antagonistically to the immune system (Gallo and Nakatsuji, 2011) (Figure 1A). The skin microbiota-local immune system synergy affects the homeostasis of the complex epithelial barrier (Belizario and Napolitano, 2015). AMPs such as defensins, cathelicidin LL-37 and dermcidin are the most important intrinsic compounds involved in modulating the mechanisms of the antimicrobial defence of

the skin (Guani-Guerra et al., 2010), which can control the skin pathogenic bacteria such as *S. aureus*. Lower levels of various AMPs in skin lesions owing to atopic dermatitis compared to the normal skin have been reported (Ong et al., 2002, Nomura et al., 2003). It is shown that patients with atopic dermatitis have certain polymorphisms in Toll-like receptors (TLRs) or TLR signalling molecules. Another mechanism has been proposed for the beneficial impact of skin microbiota on the immune system by an effect on T cell response, controlling nuclear factor-κB signalling and the production of cytokines such as tumour necrosis factor (TNF)-α and interleukin-1β (Hooper et al., 2012). Abnormal production of cytokines and cutaneous T-cell has been reported in germ-free mice without commensal skin microbes (Naik et al., 2012). Skin sites with comparable physiological properties have similar microbial communities and the role of these bacterial communities on healthy skins has not yet been well understood (Grice et al., 2009). Understanding the role of the bacterial community on the skin health and its repair and regeneration may lead to the development of new biomaterials mimicking the real skin environment.

Skin grafts have been commonly used to treat damaged skin due to burns, injuries or infection (Unal et al., 2005). In this regard, collagen is a very common biomaterial for tissue engineering (MacNeil, 2008) which is obtained either in the form of donor skin from skin banks or isolated from animal resources such as bovine, porcine or fish skin. Safety of the skin grafts is an important factor that needs considerable attention and the collagen biopolymers of bovines may have pathogenic contamination risk, immunogenicity and batch-to-batch variation.

With this regard, bacterial infection is a major cause of skin grafts failure and microorganisms such as *Streptococcus pyogenes*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Enterobacteriaceae species* (spp) have been found to be the most common bacteria involved in the skin grafts failure (Unal et al., 2005).

However, tissue engineered skin grafts synthesised by the incorporation of certain bacteria or bacteria extract may diminish the infection related graft failure. Therefore, the selection and optimisation of the skin grafts should be performed by considering the microbial community of the target site. The above-mentioned studies indicate that it is important to combine our knowledge of wound healing, the role of bacteria in

the healing process and the immune responses with biomaterials in order to synthesise skin grafts that result in a fast healing without infection-related failure or fibrosis.

A reactive skin is sensitive to physical or chemical stimulants such as heat and cold and is marked by the skin devoid of ability to repair and heal itself (Gueniche et al., 2010). The topical application of the probiotic lysate was suggested to be beneficial for skin healing in human clinical studies. *Lactobacilli (Lb)* and *Bifidobacteria* are the most studied probiotics in relation to skin disorders (Baquerizo Nole et al., 2014). In an *in vitro* study of the mammal cells, the *Bifidobacterium longum* lysate suppressed the release of calcitonin gene-related peptide (CGRP) from neurons stimulated by a chili pepper active component (capsaicin) (Figure 1B) (Gueniche et al., 2010). Application of the topical cream containing the bacterial lysate decreased skin sensitivity and increased resistance of the skin against physicochemical aggregation (Gueniche et al., 2010). In addition, the topical application of the *Bifidobacterium longum* in an *ex vivo* human skin model demonstrated improvements in the inflammatory symptoms such as decreased

vasodilation, oedema, TNF-alpha release as well as mast cell degeneration (Gueniche et al., 2010). The bacterial extract, therefore, may be used for the development of therapies related to the sensitive skin (Gueniche et al., 2010).

Lactobacillus rhamnosu GG and *Bifidobacterium longum* are also found to have protective abilities toward keratinocytes through increasing tight junction function to provide tighter control over what substances can enter into cells, preserving specific function of cell surface as well as increasing the expression of proteins in the tight junction including claudin, Zonula occludens-1 and occludin (Sultana et al., 2013). In addition to the abovementioned probiotic strains, *Lb. reuteri* and *Lb. plantarum* have been reported to have a significant role in increasing tight junction function in human keratinocytes (Sultana et al., 2013).

Figure 1 is here

Chemical and physical stress can change the function of epidermal barrier or cause skin inflammation (Peters et al., 2004). In rat model system, stress caused the release of nerve growth factor and mast cell-dependent neurogenic inflammation in skin. The neurogenic inflammation caused by stress prevented hair growth by

suppressing the hair follicle growth and reducing the proliferation of hair follicle keratinocyte (Arck et al., 2003, McKay and Bienenstock, 1994). It has been reported that probiotic bacteria can suppress the skin inflammation and revive the hair growth in the stressed mice. These results are in agreement with those reported in studies on the anti-inflammatory properties of probiotics (Rautava et al., 2005, Moayyedi et al., 2010). The effect found in the rats was reported in another study where mice were treated with *Lactobacillus* and subjected to noise stress. The *Lactobacillus* treatment was remarkably effective in counteracting the negative effect of stress on the hair growth, hair follicle regression and skin inflammation (Karimi et al., 2009). The probiotics, therefore, seem to reduce the skin inflammation and inhibitory effect of the stress on hair growth. This hypothesis has been further supported by another study using the probiotic bacteria *Lactobacillus johnsonii* as an oral supplementation on skin recovery and homeostasis after ultraviolet (UV) exposure (Peguet-Navarro et al., 2008).

2.0 Microbiota, wound healing and tissue fibrosis

~~Furthermore, the microbiota can play an important role in wound healing process (Price et al., 2011). The community of host microbes is similar to the host cell number with a metagenome of 100 to 1 compared to the host genome (Peterson et al., 2008). The presence of microbes in the wound site can have a negative effect on the wound healing and regeneration process and the colonisation of microbes can lead to chronic wounds, inflammation and fibrosis (Grice and Segre, 2012, Meneghin and Hogaboam, 2007). Nevertheless, there is still no clear understanding of the relationship between the composition of the microbial population of the wound and the ultimate wound repair. The intrinsic microbe community of the wound may have a positive effect on wound healing and there are possibilities of adaptation of certain bacteria to improve the current wound healing treatment techniques.~~

Wound is a physical damage to the integrity of the epithelium and the host body undergoes several biochemical processes to repair this damage. Damage in the epithelium can hinder the natural activity of the microbes present in the site. The microbial activity interruption, reduces the expression of microbial peptide, mucus or lipid production decreases (Scales and Huffnagle, 2013). Skin microbiota has an essential role in the function of immune system and regulation of the inflammatory processes. By exposing the mucosal surface to the open environment, the contamination of the site with non-indigenous microbes is possible which can change the balance of natural host microbes population (Scales and Huffnagle, 2013). *Proteobacteria, Firmicutes, Actinobacteria* and *Bacteroidetes* are four major bacteria phyla in the human body with unidentical distribution in different body sites

(Figure 2A) (Scales and Huffnagle, 2013), with the major population of *Actinobacteria* and *Proteobacteria* is found on the skin (Grice and Segre, 2011).

At the wound site, the frequent presence of diverse bacterial population can lead to competition among the bacteria. Some bacteria, such as *P. aeruginosa,* are able to lyse other species, such as *Staphylococcus aureus,* by using their iron to survive and colonise (Mashburn et al., 2005). *Staphylococcus aureus* is a major cause of infection in surgical implants (Gan et al., 2002). Preventing the adhesion of *S. aureus* to the surface of the medical device can prevent the infection. Bearing in mind the antagonism between the bacteria, Gan et al fabricated a silicon implant inoculated with up to 10^{10} colony forming unit (CFU) of *Lactobacillus fermentum* RC-14 (Gan et al., 2002) to prevent the adhesion of S. aureus to the implant.. The *L. fermentum* and its secreted bio-surfactant completely prevented abscess formation by *S. aureus* and its adhesion to the surgical implants. The authors suggested that extracellular matrix-binding proteins (ECMBPs) of *L. fermentum* RC-14 could effectively compete with ECMBPs of *S. aureus* for binding to the host sites and therefore prevent *S. aureus* colonisation and growth on the implant (Figure 2B) (Chan et al., 1985, Gan et al., 2002). In this regard, the antimicrobial peptides produced by *Staphylococcus epidermidis* and *Staphylococcus hominis* were reported as highly potent and strain specific agents that selectively kill *S. aureus* (Nakatsuji et al., 2017).

