Innate Immunity of the Small Intestine

Subjects: Immunology

Contributor: Thifhelimbilu Luvhengo , Susan Mabasa , Edith Molepo , Itumeleng Taunyane , Sechaba Thabo Palweni

The small intestine has a huge surface area that is further enhanced by villi and microvilli to facilitate the digestion and absorption of nutrients. The expanded surface area of the small intestine increases the likelihood of exposure to pathogens in the lumen. The small intestine must balance the need for nutrient absorption with the ability to ward off pathogens. The majority of the immune cells in the body reside in the mucosa-associated tissues and the mesenchymal tissues of the gastrointestinal tract (GIT). The gut-associated lymphoid tissues (GALT) play a vital role in the development of the immunity of the entire body, as most of the antigens that get into the body are transported to the GIT for processing by its innate immunity before being delivered to the adaptive immunity.

dysbiosis Paneth cells immunity small intestine

1. Introduction

The small intestine has a huge surface area that is further enhanced by villi and microvilli to facilitate the digestion and absorption of nutrients. The expanded surface area of the small intestine increases the likelihood of exposure to pathogens in the lumen. The small intestine must balance the need for nutrient absorption with the ability to ward off pathogens [1]. The majority of the immune cells in the body reside in the mucosa-associated tissues and the mesenchymal tissues of the gastrointestinal tract (GIT) [2]. The gut-associated lymphoid tissues (GALT) play a vital role in the development of the immunity of the entire body, as most of the antigens that get into the body are transported to the GIT for processing by its innate immunity before being delivered to the adaptive immunity [2][3][4].

A healthy life depends on maintaining the small intestine's structural integrity and normal physiological function. Both the structural integrity and normal physiological function of the small intestine are dependent on the continuous generation of new IECs by the $Lgr5^+$ ISCs to replace senescent ones [5][6][7][8][9]. A combination of the surface epithelial cells and junctional proteins provides a continuous physical barrier that is augmented by mucins [10][11]. The microbiota of the gut is also critical for the development and sustenance of the innate immunity of the small intestine [12][13][14][15][16][17]. Bacteria compete among themselves to maintain a healthy balance, while some of the viruses in the lumen of the small intestines are bacteriophages and take part in the control of potentially pathogenic bacteria [11][18][19].

2. Intestinal Epithelial Cells and Innate Immunity

Almost all the IECs play a critical role in the innate immunity of the small intestine. Although all of them except the Paneth cells have a short lifespan of around 3–5 days, they are replaced quickly following their death. Regular replacement of the surface IECs ensures an intact physical barrier. Antimicrobial peptides and proteins that are secreted by the intestinal epithelial cells (IECs) are responsible for most of the chemical defence. Antimicrobial peptides are the most effective weapons against an overgrowth of pathogens and the subsequent bridge of the innate immunity of the small intestine [20][21][22][23].

2.1. The Role of Paneth Cells in the Innate Immunity of the Small Intestine

Paneth cells are among the derivatives of the $Lgr5^+$ ISCs in the small intestine and the small intestine's major source of antimicrobial peptides and proteins [7]. Paneth cells control the microbiota in the lumen of the small intestine and the proximal parts of the large bowel. The antimicrobial peptides from Paneth cells bathe and sterilise the area where the rapidly dividing and highly vulnerable $Lgr5^+$ ISCs are found [5][9][23].

Matured Paneth cells are found at the base of the intestinal crypt of Lieberkühn in the entire small intestine from the duodenum to the terminal ileum [24][25]. Paneth cells start appearing in the small and large intestines of embryos at the end of 12 weeks, and their number increases significantly in the small intestine after 36 weeks [23][26]. The adult colon contains few, if any, Paneth cells. Goblet cells and other cells, instead of Paneth cells, are responsible for the antimicrobial activities in the colon [26]. Metaplastic Paneth cells may appear in the colon and other sites in patients who have, for example, IBD [27]. The number of Paneth cells increases during childhood and a full complement for an individual is reached later in life [28]. Each intestinal crypt in an adult ultimately contains around 5–15 Paneth cells [29]. The number of Paneth cells per intestinal crypt is, however, variable, as their density increases downwards. The highest density of Paneth cells in a healthy state is found in the ileum [30].

The HD-5 is responsible for most of the antimicrobial activities in the small intestine [20][24][31][32]. The other antimicrobial peptides and proteins that are secreted by the Paneth cells include human α-defensin 6 (HD-6), lysozyme and phospholipase [31][33]. Although the other IECs such as the absorptive enterocytes, goblet cells and tuft cells survey and regulate the gut microbiota, Paneth cells are the most critical for innate immunity in the small intestine, as they secrete the largest amount of the most potent antimicrobial peptides and proteins [21][28]. In addition, the localisation of matured Paneth cells at the base of the intestinal crypts ensures the maximal concentration of antimicrobial peptides for the defence of the highly active but most vulnerable Lgr5 ISCs [28] (**Figure 1**).

