Blood metagenome in health and psoriasis.

Supplements.

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Content

S1. Comparative characteristics of 16S and WMS-tests

	Characteristics	16S	WMS	Sources
	Basic			
1	Opportunity to detect any species, including uncultivated ones.	Yes	Yes	
2	Identifying DNA of both live and dead (partly degraded, including degraded DNA) organisms. It is impossible to identify separately.	Yes	Yes	
3	Detecting non-bacterial DNA (from eukaryotes, archaea, viruses, phages, fungi, plants, parasites, etc.).	No	Yes	Jovel 2016, Meisel 2016, Ranjan 2016
4	Level of high-quality taxon classification. 16S-test cannot technically ensure identification to within species for ~ 42% of genera, as trans-species coincidence of amplikon sequence is higher than 97%. Only WMS-test gives an opportunity to identify bacDNA to within species (strain) (Jovel 2016).	Phyla +++ Genus ++ Species -+ Strain -	Phyla +++ Genus +++ Species +++ Strain +-	Frey et al., 2015, Meisel et al., 2016, Ranjan et al., 2016, Tyakht et al., 2014
5	Representation (phylums, genera, species) is determined. To determine concentrations by representations, an additional test of initial biomaterial is carried out. qPCR (Glassing et al., 2016, Païssé et al., 2016) and dPCR (Bhat et al., 2016, Tan et al., 2015) are most often applied to determine total bacDNA by one of the universal 16S rRNA sites (Nakatsuji et al., 2013). "The internal standard method" – adding a specific amount (about 1% of the totally expected amount) of DNA of a characteristic bacterium to biomaterial – is also applied. It is such a bacterium whose bacDNA definitely cannot be present in this biomaterial (Tan et al., 2015). Before sequencing, concentration of all DNA is always determined. This can be enough to determine concentration by WMS-test results.	Yes	Yes	Bhat et al., 2016, Glassing et al., 2016, Grumaz et al., 2016, Païssé et al., 2016, Tan et al., 2015
6	Genome coverage. For WMS-test, possible even for DNA with low representation (depends on coverage depth).	One or several sites in 16S rRNA	Uniform coverage of all genome.	Ranjan et al., 2016
7	Identifying specific genes. Due to this, WMS-test results can be interpreted with precision up to within strains on marker unique genes (Jovel et al., 2016).	No	Yes	Ferretti et al., 2017, Ranjan et al., 2016
8	Identifying genes of resistance to antibiotics (resistome).	No	Yes	Frey et al., 2015

	Characteristics	16S	WMS	Sources
9	Identifying genes of virulence (pathogenicity).	No	Yes	Meisel et al., 2016
10	Functional classification of the detected species, discovery of new genes.	No	Yes	Jovel et al., 2016
11	Information for the choice of medicines.	+	++	Frey et al., 2015
	Additional characteristics and disadvantages			
12	Quantity of genera (species) of bacteria for which 16S rRNA sequence (fully or partly, for 16S-test) or strain genome sequence (for WMS-test) is established. Data for Feb 14, 2019.	~ 3360000 (RDP, r11); ~ 6800000 (SILVA, r132)	~ 186000 (including ~13500 whole) Genome	
13	Quantity of bacteria species (for 16S-test with inaccurate classification) found in one biomaterial (excrements) by increasing the size of libraries (up to 3.2×10^7).	2050	4100	Ranjan et al., 2016
14	Microbiome variety found in one biomaterial on three various metrics.	Lower	Higher	Ranjan et al., 2016
15	Test-sensitivity is limited by possible contamination. Test samples of NTC are necessary to assess contamination level. It is also essential to take constant measures to reduce this level.	Yes	Yes	Glassing et al., 2016
	WMS-test vs 16S-test.			
16	When the pathogen is unknown, when more than mere identification is required (identifying the strain, assessing pathogenic load and resistance to antibiotics). In case of mixed infections (e.g. at mixed sepsis), 16S-test often results in mistakes and has weak repeatability.	No	Yes	Frey et al., 2015
17	Opportunity to detect DNA of any species, and not only that which is included into a pre-determined list. The best 16S tests of sepsis diagnostics SepsiTest (over 345 species of bacteria and fungi) and IRIDICA (over 1000 pathogens, out of production since 2017) are unable to identify pathogen presence, if it is not from their list.	No	Yes	Frey et al., 2015, Stevenson et al., 2016
18	Identifying genomes of new, previously undetected species.	No	Yes	Frey et al., 2015, Jovel et al., 2016