Figure 2 is here

Improved proliferation of epidermal cells, vascularisation and re-epithelialisation were also reported in wounded dermal tissues of mice that were inoculated with *Pseudomonas aeruginosa* PAO1 (Kanno et al., 2011). Other *in vivo* studies focusing on topical application of probiotic bacteria have suggested reduced bacterial loads

and increased tissue repair in rodent wound models (Valdez et al., 2005, Huseini et al., 2012, Rodrigues et al., 2005). In a mouse model with burnt skin, topical application of *Lb. plantarum* prevented *P. aeruginosa* colonisation in wound by increasing phagocytosis (Rodrigues et al., 2005). Other studies have also reported that the topical application of Kefir, as a natural probiotic product containing *lactobacillus* and yeasts, with antibacterial and anti-inflammatory properties has beneficial healing impact on wounded rat models (Rodrigues et al., 2005, Rahimzadeh et al., 2014). The beneficial impact of other probiotic bacteria such as *Lb. plantarum* on wound healing properties has also been studied. *Lb. plantarum* could prevent pathogen colonisation in human burn wounds infected with *P. aeruginosa*, *S. aureus* and *S. epidermidis* (Peral et al., 2009). *Lb. plantarum* activates cytotoxic T cells and natural killer (NK) cells in order to secrete interferon gamma (IFNγ) by inducing IL-12 secretion (Hessle et al., 2000). Topical application of *Lb. plantarum* can reduce bacterial load and induce tissue formation. Also, it is reported to have promising wound healing properties for human chronic venous ulcers infected with *S. aureus* and *P. aeruginosa* (Peral et al., 2009).

Colonisation of bacteria has a negative effect on wound healing. In particular, microbial colonisation of diabetic wounds contributes to impaired wound healing. Prohibition of pathogenic bacteria or promotion of symbiotic bacteria could be considered as a low cost and non-invasive approach for the management of the wounds (Grice et al., 2010). Diabetic wounds, distinct population of bacteria and gene expression profile detected on the skin of diabetic mouse have contributed to our understanding of the interaction of microbiota and wound healing. The authors (Grice et al., 2010) in an *in vivo* study have revealed that wound microbiome and the skin correlate with the transcriptional signature of the cutaneous defence response.

In the design process of a skin graft, it is important to have a true understanding of the microbial population in the wound. However, having diverse types of bacteria on different body parts and different wounds can cause great complexity to the designing of skin grafts. Having said that, detailed bacteria identification could help determining the role of bacteria in the wound healing process (Price et al., 2011, Scales and Huffnagle, 2013).

3 The remote effect of the gut microbiota on tissue healing and regeneration

Apart from local benefits of microbes on the healing of wounded tissues, there are studies that support positive effects of gut microbiota on systematic inflammation (Souza et al., 2004, Noverr et al., 2004). These studies revealed that gut microbiota

can have remote benefits on the wound healing process. Arnold et al (Arnold et al., 2016) used a planarium (*Schmidtea mediterranea*) as a model organism in order to study the relationship between gut microbiota and tissue regeneration. *S. mediterranea* can regenerate and replace any of its either damaged or lost tissues. Studying the bacteria present in this planaria revealed the presence of *Bacteroidetes* and *Proteobacteria* as two main types of bacteria that are also found in the human body. The authors observed that the bloom of *Proteobacteria* suppressed the regeneration ability of the organism and resulted in tissue degeneration. The RNAi screening identified a TAK1 innate immune signaling module responsible for tissue degeneration and suppressed regeneration during infection. The TAK1 inflammatory signaling has been found relative to growth and expansion of the *Proteobacteria*. The authors concluded that in healthy worms, infection activated the innate immune response which resulted in cell death and degeneration. However, infection in an already injured worm can cause the innate immune system signals to cell growth and proliferation resulting in tissue regeneration. This complex inflammatory signaling has been preserved in multi-organ species including vertebrates. This research

provides opportunities for future discoveries in order to understand how alteration in microbiome can affect the immune system, consequently changing the organism ability for tissue regeneration. Cytokines such as IL-22 and IL-17 that are produced from Th17 cells contribute to the production of antimicrobial peptides, resulting in improved regeneration of epithelial cells, and increase production of mucus. In addition, IL-22 can control the microbes present in the lymphoid structures of mucus including Alcaligenes Genus. Therefore, microbiota contribute to tissue specific regulatory pathways resulting in the maintenance of the tissue homeostasis which is essential for the tissue health (Belkaid and Hand, 2014).

~~Diet shaping of gut microbiota~~

~~The beneficial effects of gut microbiota to a certain distant organ depend on the ability of a particular enterotype to establish a stable microbial community in different regions of the intestine.~~

~~Yet the role of dietary components is dominant for establishing and shaping the composition of a particular enterotype (Makki et al., 2018b), which, by definition, represents a signature combination of microbes evolved to function as a community and thrive together utilising a particular source of nutrients (Koropatkin et al., 2012a) . In the gut, there exist food chains which select the best microbial community~~

capable of digesting particular dietary components reflecting the dietary style of each individual (Leitch et al., 2007). The main components of the diet (fat, proteins, carbohydrates and fibers) require different enzymatic activities to digest. In some cases (i.e. glycans), these activities are missing in the human expressome and the dietary components should rely on microbial enzymes for their digestion (Salyers et al., 1977). To establish a successful symbiosis, the microbes pay back by providing specific molecules whose effects are beneficial for the human organisms, for example short chain fatty acids (SFCAs) such as butyrate and propionate (Rombeau and Kripke, 1990, Duncan et al., 2002). Correlations between different diet styles and gut microbiota have been already discovered and highlighted (Figure 3). A diet rich in fibers defined "prudent" contributes to preserving mucosal glycans and its overall secretion (De Filippo et al., 2010, Schnorr et al., 2014), enabling the fermentation of SCFAs, preventing chronical diseases and obesity besides regulating the appetite (Flint et al., 2012, Fukuda et al., 2011). Instead, a fat-rich diet filled with mono-sugars and proteins selects those microbes which erode the mucosa's glycans causing an array of diseases and disabling beneficial effects on

~~tissue healing and regeneration mainly due to the lack of beneficial SFCAs (Deehan and Walter, 2016).~~

~~*Figure 3 is here*~~

~~Therefore, glycans metabolism yielding beneficial enterotypes became a fervent field of study, finally aiming at designing diets rich in specific prebiotics food yielding SFCAs for treating diseases (Gao et al., 2009, Munjal et al., 2009).~~

3.1 Microbiota and skin

It has been proposed that a well-balanced gut microbiota results in a healthy aging (Arck et al., 2010). Nevertheless, the relationship between the characteristics of the gut microbiota and skin health has not been subjected to comprehensive analysis. The gut microbiota-skin relationship supports the possible link between gut, brain and skin. The origin of this concept dates back to 1980's when Teitelman et al reported that peptide-containing cells of the gut, brain and skin share an identical embryonic origin (Teitelman et al., 1981). Owing to the detection of shared signals and cellular protagonists between the gut, brain and skin, neurogenic inflammation in some gastrointestinal and skin diseases resulted in the gut-skin axis hypothesis (Arck et al., 2008, Kolls et al., 2008).