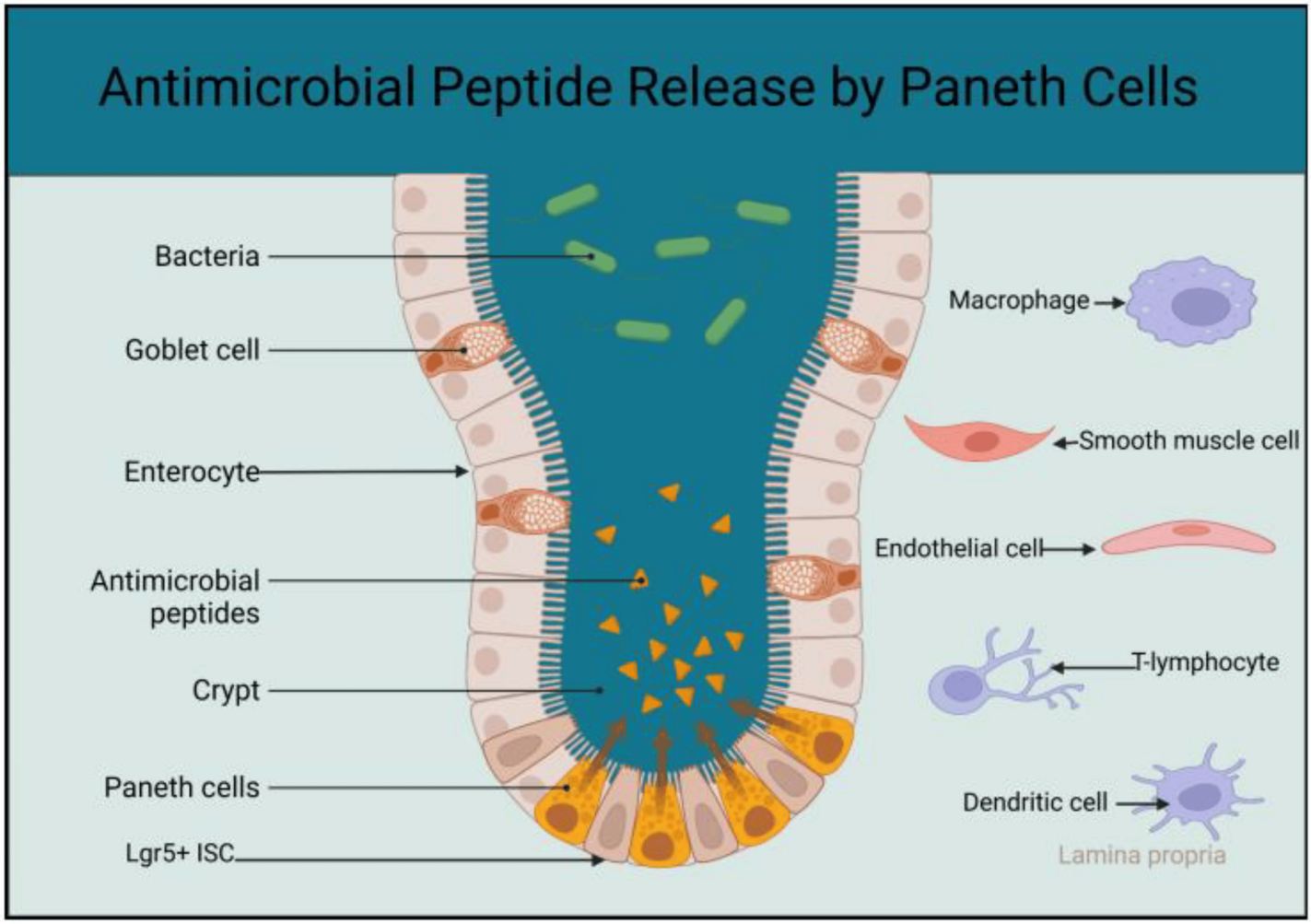

Figure 1. Schematic diagram showing the localisation of matured Paneth cells at the base of the intestinal crypt and higher concentration of antimicrobial peptides at the stem cell zone. The sketch also includes cells in the lamina propria that interact with the Paneth cells to support and regulate activities of the $Lgr5^+$ ISCs (created using BioRender.com accessed on the 25 April 2023).

Paneth cells are pyramidal in shape. They have a broader base where their nucleus is situated [33]. Paneth cells are among the secretory derivatives of the $Lgr5^+$ ISCs, and their cytoplasm contains several organelles, which include the endoplasmic reticulum and Golgi apparatus. The apical area of Paneth cells has eosinophilic granules that contain, among other constituents, HD-5, HD-6, lysosome, growth factors, Wnt signals and cytokines [24][33]. Paneth cells release their constituents after the detection of pathogens through their pathogen recognition receptor system. Paneth cells continually sample the microbiota in the lumen of the small intestine to prevent dysbiosis [33][34][35]. Paneth cells also secrete antimicrobial peptides and other products following a stimulus from the brain via the cholinergic system. The mere sight or smell of food may also lead to the activation of the Paneth cells. Additionally, Paneth cells sample the composition of nutrients in the food following ingestion [11] (**Figure 2**).