	Characteristics	16S	WMS	Sources
19	**16S-test. Disadvantage.** The number of 16S copies in genome changes within a wide range (depending on species and even strain). It results in assigned errors when determining taxon representation. Representation of taxons with a larger number of 16S copies in genome will be overestimated, with a smaller number – underestimated.	Yes		Vetrovsky et al., 2013, Tyakht et al., 2014
20	**16S-test. Disadvantage.** The choice of primers for different variable sites (from V1 to V9) to perform amplification, leads to essentially different results not only due to their different characteristics at amplification (affinity), but also due to influence on classification by taxons.	Yes		Jovel et al., 2016, Meisel et al., 2016
21	**16S-test. Disadvantage.** Mutations in variable sites 16S rRNA (from V1 to V9) can interfere with the correct classification by taxons.	Yes		
22	**WMS-test. Disadvantage**. The necessity of maximum elimination of host DNA (hDNA) from biomaterial before sequencing (biochemical methods) and after sequencing (algorithmic methods).		Yes	Ferretti et al., 2017, Frey et al., 2015
	Cost performance and specific performance data			
23	Cost at the rate of one sample. Depends on problem statement, number of samples in library, sequencer power and its working mode, protocol of processing sequencing results.	47-60 $	120-290 $	Ranjan et al., 2016, Genohub, Allseq
24	**WMS-test.** In the future, the cost may fall to below $1 per one bacterial genome (2014). It has already happened (see above). The cost can be reduced due to sample preparation or by enrichment of pathogen representation and/or host DNA elimination.		Yes	Applications 2015, Frey et al., 2015
25	Performance time (depends on equipment and problem statement)	2-5 hours	7–60 hours	Frey et al., 2015
26	Requirements to temperature control during transportation and sample preparation.	Lower	Higher	Frey et al., 2015

	Characteristics	16S	WMS	Sources
27	Proven pipeline of test implementation. Term of active use. For 16S-test, however, there are no (and cannot be any) satisfactory schemes for classification to within species (Jovel 2016).	A lot. Over 30 years.	Few. About 10 years.	Sharpton et al., 2014, Ranjan 2016, Nayfach 2016, Vincent et al., 2017, Aransay 2016 (part 12)
28	Number of publications "16S + metagenomic" vs "shotgun + metagenomic" (according to https://scholar.google.com/)	50800	24300	14.02.2019

S2. Resources of metagenomic research and sequencing

Title	Description. Notes
HMP (Human Microbiome Project)	All information about microorganisms, living on and in human body (the project was founded in 2008), contains information on more than 3,000 genomes.
KEGG	Kyoto Encyclopedia of Genes and Genomes (over 4,000 genomes)
MetaHIT	Intestine microbiome. The project was completed in 2012.
Integrated gene catalog (IGC)	Catalog of intestine microbiome genes
NCBI Reference Sequence (RefSeq) Database	NCBI. Reference DB of genomes. Statistics.
NCBI.Genbank	NCBI. DB of genomes ~ 186000 genomes of prokaryotes, including ~ 13500 whole ones.
NCBI Microbial Genomes Resources	NCBI. DB of bacterial genomes. Taxonomical tree.
NCBI. Sequence Read Archive	NCBI. DB of metagenomic projects.
Genomes OnLine Database	DB of genomes.
MG-RAST	DB of metagenomic projects.
Allseq. The Sequencing Marketplace.	Information on sequencers.
Genohub	Information resource on sequencing methods and provider choice. Search of provider.
Science Exchange	Information resource on sequencing methods and provider choice. Search of provider.
Omictools	Search of software for processing biological (including metagenomic) research results
Center for Genomic Epidemiology	Resource for infectious disease specialist
The European Bioinformatics Institute. Metagenomics.	DB of metagenomic projects.

S3. Main researches classification and comparison.

Sampling type	16S-test		WMS-test	
	Psoriatic patients	**Healthy persons**	**Psoriatic patients**	**Healthy persons**
Serum	Codoner et al., 2018	Cho et al., 2019; Dong et al., 2019 (low quality)		
Plasma	Munz et al., 2010	Païssé et al., 2016 (+); Whittle et al., 2019; Qui et al., 2019;		Dinakaran et al., 2014 (+); Long et al., 2016; Grumaz et al., 2016 (+); Kowarsky et al., 2017 (HP – pregnancy);
Whole blood, phagocytes	Okubo et al., 2002 (monocytes – without metagenome, +);	Païssé et al., 2016 (and its fractions, +); Lelouvier et al., 2016 (leukocytic mass, +); Gosiewski et al., 2017; Panaiotov et al., 2018; Puri et al., 2018 (+); Li et al., 2018 (including neutrophils, +); Qian et al., 2018 (leukocytic mass, +), Shah et al., 2019 (leukocytic mass, +); Serena et al., 2019;	NCS1 (in future, +)	NCS1 (in future, +)

Note: + - concentration was (will be) determined.