An altered community of gut microbes was found to be associated with skin diseases such as eczema (Kalliomaki and Isolauri, 2002). Further research is required to elucidate the mechanism and biochemical reactions responsible for the effect of gut microbes on the skin inflammation. Okada et al studied the healing process in germ-free and conventional wounds in mice and found that conventional wounds had higher tensile strength and higher hydroxyproline concentration as compared to germ-free control samples (Okada, 1994). The conventional mice also showed a better health condition, with a balanced nitrogen level in the wound as compared to germ-free mice. The authors suggested that gut microbiota has a positive effect on wound healing process by providing nutrients for the damaged tissue. Understanding the relationship between gut microbiome, tissue repair and immune system can have a diverse range of therapeutic applications; the possibility of developing natural or genetically driven microbe-based supplement to cure or prevent immune system-related diseases such as allergic reactions (Kalliomaki and Isolauri, 2002). However, in the particular case of tissue regeneration, this is still very far from real applications.

3.2 Microbiota and liver regeneration

The liver is an extraordinary organ that has the ability to regenerate itself and recover from injury. The liver regeneration is a complex process that involves gene expression, secretion of growth factors and tissue re-growth by the activity of hypocytes and mitogens. ~~It is remarkably important to comprehend the mechanism underlying the liver ability to heal, regenerate and restore its normal function that would help develop better treatment for liver disease and the organ transplantation. The roles of the growth factors, mitogens and cytokines have been, therefore, extensively studied and reviewed (Michalopoulos, 2014, Monga, 2014, Fausto, 1992).~~

Studies on the mechanism and process involved in the liver restoration have traditionally focused on pathways within the liver. However, an active metabolism is also essential for liver regeneration in order to supply energy for the process of synthesising the required precursors for the cell growth, proliferation and remodelling of the tissue. In this regard, nuclear receptors with important role and action in the metabolism have also been extensively investigated (Liu et al., 2013, Péan et al.,

2013). However, the possible link between liver restoration and the signaling pathways modulated by the gut microbiota has not received much attention. It is known that the gut microbiota is involved in the development of non-alcoholic and alcoholic liver diseases (Le Roy et al., 2013, Llopis et al., 2016) and there is growing evidence in literature supporting the role of gut microbiota and their metabolites on the regeneration of the liver tissue. Given the existence of signalling pathway between gut and liver, the metabolites synthesised by the microbiota have an immense effect on the liver function and regeneration (Le Roy et al., 2013, Llopis et al., 2016).

3.2.1 Bacterial endotoxin and liver regeneration

Gram-negative bacteria species such as *Neisseria* spp have certain glycolipids in their cell wall membrane known as endotoxin that refers to lipopolysaccharides (LPS). These lipopolysaccharides are composed of O-antigen, lipid A (hydrophobic component) and core oligosaccharide (hydrophilic component). O-antigen is located on the outer surface of the bacteria and is detected by the antibodies of the host. Lipid A activates the immune system of mammalian through TLR4 leading to

~~production of inflammatory mediators that may result in septic shock depending on the endotoxin activity and amount of LPS present (Aderem and Ulevitch, 2000).~~ LPS is usually administered to induce liver injury in "*in vivo*" studies, which implies that the bacteria can have a destructive impact on liver regeneration. However, a balanced presence of endotoxin was found useful for liver regeneration.

The LPS synthesised by gut microbiota has been found effective in inducing the hepatic DNA and hepatotropic factors synthesis (Cornell, 1985a). However, the use of antibiotic drugs such as cafezoline or neomycin in mice resulted in gut LPS elimination and therefore mice failed to synthesise hepatic DNA ~~In addition, mice failed to synthesise hepatic DNA when the gut LPS was eliminated through reduction of bacterial endotoxins and bile acids as a result of sterilisation of the gut using various antibiotic drugs such as cafezoline or neomycin~~ (Cornell, 1985b). Cornell and co-worker found that the germ-free animals were unable to release cytokines owing to the lack of gut derived endotoxin. They also suggested that the depression and delayed regeneration of liver in germ-free animal could be due to the lack of bacterial LPS (Cornell, 1985b).

~~In the treatment of periodontal disease, guided tissue regeneration (GTR) is considered as an important regenerative therapy for the treatment of periodontal disease. Nevertheless, this therapeutic intervention is vulnerable to bacterial contamination leading to low tissue regeneration (Mehrotra et al., 2017). Mehrotra and co-workers reported a beneficial effect of amoxicillin and metronidazole onto GTR membrane preventing the colonisation of bacteria such as *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis*. In another study (Cheng et al., 2015), the use of GTR membranes composed of PTFE, collagen and glycoside fiber, resulted in significant reduction in the adhesion of pathogenic bacteria and better performance of GTR membranes for treatment of periodontal disease.~~

The administration of hepatocyte growth factor (HGF) alone results in moderate levels of AP-1-DNA binding activity. However, after combining the LPS and HGF, a higher level of AP-1-DNA binding activity was observed, which was higher than that of LPS or HGF treated alone (Gao et al., 1999). The positive impact of the combination of LPS and HGF on hepatocyte proliferation demonstrated the positive role of gut microbiota in the process of liver regeneration (Liu et al., 2015). The

authors concluded that LPS potentiate the effect of HGF on hepatocyte replication by 4.5-fold more than that observed with HGF alone (Figure 3A).

Nevertheless, not all endotoxins are beneficial for liver restoration and specific bacteria have different effects on the liver regeneration. Increased hepatic inflammation and endotoxin levels lead to liver rejection and cause liver damage in mice subjected to orthotropic liver transplantation (Cornell, 1985b). While ampicillin exhibited a negative effect on liver regeneration by breaking hepatic innate immune tolerance, which is usually maintained by the gut microbiota (Wu et al., 2015), norfloxacin, as a fluoroquinolone antibiotics class, had a neutral effect toward the proliferation of hepatocyte cells (MacIntosh et al., 1992). Increasing the populations of *Bifidobacterium*, *Eubacterium,* *Lactobacillus* and Bacteroides together with decreasing *Enterobacteriaceae* populations were found to be beneficial for the prevention of liver injury in rats by reducing the level of portal LPS and decreasing the activation of Kupffer cells (Arai et al., 1998). Therefore, in order to protect a grafted liver from early failure, the authors suggested a selective decontamination of the gut, *targeting Enterobacteriaceae* (Arai et al., 1998). However, a long term use of

antibiotics could impair the balance of gut microbiota and negatively affect the liver function and regeneration (Wu et al., 2015) (Figure 3B). It is understood that a mild translocation of bacteria, consequent release of endotoxins, is necessary to induce liver regeneration as well as to protect the graft from early failure, but a complete bacterial imbalance has a negative influence on the liver regeneration (Wu et al., 2015, Liu et al., 2015).

Figure 3 is here

3.2.2 The interaction between gut microbiota, bile acids and liver regeneration

Bile acids (BAs) have an important role in liver regeneration by regulating metabolic processes and mediating the intestinal nutrient absorption. The hydrophobic properties of BAs facilitate the lipid absorption by acting similar to a detergent. However, the hydrophobic characteristics can also be harmful for the cell membranes. Therefore, the optimum concentration of the bile acids positively influences the liver regeneration while the imbalance in BAs and their overload can have toxic effects for the liver regeneration (Jessica et al., 2014, Liu et al., 2015). Hepatic and microbial enzymes were found to affect the synthesis of different BAs.

The bacterial enzymes can change the properties of BAs such as their aqueous solubility and activity. In human, primary BAs such as cholic acid (CA) and chenodeoxycholic acid (CDCA) can be subjected to oxidation, deconjugation and dihydroxylation as a result of bacterial metabolism leading to numerous secondary BAs (Gérard, 2014, Chiang, 2002). Therefore, the composition and properties of BAs in germ free animals are very different as compared to the conventional models (Swann et al., 2011).

A number of studies have indicated significant role for gut microbiota in modulating, composition and concentration of BAs, which eventually affects the liver regeneration (Kakiyama et al., 2014, Kakiyama et al., 2013). For example, a positive significant relationship was observed between the primary BAs levels and *Enterobacteriaceae* and *Ruminococcaceae* growth in cirrhotic patients (Kakiyama et al., 2013). In addition, BAs can also affect the microbial population in the gut and change the composition and population of the bacteria (Islam et al., 2011, Inagaki et al., 2006). Overall, there is an interaction between BAs composition and gut microbial population, which can affect liver regeneration.