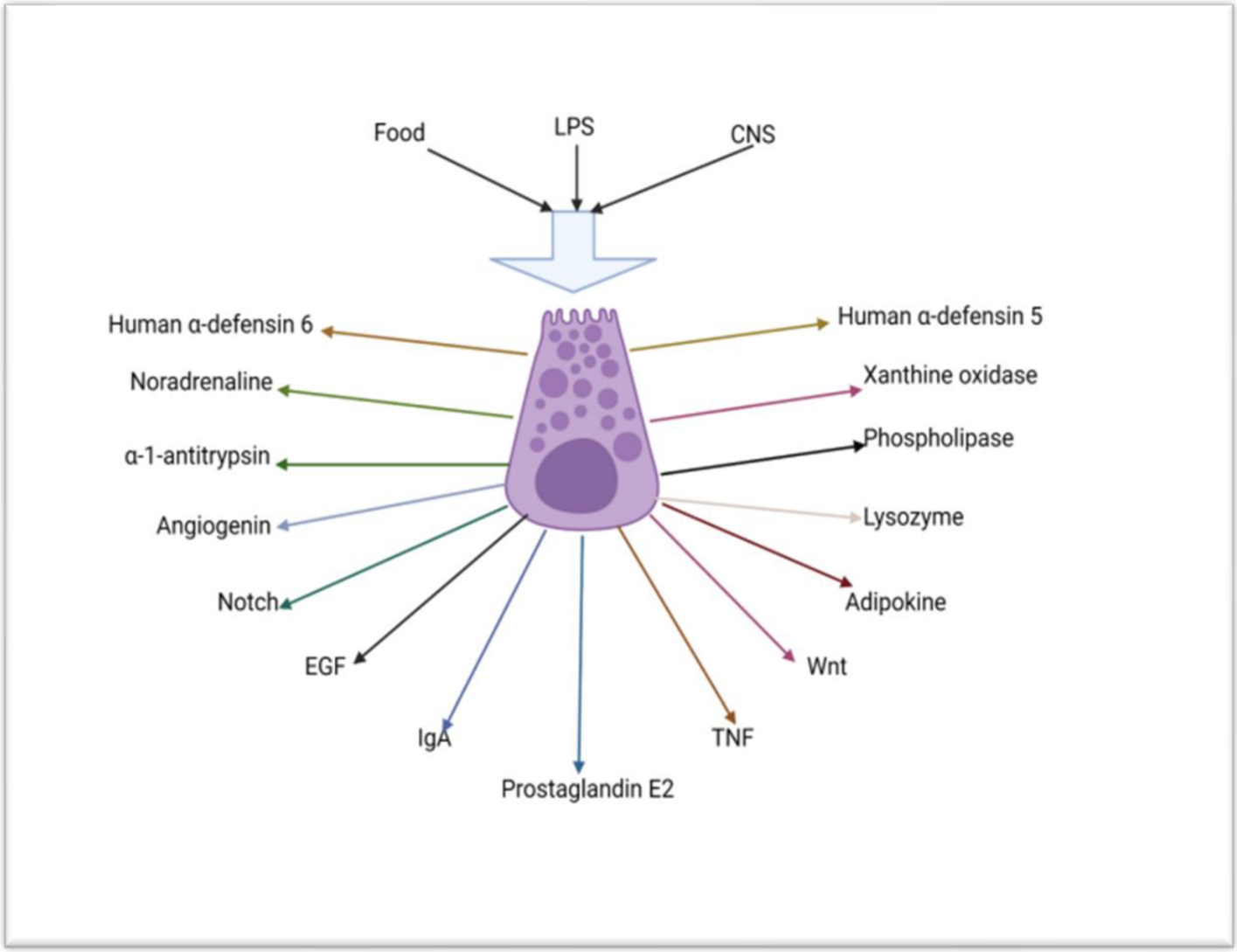

Figure 2. Schematic diagram depicting the mechanism of stimulation and some of the substances that are secreted by the Paneth cell (created using BioRender.com 9 of April 2023). LPS = lipopolysaccharide, CNS = central nervous system, Notch = neurogenic locus notch homolog protein 2, EGF = epidermal growth factor, IgA = IgA immunoglobulin, TNF = tumour necrosis factor, Wnt = wingless/integrated.

Some of the antimicrobial proteins and peptides secreted by the Paneth cells are stored as zymogens in the cytoplasmic granule and are activated just before release [33]. Once activated, HD-5 can kill all bacteria, fungi and parasites and some viruses [36]. Paradoxically, HD-5 can enhance proliferation of certain viruses [33][37]. Human defensin 5 is lipophilic and kills pathogenic bacteria by creating pores on the cell membrane, which increases the permeability, thus making the bacteria swell up and subsequently burst [37][38][39]. Human α-defensin 6 does not have anti-microbiocidal activity but is able to create nanonets around pathogens, thus trapping and containing them [35] (**Figure 3**).

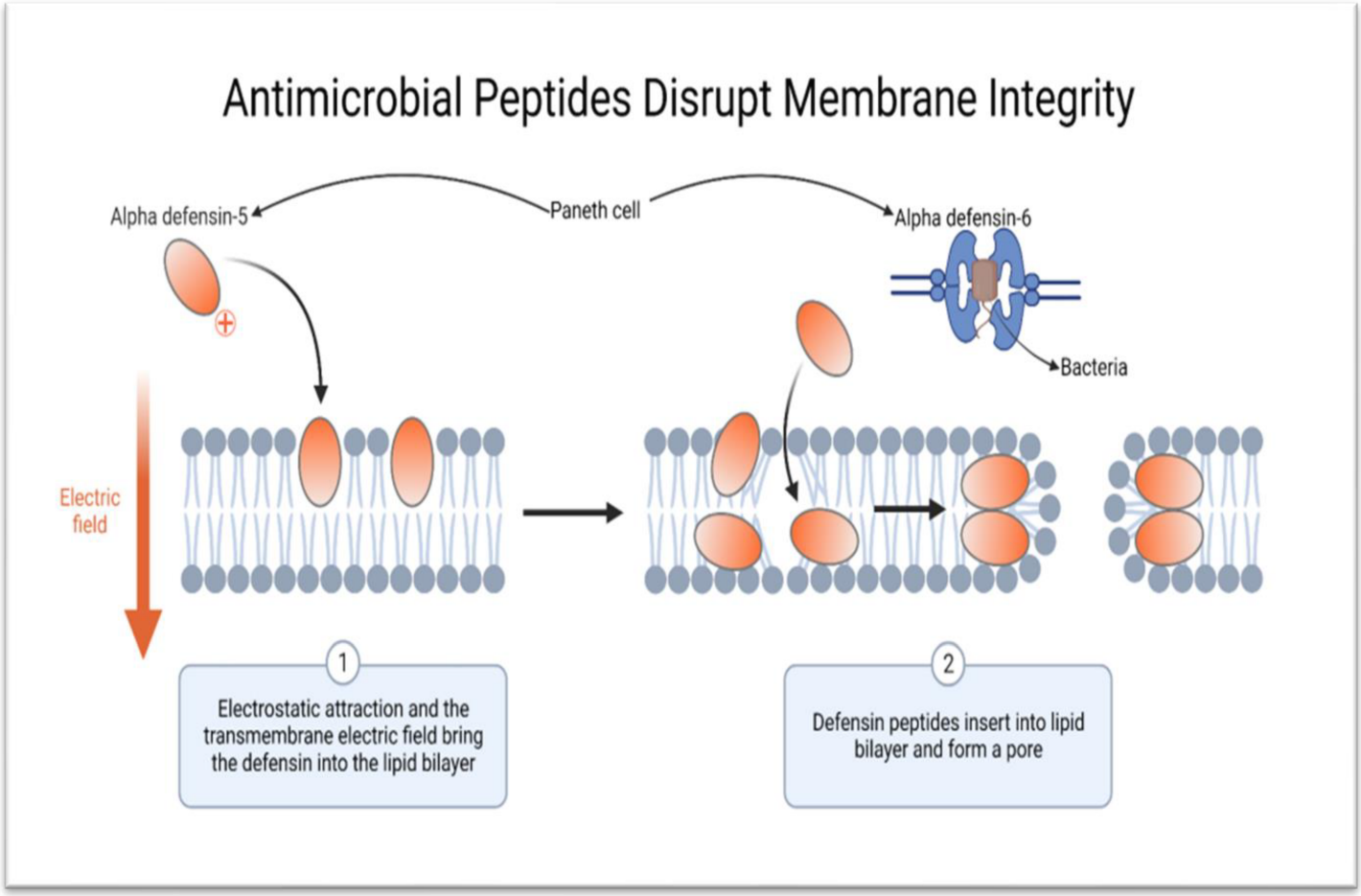

Figure 3. Schematic diagram showing the mechanism of action of HD-5 and HD-6. HD-5 kills bacteria and other microorganisms by creating pores on the cell membrane, while HD-6 forms nanonets to entrap pathogens (created using BioRender.com on 9 of February 2023).