3.3 Microbiota, bone metabolism and growth

Bone is constantly under remodelling process during the entire life due to the coordination of osteoclasts and osteoblasts. Osteoclasts are responsible for bone resorption while new bone formation occurs by osteoblast actions.

3.3.1 Probiotics and bone health

Probiotics and in particular lactic acid bacteria such as *Lactococcus* and *Lactobacillus* are reported beneficial in reducing bone loss in different bone disease models (Kimoto-Nira et al., 2007, Narva et al., 2004a). In mice models, the oral administration of *Lactococcus lactis* supressed age-related bone loss by modulating the immune response (Kimoto-Nira et al., 2007). Higher bone mineral density and content were observed for rats fed with fermented milk containing *L. helveticus* as compared to the control animals. In human trial, the consumption of the *L. helveticus* fermented milk increased the serum calcium levels in postmenopausal women and supressed the level of parathyroid hormone (PTH) (Narva et al., 2004a, Narva et al., 2004b, Narva et al., 2007). The possible long-term effect of probiotic supplementation such as *L. helveticus* will help better understand the potential

~~beneficial effects of probiotics in relation to bone health. In a number of studies, the probiotic *Lactobacillus reuteri* 6475 was reported beneficial for bone health. *Lactobacillus reuteri* 6475 was found effective in increasing bone density and supressing intestinal inflammation in healthy male mice (McCabe et al., 2013) (Figure 5A; a, b), has improved bone health in ovariectomized mouse (Britton et al., 2014) and increased bone density in female mice with induced mild inflammation by surgery (Collins et al., 2016) (Figure 5A; c). The studies revealed that *L. reuteri* treatment improved bone growth by immunomodulation of osteoclastogenesis pathways and oestrogen signalling (Britton et al., 2014, Jones et al., 2011).~~

~~3.3.2 Microbiota regulates bone metabolism~~

Bone is constantly under remodelling process during the entire life due to the coordination of osteoclasts and osteoblasts. Osteoclasts are responsible for bone resorption while new bone formation occurs by osteoblast actions. Bone and gut microbiota communicate through a complex gut-bone axis. It has been traditionally known that bone is linked with gut due to its requirement of calcium absorption and mineralisation. A diverse range of mechanisms such as nerve,

immune system and hormonal control are involved in the gut-bone axis. Increased activity of osteoclast is the main cause of bone resorption that is normally mediated by inducing the activity of the immune system. In this regard, signals from gut bacteria have been shown to be responsible for activation of T cells in the bone (Karieb and Fox, 2013). This section discusses the interactions between the gut and bone and addresses the impact of gut microbiota on the bone health and growth.

3.3.1 Microbiota and endocrine system

Hormones play an important role in the bone metabolism. Gut microbiota can interact with the endocrine system and eventually secret hormones or hormone-like products that have impact on host health, such as bone health and growth (Neuman et al., 2015). Gut microbial colonisation in the germ free mice led to a significant increase in the serum IGF-1, which consequently resulted in an improved bone growth and mass. It has been suggested that production of short chain fatty acids (SCFA) may be the mechanism, by which microbiota increases the level of IGF-1.

The potential of altering microbiome or metabolites can open new opportunities to optimise bone growth (Yan et al., 2016).

3.3.2 Microbiota and calcium absorption

Dietary calcium can only be absorbed through intestine in the presence of vitamin D as an essential requirement for calcium homeostasis. Gut microbiota can influence the absorption of calcium and vitamin D as the essential components required for bone health. Deficiency of either calcium or vitamin D may result in osteoporosis (Morris et al., 2010). Depending on the level of 1, 25- dihydroxy vitamin D, calcium is absorbed by transcellular pathways of ion pumps or ion channels (Fleet and Schoch, 2010). The rate of calcium intake in human is around 30% of the calcium in foods for adults (Kuwabara and Tanaka, 2015), which can be increased by probiotic bacteria such as *Lactobacillus salivarius* that stimulate calcium uptake (Gilman and Cashman, 2006). Three major proteins are involved in the transcellular pathways to facilitate calcium absorption from the gut lumen into cells; 1) transient receptor potential vanilloid type 6 (TRPV6/CaT1/ECaC2), 2) intracellular calcium transportation that functions with calbindin- D9k and 3) plasma membrane calcium

ATPase 1b (PMCA1b) which is responsible for excreting calcium outside cells into the blood (Hoenderop et al., 2005, Xu et al., 2017). Calcium paracellular diffusion occurs thanks to flux of calcium ions across intestinal epithelium which is governed by tight junction proteins located between the epithelial cells (Xu et al., 2017, Alexander et al., 2014). Probiotic bacteria can change calcium absorption and transportation by influencing the expression of tight junction proteins.

3.3.3 Microbiota and immune system

Osteoimmunology has been formed because of the close interaction between bone metabolism and immune system. Gut microbiota provides protection against pathogenic microbes and reduces the impact of immune system on symbiotic or beneficial bacteria in the gut (Whisner and Weaver, 2017).

Microbiota acts as a messenger between the bone and the immune system (Pacifici, 2008, Manolagas, 2010). The interaction between the gut microbiota, immune system, bone health and bone remodelling has been investigated previously in several studies (Sjogren et al., 2012, Cox et al., 2014, Cho et al., 2012a).

Sjogren and colleagues (Sjogren et al., 2012) used germ free mouse models in order to investigate the role of microbiota in bone health. Higher bone density was observed for the female germ free mice and the presence of gut microbiota was found correlated with higher precursor cells of osteoclast in bone surface and marrow. The authors suggested that bone resorption by osteoclast was induced by the impact of gut microbiota on immune system (Sjogren et al., 2012). It has been proposed that gut microbiota could be responsible for activating T cells via production of stimulating antigens (Weitzmann and Pacifici, 2007). The alteration of microbial composition was found to be correlated with the production of IFN-γ and IL-17 as the precursors of osteoblast and osteoclast cells (Adamopoulos et al., 2010, Duque et al., 2011).

In agreement with Sjogren and colleagues, administration of antibiotics such as penicillin, vancomycin and chlortetracyclin was found to increase the bone mineral density of the female mice. Nevertheless, the age and sex of the animals could affect the results and the antibiotic treatment was most effective at birth which leads to a

longer effect on improving bone density in the female rats (Cho et al., 2012b, Cox et al., 2014).

Conventional infant male mice had better trabecular and cortical bone density as compared to the germ free mice representative of the positive of gut microbiota (Schwarzer et al., 2016) as shown in Figure 4A. The authors found that microbiota interaction with somatotropic hormone axis drives systemic growth in mice models and concluded that the host's microbiota supports juvenile growth (Schwarzer et al., 2016). In a recent study, microbiotas from healthy and malnourished children were transplanted in order to separate groups of germ-free mice. Unlike microbiota from healthy children, microbiota from children with malnutrition resulted in impaired growth with altered bone morphology showing that not only the existence but also the composition of the gut microbiota can impact the bone morphology (Blanton et al., 2016) (Figure 4B). Antibiotics have also been found to be effective in improving bone mass. Cho et al (Cho et al., 2012b) observed an increase in the bone metabolism hormone when treated with subtherapeutic antibiotics. The authors suggested that antibiotics altered the gut microbiota population and consequently its

metabolic activity. Therefore, there is a possibility to control the metabolic homeostasis through various antibiotic treatments. In another study (Yan et al., 2016), gut microbiota promoted bone formation and metabolism. The authors suggested that the level of insulin-like growth factor (IGF-1) increased by increasing the colonisation of microbes. Therefore, bone growth inducing effect of gut microbiota can be attributed to the microbes that affect IGF-1. Consequently, it is concluded that microbes can be used to optimise the bone metabolism and improve bone growth and health.