Lysozyme and IgA, also secreted by the Paneth cells, add to the antimicrobial activities in the lumen of the small intestine [30]. The other functions of the Paneth cells that are critical for the maintenance of robust innate immunity in the small intestine include the regulation of proliferation and differentiation of the $Lgr5^+$ ISCs, metabolic support of the $Lgr5^+$ ISCs and liaison with cells involved in adaptive immunity [2][4][5][7][34][36][37][40]. Abnormality in the number or function of Paneth cells is seen in numerous diseases, including viral infections [30], necrotising enterocolitis [26], prolonged use of total parental nutrition [41], starvation [42], Crohn's disease [27][34][43][44][45][46], smoking [45] and ageing [47]. A change in the total number of Paneth cells or a deterioration in the quality of their function may also occur during chronic HIV infections [48].

2.2. Absorptive Enterocytes, Goblet Cells, Tuft Cells, M-Cells and Junctional and Innate Immunity of the Small Intestine

Goblet cells augment the antimicrobial defence by secreting mucous made up of mucins, water and trefoil factors. MUC2 is the major constituent of the mucus and helps to form a carpet of mucus that maintains a higher

concentration of antimicrobial peptides in the area adjacent to the surface of the IECs [24]. Secretory mucus is an essential nutrient for some commensal organisms. The absorptive enterocytes are the most abundant IECs [5].

Absorptive enterocytes have pathogen recognition receptors, which they use to sample the contents in the lumen of the small intestine and therefore participate in innate gut defence [49]. Like any other epithelial cell throughout the body, the absorptive enterocytes secrete β-defensin and not HD-5 or HD-6. Other IECs that participate in the regulation of the microbiota in the lumen of the small intestine are the tuft cells and the M-cells [1][50][51][52][53]. The tuft cells sample the gut microbiota like the Paneth cells but to a limited extent [53][54][55]. Secretions from the tuft cells are limited to cytokines [56]. Tuft cells have not been shown to secrete antimicrobial peptides, growth factors or catecholamines [56]. The junctional proteins also add to the innate immunity of the small intestine [10][11][18].

3. Gut Microbiota and Innate Immunity in the Small Intestine

The gut lumen contains numerous species of bacteria, viruses, fungi, parasites and archaea [57]. Around 10^{14} bacteria reside in the colon, but the small intestine contains fewer microorganisms [28]. Colonisation of the gut starts in utero and increases during childbirth [58][59]. Further changes in the gut microbiota composition occur during breastfeeding and weaning [58][59]. The normal gut flora of an individual is established during early childhood or adolescence. Once established, the gut microbiota is involved in the regulation of the physiological function and innate immunity of the small intestine [58][60]. The gut microbiota also influences the proliferation and differentiation of the $Lgr5^+$ ISCs and assists with the digestion of food [61]. Some of the commensals in the microbiota help process nutrients such as vitamins and short-chain fatty acids (SCFAs) like acetate and butyrate [61][62]. Complex dietary fibres would be difficult to digest and absorb without the assistance of commensal bacteria [61][62].

Certain species of bacteria help sustain the prevailing anti-inflammatory state to prevent damage to the intestinal epithelium, increased permeability, translocation of endotoxins and chronic systemic inflammation [63]. The other roles of the commensal organisms include preventing excessive production of ROS or RNS [3]. Furthermore, some of the commensal bacteria in the microbiota possess quorum sensors and secrete bacteriocins to kill the pathogenic species [17]. In addition, several species of bacteria can influence the cells involved in adaptive immunity in the lamina propria of the small intestine [3]. Several bacteria can modulate the hormonal milieu in the GIT and the entire body by participating in the microbiota-gut-brain axis. In return, commensal organisms depend on the nutrients in the diet, residue following digestion of nutrients and mucins secreted by goblet cells [64].

More than 80% of the bacteria in a healthy adult human belong to the Firmicutes and Bifidobacterium phyla [65]. Changing diet, use of antibiotics, chronic illness and excisional or bypass surgery in the GIT may lead to dysbiosis [66][67]. Dysbiosis may involve the entire length or certain niches along the GIT. Dysbiosis commonly leads to a reduction in the diversity of the microbial species and the dominance of pathogenic organisms like the Bacteroides [3][18][28][62][63]. Dysbiosis not only involves bacteria but may also include the virome [57]. Dysbiosis and the emergence of pathogenic species may lead to an increase in the production of ROS [68]. High levels of ROS in the lumen of the gut can damage the intestinal epithelium [68]. Concomitantly, pathogenic gram-negative or gram-

positive bacteria may initiate an inflammatory response by releasing pro-inflammatory lipopolysaccharides or peptidoglycan, respectively [63][69] (**Figure 4**).

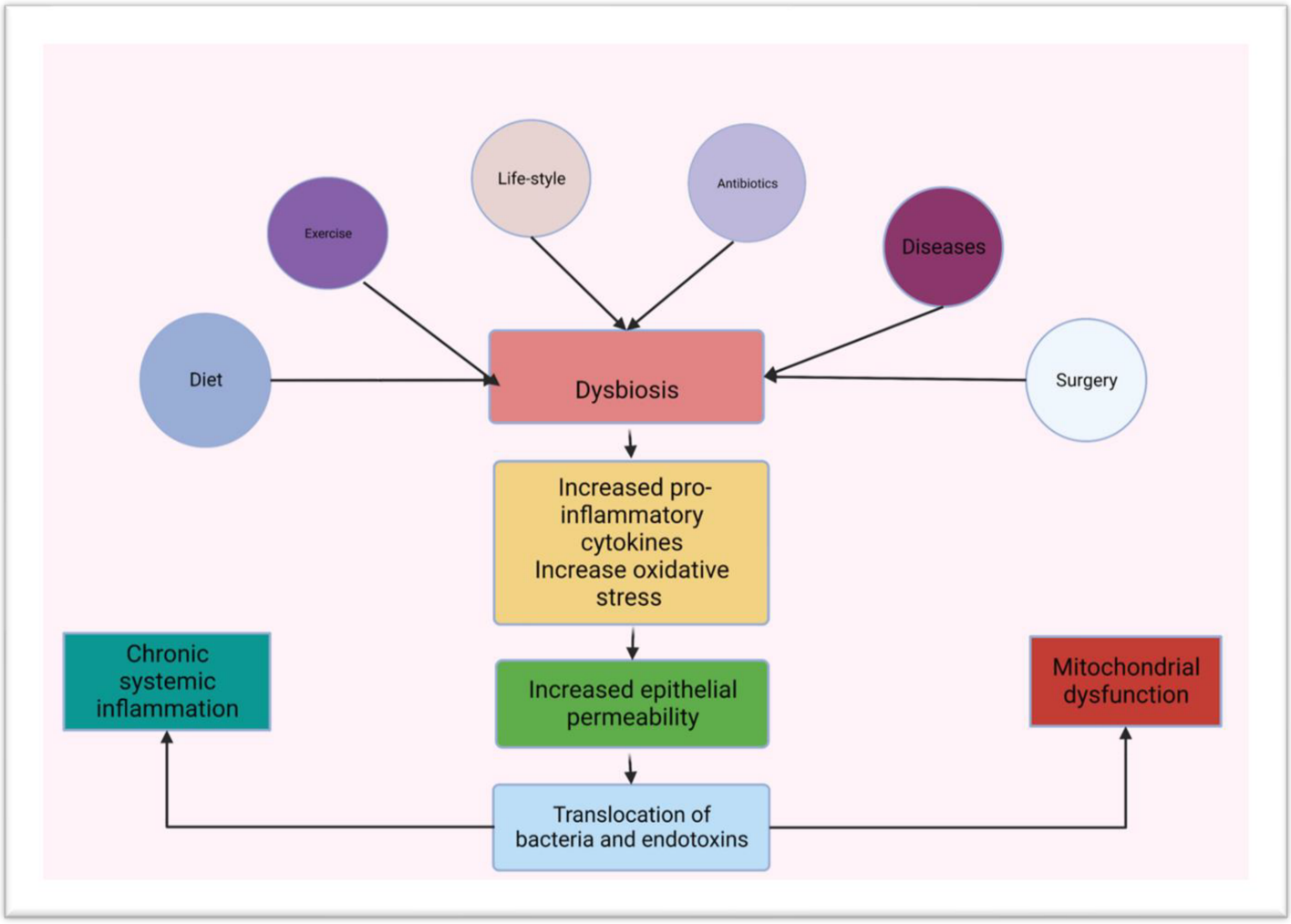

Figure 4. Schematic diagram showing predisposing factors for dysbiosis and a link between dysbiosis, chronic inflammation and mitochondrial dysfunction (created using BioRender.com on the 3 of March 2023).

Inflammation of the epithelium of the small intestine increases its permeability, leading to the translocation of bacteria and their products [70]. Ongoing translocation of bacteria and endotoxins causes endotoxaemia and chronic systemic inflammation [71]. Chronic systemic inflammation creates an environment that is obesogenic and diabetogenic [66]. Chronic systemic inflammation also increases the generation of ROSRNS from mitochondria in tissues and organs throughout the body [28][72]. Some cells in organs throughout the body such as the β-cells of the islets of Langerhans in the pancreas have a limited capacity to neutralise reactive species, which can perpetuate the damage to their mitochondria [3].

The high level of glucose in the blood and tissues creates a mismatch between the aerobic glycolysis and the oxygen-dependent tricarboxylic acid cycle, which increases the production of ROS and RNS [69][73][74]. Chronic inflammation also impairs mitophagy in the mitochondria and affects the ability of the mitochondria to recycle and preserve essential constituents through either fusion or fission [75]. Dysbiosis, increased ROS production,

increased gut permeability, translocation of bacteria and chronic systemic inflammation are the pathological basis of common non-communicable diseases like obesity [76], depression [77], cancer [76][78][79] and DM [68][80][81]. Over 90% of individuals who have DM are obese [58]. The adipokines from the adipose tissue in individuals who are obese sustain and worsen the inflammatory process [79][82].

References

1. Kobayashi, N.; Takahashi, D.; Takano, S.; Kimura, S.; Hase, K. The Roles of Peyer's Patches and Microfold Cells in the Gut Immune System: Relevence to Autoimmune Diseases. Front. Immunol. 2019, 10, 2345.
2. Basak, O.; van de Born, M.; Korving, J.; Beumer, J.; van der Elst, S.; van Es, J.H.; Clevers, H. Mapping early fate determination in Lgr5+ crypt stem cells using a novel ki67-RFP allele. EMBO J. 2014, 3, 2057–2068.
3. Han, H.; Li, Y.; Fang, J.; Liu, G.; Yin, J.; Li, T.; Yin, Y. Gut Microbiota and Type 1 Diabetes. Int. J. Mol. Sci. 2018, 19, 995.
4. Clevers, H. The intestinal crypt, a prototype stem cell compartment. Cell 2013, 154, 274–284.
5. Beumer, J.; Clevers, H. Cell fate specification and differentiation in the adult mammalian intestine. Nat. Rev. Mol. Cell. Biol. 2020, 22, 39–53.
6. Nakamura, K.; Sakuragi, N.; Takakuwa, A.; Ayabe, T. Paneth cell α-defensins and enteric microbiota in health and disease. Biosci. Microbiota Food Health 2016, 35, 57–67.
7. Zhu, G.; Hu, J.; Xi, R. The cellular niche for intestinal stem cells: A team effort. Cell Regen. 2021, 10, 1.
8. Frost, M.D.; Frank, U.; Weiss, F.U.; Sendler, M.; Kacprowski, T.; Ruhlemann, M.; Bang, C.; Franke, A.; Volker, U.; Volzeke, H.; et al. The Gut Microbiome in Patients with Chronic Pancreatitis Is Characterized by Significant Dysbiosis and Overgrowth by Opportunistic Pathogens. Clin. Transl. Gastroenterol. 2020, 11, e00232.
9. Ribeiro, A.B.D.T.M.; Heimesaat, M.M.; Bereswill, S. Changes of the intestinal microbiome-host homeostasis in HIV-infected individuals-a focus on bacterial gut microbiome. Eur. J. Microbiol. Immunol. 2017, 7, 158–167.
10. Cari, L.; Rosati, L.; Leoncini, G.; Lusenti, E.; Gentili, M.; Nocentini, C.; Riccardi, C.; Migliorati, G.; Ronchetti, S. Association of GILZ with MUC2, TLR2 and TLR4 in Inflammatory Bowel Disease. Int. J. Mol. Sci. 2023, 24, 2235.
11. Salazar, J.; Angarita, L.; Morillo, V.; Navarro, C.; Martinez, M.S.; Chacin, M.; Torres, W.; Rajotia, A.; Rojas, M.; Cano, C.; et al. Microbiota and Diabetes Mellitus: Role of Lipid Mediators. Nutrients