In addition to altering and inducing immune system and hormonal level, the probiotic bacteria can also contribute to the bone health by improving the absorption and solubility of minerals by altering the barrier function (Ritchlin et al., 2003). In order to reveal the true impact of gut microbiota on the bone regeneration and health, several other parameters such as age, sex, genetic background, colonisation time and facilities used for the animal need to be explored (Figure 5). In addition, the composition of microbial population and the effect of disease on this population need to be investigated for facilitating the possibility of comparing the results in terms of

microbial composition. Taken together, there is a possibility to use probiotics, prebiotics and antibiotics to modulate the microbiota as a treatment for different bone diseases such as osteoporosis and hence to improve the bone health.

Figure 4 and 5 is here

3.4 **Gut microbiota and intestinal regeneration**

Inflammatory bowel diseases such as colitis (UC), infection and physical trauma can damage the intestinal mucosa (Hou et al., 2017). Despite the exact mechanism for gastrointestinal diseases might have not been clearly understood, the microbiota was found to play an important role in promoting gut healing and function of mucosal epithelial function (Hou et al., 2017, Thomas, 2016). Gut injuries are linked with changes in the microenvironment which can induce the proliferation and growth of bacterial species, which induce healing and regeneration of the tissue. Using a mouse endoscope wound model, Alam and co-workers (Alam et al., 2016) induced a lesion in the colonic mucosa and observed a significant increase in anaerobic bacteria, in particular Akkermansia species (SPP), during the early stage of regenerative mucosa. Akkermansia spp. was found to be promoting the proliferation of enterocytes adjacent to the colonic wounds. The results indicated how

endogenously ordered species could promote repair and regeneration of mucosal wounds. The microbiome has the potential to be explored as therapeutics for tissue regeneration and wound healing. It was found that the induction of wound changed the bacterial composition on the site. The concentration of oxygen in the injured mucosa was lower than baseline after two days of the injury which was associated with the neutrophils that reduced the oxygen level while the site was populated with the anaerobic Akkermansia spp.(Alam et al., 2016, Thomas, 2016). The gut microbiota can also protect the gut mucosa by preventing the adherence of pathogens (Kellow et al., 2006). Therefore, the dysbiosis of microbiota may result in the adhesion of the harmful pathogens leading to the irritable bowel syndrome (IBS) (Guinane and Cotter, 2013). Recent studies demonstrated that the interplay between gut and the microbiota could induce modulation of stress response and induce the proliferation of stem cells and epithelial regeneration (Buchon et al., 2009). It has been demonstrated that gut microbiota can shape the intestinal mucosal T cells and consequently impact the intestinal homeostasis in order to promote healing and regeneration (Sommer and Bäckhed, 2013).

3.5 Gut microbiota and nervous system regeneration

Studies have shown a complex and bidirectional interaction between the gastrointestinal tract and central nervous system (CNS), also known as gut-brain axis (Mayer, 2011). The gut microbiota was found to be modulating the development of the CNS and the pathogenesis of CNS-related diseases (Benakis et al., 2016, Winek et al., 2016). The gut microbiota-CNS communication is either direct through interaction with immune cells/nerve fibers or indirect via the secretion of metabolites which bypass the blood-brain barrier.

Evidence has revealed that gut microorganisms have an important role in synthesising substances such as serotonin, thus balancing the level of the amyloid beta (Aβ) proteins resulting in formation of the Aβ plaques. Reduced amount of Aβ plaques is associated with lower risk of neurodegenerative diseases such as Alzheimer's disease (Cirrito et al., 2011). In addition, some bacteria can also secrete amyloid, causing an imbalance between Aβ peptide production and clearance in the CNS, leading to a high risk of Alzheimer's disease (Cirrito et al., 2011, Zhao and Lukiw, 2015). *Escherichia coli, Salmonella enterica, Salmonella typhimurium,*

Bacillus subtilis, *Mycobacterium tuberculosis* and *Staphylococcus aureus* are examples of bacteria that produce bacterial amyloid (Sharon et al., 2016) which may lead to Aβ plaque formation and Alzheimer's disease (Sharon et al., 2016). In patients with Alzheimer's disease, gut microbiome is associated with changes in cerebrospinal fluid (CSF) such as $A\beta_{42}$, $A\beta_{40}$ and p-tau, involved in the pathogenesis of Alzheimer's disease (Vogt et al., 2017).

Schizophrenia is a neuropsychiatric disorder. Patients with schizophrenia are shown to be at higher risk of developing autoimmune disorders than the normal population (Strous and Shoenfeld, 2006). It has been shown that gut microbiota can lead to an immune response by producing more T helper (Th) 17 cells, a subset of pro-inflammatory T cells. A high proportion of Th17 cells exists in schizophrenia patients (Ding et al., 2014). Overall, the pathology of neurodegenerative diseases has been partly attributed to neuro inflammation (Cappellano et al., 2013, Glass et al., 2010). Microglia is the main form of active immune defence in the CNS, which has an important role in scavenging dead cells, killing pathogens as well as developing the brain, consequently prevention and promotion of neurodegenerative processes.

Experimental data show the significance of gut microbiota in the development and maturation of microglia (Mosher and Wyss-Coray, 2015). Unger and colleagues have reported that patients with Parkinson's disease have lower levels of short chain fatty acids, a product of microbial fermentation in faeces compared with controls, which can cause maturation of microglia and hence the maintenance of the microglia (Unger et al., 2016).

In addition, although evidence has shown that gene-environmental factors interactions have an essential role in developing neuropsychiatric disorders, recent studies have found that the gut microbiota plays a significant role in the synthesis of key metabolites that affect gene expression and myelination in the prefrontal cortex and consequently neuropsychiatric disorders (Gacias et al., 2016). The prefrontal cortex is a dynamic region in the brain, with its dysfunction associated with neuropsychiatric and neurodevelopmental disorders including schizophrenia and autism (Goto et al., 2010, Amaral et al., 2008). Gacias and colleagues (Gacias et al., 2016) found that the gut microbiota can modulate transcript levels in the medial prefrontal cortex and impact the region-specific myelination. Furthermore, Hoban et

al (Hoban et al., 2016) presented that the microbiome is necessary for the regulation of the myelin-related genes, which has implications for cortical myelination. The gut microbiota has therefore a potential therapeutic for disorders involving dynamic myelination in the prefrontal cortex.

Kigerl et al (Kigerl et al., 2016) examined the effect of gut dysbiosis on the recovery of neurological function after traumatic spinal cord injury in mice. They found that inducing gut dysbiosis in mice before spinal cord injury can worsen the neurological impairment and its pathology after the spinal cord injury. In contrast, treatment of mice with spinal cord injury using probiotics resulted in a protective immune response in the gut-associated lymphoid tissues (GALTs) and improved the locomotor recovery. This suggests a promising role of the gut microbiota in the recovery of neurological function and neuropathology after neurological injuries such as the spinal cord injury.

3.5.1 Microbiota and enteric nervous system (ENS)

ENS development starts during embryogenesis which is primarily a sterile environment and its development and maturation continue postnatal under the effect

of microbiota (Hooper et al., 2012). There are a number of mechanisms by which the microbiota can influence the development and organisation of the ENS. The pattern-recognition receptors (PRRs) can recognise specific microbiota members. Therefore, they have an important role in innate immunity and protection against pathogenic microorganisms (Chu and Mazmanian, 2013). The RRRs are proteins that are mainly expressed by the cells of innate immune system such as dendritic cells and epithelial cells. Intestinal epithelial cells and the innate immune system, as the first line of defence against bacteria, can produce factors in response to microbiota. Therefore, they are likely to affect the development and homeostasis of the ENS (Prescott et al., 2013). TLRs, as a subgroup of RRRs, play an important role in the relationship between gut microbiota and the host (Mazmanian et al., 2005, Rakoff-Nahoum et al., 2004). Previous studies have shown that TLRs such as TLR3, TLR4 and TLR7 are expressed by the enteric neurons and glia. It suggests that ENS lineage can directly respond to the stimulations derived from the microbiota (Barajon et al., 2009, Takeuchi and Akira, 2010). *In vitro* studies of germ-free/antibiotic, treated animals

have shown reduced motility and less neuronal nitric oxide synthase-positive ($nNOS^+$) in mice, which is partly mediated via TLR4 (Anitha et al., 2012).

Production of the glial cell line–derived neurotrophic factor (GDNF) is stimulated by pro-inflammatory cytokines (e.g. IL-1β and TNF-α) that is produced by the host in response to TLR activation by the bacteria (Takeuchi and Akira, 2010). It is suggested that development and maturation of the ENS rely on a complex interplay between immune regulators and neuroregulators (Figure 6).

Figure 6 is here

4 Conclusion

Gut microbiota is known as a hidden organ that has an active metabolism and the study on local and systematic role of microbes in tissue repair and regeneration is emerging. This review provides evidence indicating cross-talk between microbes and various body organs such as skin, bone and liver suggesting the role of microbes in tissue recovery and regeneration. Microbes affect the absorption of nutrients, control metabolites and inflammation. The metabolites derived from microbiota signal to

remote organs in the body connecting gut microbiota to the immune, hormone and metabolism of the host among others.

Therefore, the unnegotiable role of microbes in tissue regeneration needs to be given due consideration when a tissue implant or biomaterial materials are designed. Currently, there is a lack of information on the possible mechanistic interaction between alteration of microbiota and the host physiological responses. Another limitation for incorporation of microbes in tissue engineering biomaterials is the complex growth requirement of the microbes which makes their isolation difficult. We must fully understand the function of the intestine during health and disease.

In general, microbes such as *lactobacilli* have the ability to protect against some infection by triggering cell signaling effect, stimulation of the immune defense and competition for host extracellular matrix binding sites. However, the exact mechanisms of this protection are not completely understood.

Recent studies have discovered the significance of gut microbiota in regulating tissue health and regeneration. In this regard, more attention has been paid to how tissue health is regulated by gut microbiota. In tissues such as bone, the presence of

gut bacteria could result in better growth or bone loss and the impact of microbiota has been found to be dependent on context and the microbial composition. Having said that, it is essential to have better identification and characterisation of microbial composition and have a better understanding of the tissue regeneration that correlates with changes in the microbial community. It will be imperative to better utilise approaches such as nutrigenomic and metabolomics to achieve a better understanding of the impact of gut microbiota on different tissue function, regeneration and health.

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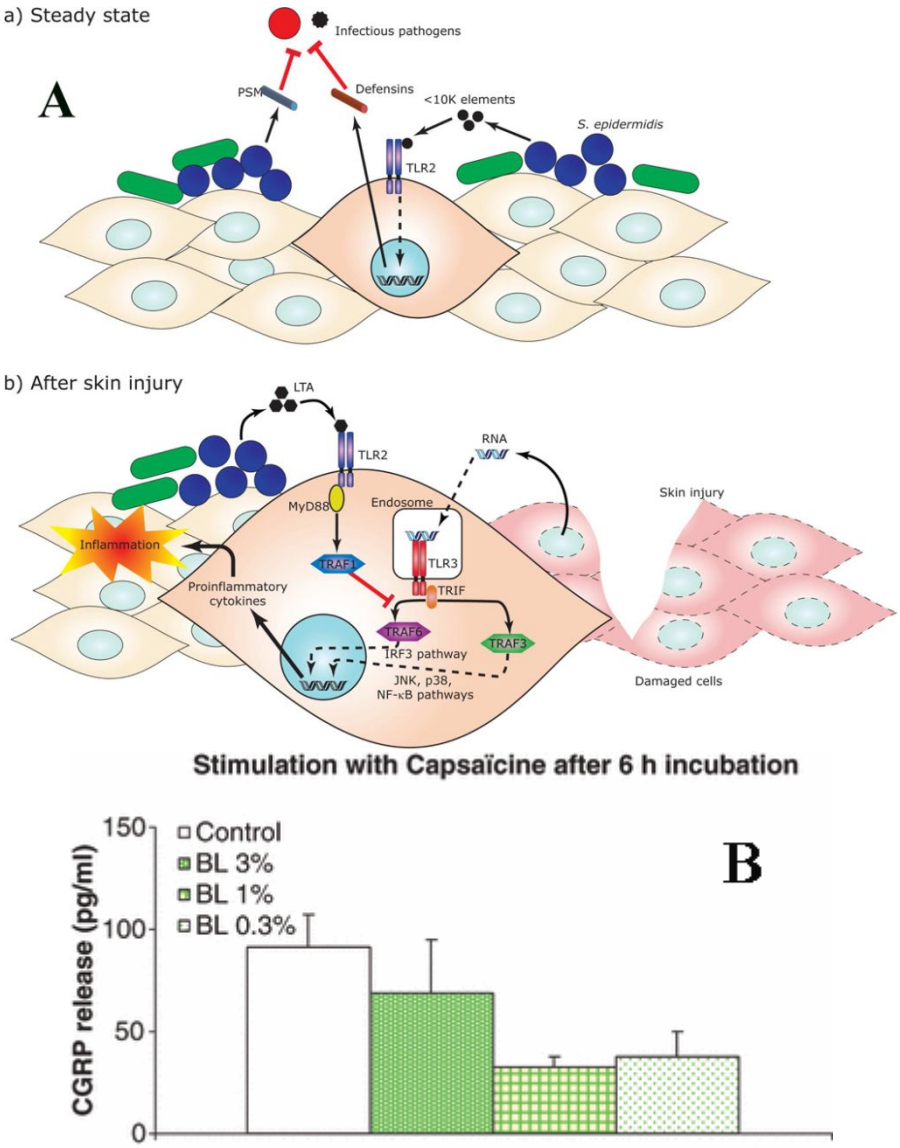

Figure 1. A. Molecular interactions of microbial symbiosis in skin innate immune systems. (a) In a steady state, *S. epidermidis* produces antimicrobial peptides (e.g. PSMδ and PSMγ) which act as a barrier against pathogenic microbes. *S. epidermidis,* in addition, releases molecules to enhance the expression of host defence peptides in the *skin* keratinocytes through TLR2 signalling. (b) After an injury to skin, TLR3 in keratinocytes are activated by the host RNA. The healing process can be delayed in case of uncontrolled inflammation. Excess release of inflammatory cytokine from keratinocytes is controlled by Staphylococcal LTA through a TLR2-dependent mechanism. IFR, IFN-regulatory factor; JNK, C-Jun kinase; MyD88, Myeloid differentiation primary response gene 88; NF-kB, nuclear factor kappa-B; TRAF, TNF receptor-associated factor; TRIF, TIR-domain-containing adapter-inducing interferon-β. Reproduced with permission from(Gallo and Nakatsuji, 2011) Copyright [2018][Elsevier]. **B.** Application of the topical cream containing *Bifidobacterium longum* lysate decreased skin sensitivity and increased skin resistance against physicochemical aggression. Effect of 6 hours pre-incubation with *Bifidobacterium longum* sp. extract (BL) on capsaicin-induced CGRP release by sensory neurones. Compared to control group which was treated with capsaicin alone, a significant decrease of 41% and 36% CGRP release was observed ($p < 0.01$) after treatment with 1% and 0.3% of BL compared with the control group ($p < 0.01$). Reproduced with permission from (Gueniche et al., 2010) Open Access.