2020, 12, 3039.

12. Sharma, S.; Tripathi, P. Gut microbiome and type 2 diabetes: Where we are and where to go? J. Nutr. Biochem. 2018, 63, 101–108.
13. Shin, N.R.; Whon, T.W.; Bae, J.W. Proteobacteria: Microbial signature of dysbiosis in gut microbiota. Trends Biotechnol. 2015, 33, 496–503.
14. Al-Rashidi, H.E. Gut microbiota and immunity relevance in eubiosis and dysbiosis. Saudi J. Biol. Sci. 2022, 29, 1628–1643.
15. Lazar, V.; Ditu, L.M.; Pircalabioru, G.G.; Curutiu, C.; Holban, A.M.; Picu, A.; Petcu, L.; Chifiriuc, M.C. Aspects of gut microbiota and immune system interactions in infectious diseases, immunopathology, and cancer. Front. Immunol. 2018, 9, 1830.
16. Hackam, D.J.; Sodhi, C.P. Toll-Like Receptor-Mediated Intestinal Inflammatory Imbalances in the Pathogenesis of Necrotizing Enterocolitis. Cell. Mol. Gastroenterol. Hepatol. 2018, 6, 229–238.e1.
17. Lievin-Le Moal, V.; Servin, A.L. The frontline of enteric host defense against unwelcome intrusion of harmful microorganisms: Mucins, antimicrobial peptides, and microbiota. Clin. Microbiol. Rev. 2006, 19, 315–337.
18. Allam-Ndoul, B.; Castonguay-Paradis, S.; Veilleux, A. Gut Microbiota and Intestinal Trans-Epithelial Permeability. Int. J. Mol. Sci. 2020, 21, 6402.
19. Mukerjee, S.; Hooper, L.V. Antimicrobial Defense of the Intestine. Immunity 2015, 42, 28.
20. Sankaran-Walters, S.; Hart, R.; Dills, C. Guardians of the Gut Enteric Defensins. Front. Microbiol. 2017, 8, 647.
21. Bevins, C.L. Events at the host-microbial interface of the gastrointestinal tract. V. Paneth cell alpha-defensins in intestinal host defense. Am. J. Physiol. Liver Physiol. 2005, 289, G173–G176.
22. Cray, P.; Sheahan, B.J.; Dekaney, C.M. Secretory Sorcery: Paneth Cell Control of Intestinal Repair and Homeostasis. Cell. Mol. Gastroenterol. Hepatol. 2021, 12, 1239–1250.
23. Dinsdale, D.; Biles, B. Postnatal changes in the distribution and elemental composition of Paneth cells in normal and corticosteroid-treated rats. Cell Tissue Res. 1986, 246, 183–187.
24. Zhang, M.; Wu, C. The relationship between intestinal goblet cells and the immune response. Biosci. Rep. 2020, 40, BSR20201471.
25. Singh, R.; Balasubramanian, I.; Zhang, L.; Gao, N. Metaplastic Paneth Cells in Extra-Intestinal Mucosal Niche Indicate a Link to Microbiome and Inflammation. Front. Physiol. 2020, 11, 280.
26. Lueschow, S.R.; McElroy, S.J. The Paneth Cell: The Curator and Defender of the Immature Small Intestine. Front. Physiol. 2020, 11, 587.

27. Lee, V.H.; Gulati, A.S. Implications of Paneth cell dysfunction on gastrointestinal health and disease. Curr. Opin. 2022, 38, 535–540.
28. Ma, Q.; Li, Y.; Li, P.; Wang, M.; Wang, J.; Tang, Z.; Wang, T.; Luo, L.; Wang, C.; Wang, T.; et al. Research progress in the relationship between type 2 diabetes mellitus and intestinal flora. Biomed. Pharmacother. 2019, 117, 109138.
29. Grinat, J.; Kosel, F.; Goveas, N.; Kranz, A.; Alexopoulou, D.; Rajewsky, K.; Sigal, M.; Stewart, A.F.; Heuberger, J. Epigenetic modifier balances Mapk and Wnt signalling in differentiation of goblet and Paneth cells. Life Sci. Alliance 2022, 5, e202101187.
30. Holly, M.K.; Smith, J.G. Paneth Cells during Viral Infection and Pathogenesis. Viruses 2018, 10, 225.
31. Salzman, N.H.; Underwood, M.A.; Bevins, C.L. Paneth cells, defensins, and the commensal microbiota: A hypothesis on intimate interplay at the intestinal mucosa. Semin. Immunol. 2007, 19, 70–83.
32. Farin, H.F.; Karthaus, W.R.; Kujala, P.; Rakhshandehroo, M.; Schwank, G.; Vries, R.G.J.; Kalkhoven, E.; Nieuwenhuis, E.E.S.; Clevers, H. Paneth cell extrusion and release of antimicrobial products is directly controlled by immune cell-derived IFN-γ. J. Exp. Med. 2014, 211, 1393–1405.
33. Ouellette, A.J. Paneth cell α-defensins in enteric immunity. Cell. Mol. Life Sci. 2011, 68, 2215–2229.
34. Gassler, N. Paneth cells in intestinal physiology and pathophysiology. World J. Gastrointest. Pathophysiol. 2017, 8, 150–160.
35. Chairatana, P.; Nolan, E.M. Human α-Defensin 6: A Small Peptide that Self-Assembles and Protects the Host by Entangling Microbes. Acc. Chem. Res. 2017, 50, 960–967.
36. Dayton, T.L.; Clevers, H. Beyond growth signaling: Paneth cells metabolically support ISCs. Cell Res. 2017, 27, 851–852.
37. Fruitwala, S.; El-Naccache, D.W.; Chang, T.L. Multifaceted immune functions of human defensins and underlying mechanisms. Semin. Cell Dev. Biol. 2019, 88, 163–172.
38. Hein, M.J.A.; Kvansakul, M.; Lay, F.T.; Phan, T.K.; Hulett, M.D. Defensin-lipid interactions in membrane targeting: Mechanisms of action and opportunities for the development of antimicrobial and anticancer therapeutics. Biochem. Soc. Trans. 2022, 50, 423–437.
39. Gao, X.; Ding, J.; Liao, C.; Xu, J.; Liu, X.; Lu, W. Defensins: The natural peptide antibiotic. Adv. Drug Deliv. Rev. 2021, 179, 114008.
40. Jackson, D.; Theiss, A.L. Intestinal Stem Cell Regulation via Glycolytic Activity of Neighboring Paneth Cells. J. Gastroenterol. Hepatol. Endosc. 2017, 2, 1019.