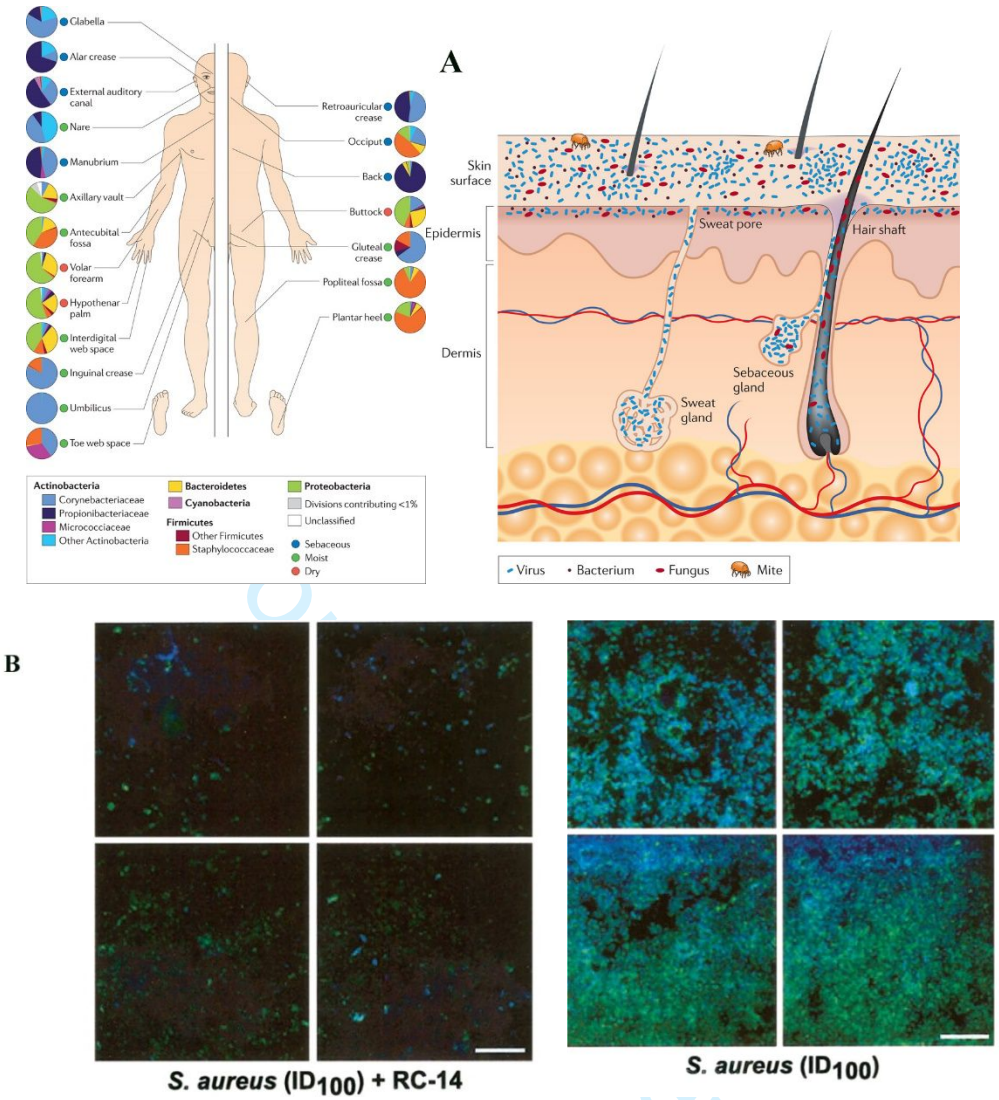

Figure 2. A. Various bacteria colonise at different sites of the body (a). The skin hosts a variety of microorganisms including fungi, bacteria and viruses that reside on both the surface and deep in the glands (b). Reproduced from (Grice and Segre, 2011) with permission from Nature Reviews Microbiology. **B.** Fluorescent microscopy images of implants inoculated with *Lactobacillus fermentum* RC-14. The *L fermentum* prevented the adhesion and growth of *S. aureus* on the silicon surgical implant. Reproduced from (Gan et al., 2002), Open Access.

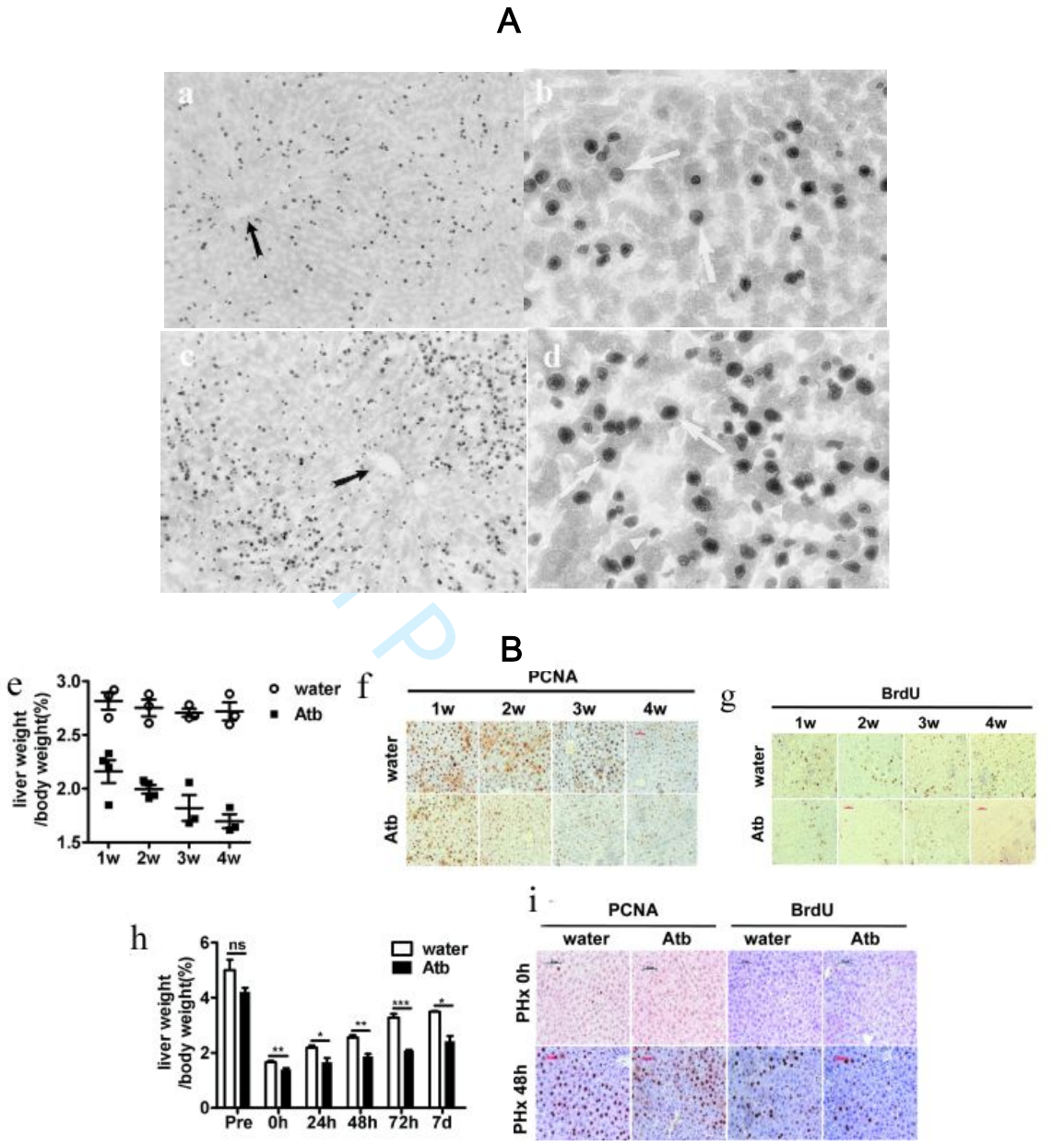

Figure 3.A. The positive role of gut microbiota in the process of liver regeneration (5-bromo-28-deoxyuridine (BrdU) labelling results).

Moderate numbers of replicating hepatocytes (*white arrows*) are present in rats that received high-dose (10 mg/kg) of hepatocyte growth factor HGF at 24 (a) to 33 (b) hours. However, large numbers of replicating hepatocytes are present in rats that received endotoxin lipopolysaccharides (LPS) at 5 mg/kg with high-dose HGF at 33(c) to 42(d) hours.

White arrow heads indicate labelled nonparenchymal cells and central vein is indicated by *black arrows*. Original magnification [a, c]×10 [b, d]×40.). Reproduced with permission from (Gao et al., 1999) Copyright [2018][Elsevier]

B. Long-term use of antibiotics (Atb) had a negative effect on the liver regeneration and liver regeneration is inhibited in mice treated with Atb-containing water.