41. Heneghan, A.F.; Pierre, J.F.; Tandee, K.; Shanmuganayagam, D.; Wang, X.; Reed, J.D.; Steele, J.L.; Kudsk, K.A. Parenteral Nutrition Decreases Paneth cell function and Intestinal Bactericidal Activity while Increasing Susceptibility to Bacterial Enteroinvasion. J. Parenter. Enter. Nutr. 2014, 38, 817–824.
42. Hodin, C.M.; Lenaerts, K.; Grootjans, J.; de Haan, J.J.; Hadfoune, M.; Verheyen, F.K.; Kiyama, H.; Heineman, E.; Buurman, W.A. Starvation Compromises Paneth Cells. Am. J. Pathol. 2011, 179, 2885.
43. Yang, E.; Shen, J. The Roles and functions of Paneth cells in Crohn's disease: A critical review. Cell Prolif. 2020, 54, e12958.
44. Liu, T.C.; Gurram, B.; Baldridge, M.T.; Head, R.; Lam, V.; Luo, C.; Cao, Y.; Simpson, P.; Hayward, M.; Holtz, M.L.; et al. Paneth cell defects in Crohn's disease patients promotes dysbiosis. J. Clin. Investig. 2016, 1, e86907.
45. Liu, T.C.; Kern, J.T.; VanDussen, K.L.; Xiong, S.; Kaiko, G.E.; Wilen, C.B.; Rajala, M.W.; Caruso, R.; Holtzman, M.J.; Gao, F.; et al. Interaction between smoking and ATG16L1T300A triggers Paneth cell defects in Crohn's disease. J. Clin. Investig. 2018, 128, 5110–5122.
46. Stappenbeck, T.S.; McGovern, D.P.B. Paneth Cell Alterations in the Development and Phenotype of Crohn's Disease. Gastroenterology 2017, 152, 322–326.
47. Donaldson, D.S.; Shih, B.B.; Mabbott, N.A. Aging-Related Impairments to M Cells in Peyers's Patches Coincide with Disturbances to Paneth Cells. Front. Immunol. 2021, 12, 761949.
48. Kelly, P.; Feakins, R.; Domizio, P.; Murphy, J.; Bevins, C.; Wilson, J.; McPhail, G.; Poulsom, R.; Dhaliwal, W. Paneth cell granule depletion in the human intestine under infective and nutrional stress. Clin. Exp. Immunol. 2004, 135, 303–309.
49. Latorre, E.; Layunta, E.; Grasa, L.; Pardo, J.; Garcia, S.; Alcalde, A.I.; Mesonero, J.E. Toll-like receptots 2 and 4 modulate intestinal IL-10 differently in ileum and colon. United Eur. Gastroenterol. J. 2018, 6, 446–453.
50. Kwon, M.S.; Chung, H.K.; Xiao, L.; Yu, T.X.; Wang, S.R.; Piao, J.J.; Rao, J.N.; Gorospe, M.; Wang, J.Y. MicroRNA-195 regulates Tuft cell function in the intestinal epithelium by altering translation of DCLK1. Am. J. Physiol. Cell Physiol. 2021, 320, C1042–C1054.
51. Schneider, C.; O'Leary, C.E.; Locksley, R.M. Regulation of immune responses by tuft cells. Nat. Rev. Immunol. 2019, 19, 584–593.
52. Billipp, T.E.; Nadjsombati, M.S.; von Moltke, J. Tuning tuft cells: New ligands and effector functions reveal tissue-specific function. Curr. Opin. Immunol. 2021, 68, 98–106.
53. O'Leary, C.E.; Schneider, C.; Locksley, R.M. Tuft cells-systemically dispersed sensory epithelia integrating immune and neural circuitry. Annu. Rev. Immuno.l 2019, 37, 47–72.

54. Han, S.J.; Kim, M.; D'Agati, V.D.; Lee, H.T. Norepinephrine released by intestinal Paneth cells exacerbates ischemic AKI. Am. J. Physiol. Ren. Physiol. 2020, 318, F260–F272.
55. Hills, R.D.; Pontefract, B.A.; Mishcon, H.R.; Black, C.A.; Sutton, S.C.; Theberge, C.R. Gut Microbiome: Profound Implications for Diet and Disease. Nutrients 2019, 11, 1613.
56. Chen, Y.; Zhou, J.; Wang, L. Role and Mechanism of Gut in Human Disease. Front. Cell. Infect. Microbiol. 2021, 11, 625913.
57. Siljander, H.; Honkanen, J.; Knip, M. Micriobiome and Type 1 diabetes. EBioMedicine 2019, 46, 512–521.
58. Ortega, M.A.; Fraile-Martinez, O.; Naya, I.; Garcia-Honduvilla, N.; Alvarez-Mon, M.; Bujan, J.; Asunsolo, A.; de la Torre, B. Type 2 Diabetes Mellitus Associated with Obesity (Diabesity). The Central Role of Gut Microbiota and Its Translational Applications. Nutrients 2020, 12, 2749.
59. Stecher, B.; Hardt, W.D. Mechanisms controlling pathogen colonization of the gut. Curr. Opin. Microbiol. 2011, 14, 82–91.
60. Khanna, S.; Tosh, P.K. A clinician's primer of the role of the microbiome in human health and disease. Mayo Clin. Proc. 2014, 89, 107–114.
61. Hasain, Z.; Mokhtar, N.M.; Kamaruddin, N.A.; Ismail, N.A.M.; Razalli, N.H.; Gnanou, J.V.; Ali, R.A.R. Gut Microbia and Gestational Daibetes Mellitus: A Review of Host-Gut Microbiota Interactions and Their Therapeutic Potential. Front. Cell. Infect. Microbiol. 2020, 10, 188.
62. Cani, P.D. Human gut microbiome: Hopes, threats and promises. Gut 2018, 67, 1716–1725.
63. Tsai, Y.L.; Lin, T.L.; Chang, C.J.; Wu, T.R.; Lai, W.F.; Lu, C.C.; Lai, H.C. Probiotics, prebiotics and amelioration of diseases. J. Biomed. Sci. 2019, 26, 3.
64. Stern, J.; Miller, G.; Li, X.; Saxena, D. Virome and bacteriome: Two sides of the same coin. Curr. Opin. Virol. 2019, 37, 37–43.
65. Yang, K.; Niu, J.; Zuo, T.; Sun, Y.; Xu, Z.; Tang, W.; Liu, Q.; Zhang, J.; Ng, E.K.W.; Wong, S.K.H.; et al. Alterations in the Gut Virome in Obesity and Type 2 Diabetes Mellitus. Gastroenterology 2021, 161, 1257–1269.
66. Xu, J.; Xu, X.; Chen, X.; Cai, X.; Yang, S.; Sheng, Y.; Wang, T. Regulation of an antioxidant blend on intestinal redox status and major microbiota in early weaned piglets. Nutrition 2014, 30, 584–589.
67. Yokoi, Y.; Nakamura, K.; Yoneda, T.; Kikuchi, M.; Sugimoto, R.; Shimizu, Y.; Ayabe, T. Paneth cell granule dynamics on secretory responses to bacterial stimuli in enteroids. Sci. Rep. 2019, 9, 2710.

68. Singh, V.; Ahlawat, S.; Mohan, H.; Gill, S.S.; Sharma, K.K. Balancing reactive oxygen species generation by rebooting gut microbiota. J. Appl. Microbiol. 2022, 132, 4112–4129.
69. Jimenez-Uribe, A.P.; Hernandez-Cruz, E.Y.; Ramirez-Magana, K.J.; Pedraza-Chaverri, J.P. Involvement of Tricarboxylic Acid Cycle Metabolites in Kidney Diseases. Biomolecules 2021, 11, 1259.
70. Nagpal, R.; Newman, T.M.; Wang, S.; Jain, S.; Lovato, J.F.; Yadav, H. Obesity-Linked Gut Microbiome Dysbiosis Associated with Derangements in Gut Permeability and Intestinal Cellular Homeostasis Independent of Diet. J. Diabetes Res. 2018, 2018, 3462092.
71. Zhou, Z.; Sun, B.; Yu, D.; Zhu, C. Gut Microbiota: An Important Player in Type 2 Diabetes Mellitus. Front. Cell. Infect. Microbiol. 2022, 12, 834485.
72. Singh, R.B.; Fedacko, J.; Fatima, G.; Magomedova, A.; Watanabe, S.; Elkilany, G. Why and How the Indo-Mediterranean Diet May Be Superior to Other Diets: The Role of Antioxidants in the Diet. Nutrients 2022, 14, 898.
73. Darenskaya, M.A.; Kolesnikova, L.I.; Kolesnikov, S.I. Oxidative Stress: Pathogenetic Role in Diabetes in Diabetes Mellitus and Its Complications and Therapeutic Approaches to Correction. Bull. Exp. Biol. Med. 2021, 171, 179–189.
74. Karam, B.S.; Chavez-Moreno, A.; Koh, W.; Akar, J.G.; Akar, F.G. Oxidative stress and inflammation as central mediators of atrial fibrillation in obesity and diabetes. Cardiovasc. Diabetol. 2017, 16, 120.
75. Shan, Z.; Fa, W.H.; Tian, C.R.; Yuan, C.S.; Jie, N. Mitophagy and mitochondrial dynamics in type 2 diabetes mellitus treatment. Aging 2022, 14, 2902–2919.
76. Berger, N.A. Young Adult Cancer: Influence of the Obesity Pandemic. Obesity 2018, 26, 641–650.
77. Capuco, A.; Urits, I.; Hasoon, J.; Chun, R.; Gerald, B.; Wang, J.K.; Kassem, H.; Ngo, A.L.; Abd-Elsayed, A.; Simopoulos, T.; et al. Current Perspectives on Gut Microbiome Dysbiosis and Depression. Adv. Ther. 2020, 37, 1328–1346.
78. Khandekar, M.J.; Cohen, P.; Spiegelman, B.M. Molecular mechanisms of cancer development in obesity. Nat. Rev. Cancer 2011, 11, 886–895.
79. Kawai, T.; Autieri, M.V.; Scalia, R. Adipose tissue inflammation and metabolic dysfunction in obesity. Am. J. Physiol. 2021, 320, C375–C391.
80. Tao, Z.; Shi, A.; Zhao, J. Epidemiological Perspectives of Diabetes. Cell Biochem. Biophys. 2015, 73, 181–185.
81. Pircalabioru, G.G.; Corcionivoschi, N.; Gundogdu, O.; Chifiriuc, M.C.; Marutescu, L.G.; Ispas, B.; Savu, O. Dysbiosis in the Development of Type! Diabetes and Associated Complications: From Mechanisms to Targeted Gut Microbes Manipulation Therapies. Int. J. Mol. Sci. 2021, 22, 2763.

82. Iyengar, N.M.; Gucalp, A.; Dannenberg, A.J.; Hudis, C.A. Obesity and Cancer Mechanisms: Tumor Microenvironment and Inflammation. J. Clin. Oncol. 2016, 34, 4270–4276.

Retrieved from https://encyclopedia.pub/entry/history/show/102507