Intestinal bacterial load determines liver regeneration. For 1, 2, 3 or 4 weeks before partial hepatectomy (PHx), mice received Atb in their drinking water. (e) The percentage of remaining liver weight to body weight 48 hours after PHx. (f, g) Impaired liver regeneration and a significant decrease in the number of

PCNA- and BrdU-positive hepatocytes closely correlated with diminished bacterial load over time in Atb-treated mice (original magnification 200×); (Wu et al., 2015)
For 4 weeks before PHx, mice received Atb in their drinking water. (h) The percentage of the remaining liver weight to body weight before and after PHx. (i) in Atb treated mice, a significant decrease in the number of PCNA- and BrdU-positive hepatocytes per field observed (original magnification 200×). Reproduced with permission from (Wu et al., 2015) Copyright [2018][Wiley].

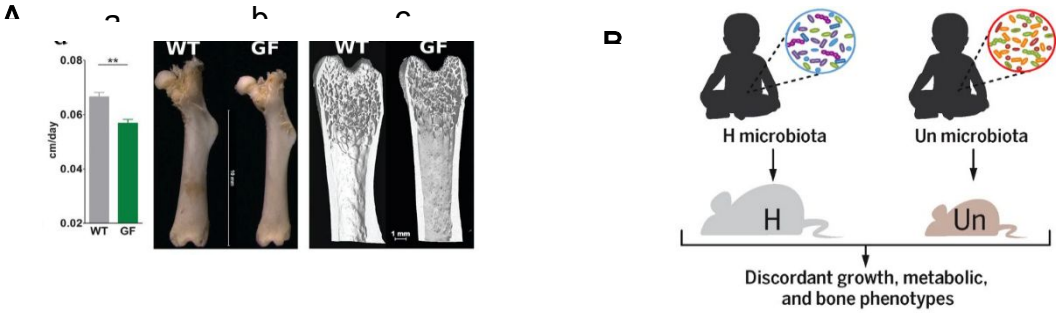

Figure 4.

A. The microbiota maintains mouse juvenile growth and body size (**a**) gains after weaning (day 21 to day 56) of WT (gray) (n = 16) and GF (green) (n = 12) infant male mice bred with their mothers from birth until day 21, weaned and then fed a breeding diet from 21 to 56 days old. (**b**) Photograph of representative femur bones at day 56. (**c**) Three-dimensional reconstructions of representative distal parts of femur bones at day 56. Error bars indicate SEM., **p < 0.01. Reproduced with permission from (Schwarzer et al., 2016) Copyright [2018][The American Association for the Advancement of Science].

B. Preclinical evidence that gut microbiota immaturity is causally related to childhood undernutrition. Fecal samples from healthy (H) or stunted and underweight (Un) infants and children were transplanted into separate groups of young germ-free mice that were fed a Malawian diet. The immature microbiota of Un donors transmitted impaired growth phenotypes to the mice. Reproduced with permission from (Blanton et al., 2016) Copyright [2018][The American Association for the Advancement of Science].

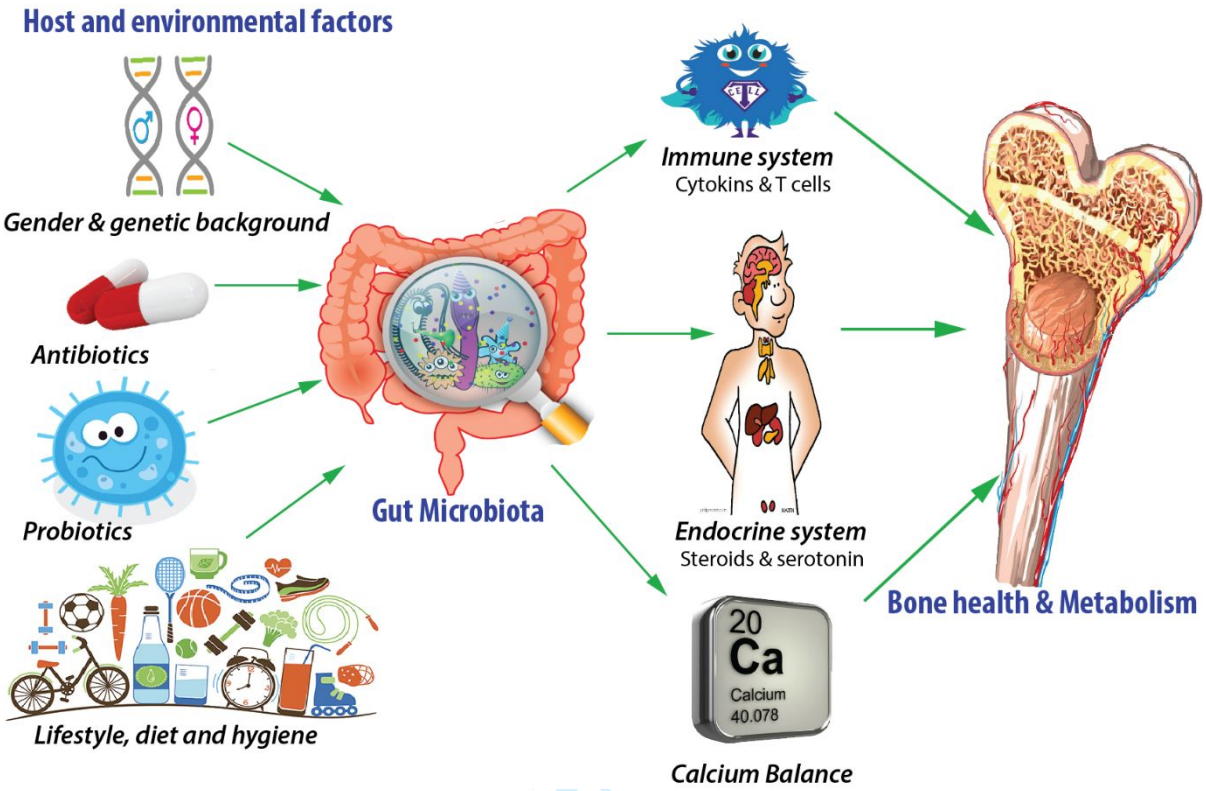

Figure 5. The gut microbiota and bone metabolism.

Gut microbiota regulates bone metabolism, regeneration and health through immune system, endocrine system and impacts on calcium absorption. Host and environmental factors such as probiotics, antibiotics, gender, genetics and lifestyle also influence the signalling of gut-bone axis and consequently alter the bone mineral density, bone strength and bone volume fraction.

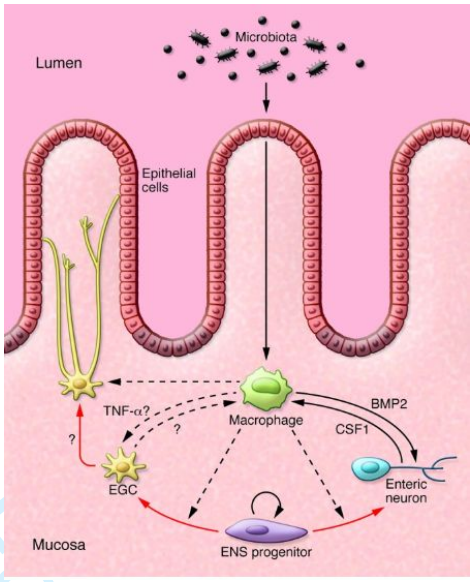

Figure 6. Potential interactions between microbiota, immune cells and enteric nervous system (ENS) lineages. Immune cells (macrophage) can influence the differentiation of ENS progenitors and the homeostasis of mature neurons and glial cells. In turn, enteric neurons and glia might also influence the responses of cells of the innate and adaptive immune system (Muller et al., 2014). Red arrows indicate lineage relationships. Solid black arrows indicate cell communication with known molecular mediators. Dotted black lines indicate putative interactions *in vivo*. Reproduced from (Kabouridis and Pachnis, 2015). Open Access