Main researches in which metagenome is defined and also several key works on psoriasis can be grouped in two key parameters: biomaterial sampling type (serum or plasma or whole blood, phagocytes) and sequencing technique (16S-test or WMS-test) (See table above).

Blood serum metagenome of psoriatic patients was defined once and as it is possible to judge by results, unsuccessfully (Ramírez-Boscá et al., 2015, Codoner et al., 2018). Metagenome has not been found neither in one of 27 HP, nor in 75% from more than 50 PP. Similar problems have arisen in work (Dong et al., 2019), metagenome has been defined only at 101 of 311 inspected. On the other hand in work (Cho et al., 2019) metagenome has been defined at all inspected (324 patients and 402 HP).

Can be one of reasons of failures the wrong preparation and/or storage of biomaterial before DNA isolation. All or most part of bacDNA will be lost if not to provide maximum termination of its degradation after blood sampling. The most widespread technology of receiving serum presumes staying of blood for 15-30 minutes at room temperature for coagulation and subsequent centrifuging at low temperature. If this protocol for some samples lasts longer and/or is carried out without necessary cooling, then enzymes will degrade bacDNA and blood phagocytes will endocyte it. In work (Cho et al., 2019) requirements of this protocol have been completely fulfilled for all samples.

In the majority of researches metagenome was defined for plasma (Dinakaran et al., 2014, Long et al., 2016, Grumaz et al., 2016, Kowarsky et al., 2017, Whittle et al., 2019). After publication of pioneer work (Païssé et al., 2016), results of several more researches in which whole blood metagenome was also defined have been published (Lelouvier et al., 2016, Gosiewski et al.,

2017, Panaiotov et al., 2018, Puri et al., 2018, Li et al., 2018, Qian et al., 2018, Shah et al., 2019, Serena et al., 2019).

In some of these works concentration of bacDNA in whole blood (noted +) was defined that has allowed to compare for the first time these data for healthy persons (Table 2 in main text). In all these works metagenome was defined by 16S-test and, therefore, only to within genus of bacteria.

Only in these works the possibility of comparison of absolute bacDNA concentration (as in general, and for separate genera) has appeared at disease with control healthy group.

WMS-test allows to define metagenome to within species of bacteria. Unfortunately it has been made only for plasma (Dinakaran et al., 2014, Long et al., 2016, Grumaz et al., 2016, Kowarsky et al., 2017). In work (Dinakaran et al., 2014) WMS-test has been executed only for 3 patients and 3 HP that it is obviously not enough for statistically significant conclusions. In work (Long et al., 2016) bacDNA concentration was not defined and contamination level was not estimated that does its results less significant.

In work (Kowarsky et al., 2017) effective and versatile control of contamination level has been applied, but bacDNA concentration was not defined. Results of (Grumaz et al., 2016) in which concentration of all cell-free DNA was defined that indirectly allows to estimate plasma bacDNA concentration are most interesting.

Before WMS-test performance for obtaining information about metagenome it is reasonable to carry out preliminary elimination of host DNA (Opota et al., 2015, Yigit et al., 2016, Marotz et al., 2018). It allows to increase significantly % of reads of non-host DNA (including bacDNA) in results of sequencing and by that to increase their reliability. Most effectively such elimination is carried out by NebNext Microbiome DNA Enrichment. However in works using WMS-test the preliminary elimination of host DNA was not carried out and, as a result, from 96% to 99,5% of reads were mapped on human genome.

In future researches with sequencing it is reasonable to obtain information about metagenome to within species, i.e. by WMS-test. BacDNA concentration in whole blood is three orders higher in comparison with its concentration in plasma. Therefore as biomaterial it is necessary to use whole blood (optimum - postprandial). It will provide definition of values of bacDNA concentration for minority species above potential contamination level (Païssé et al., 2016). Assessment of contamination level has to be most exact and correct (Kowarsky et al., 2017). Before WMS-test performance for definition of whole blood metagenome it is necessary to carry out the greatest possible elimination of host DNA. As a result of such research significant and detailed information about blood metagenome at any diseases will be obtained.

Metagenome of plasma or whole blood of psoriatic patients in one of works was not defined. WMS-test was not used for studying of any fraction of blood of psoriatic patients. About bacDNA concentration in blood monocytes of psoriatic patients it is possible to judge only by work (Okubo et al., 2002). In future researches of psoriatic patients it is necessary to define whole blood metagenome by WMS-test, and also bacDNA concentration. Only such approach will give the chance to reveal correlation of psoriasis severity with total bacDNA concentration of presumed psoriagenic and/or pathogenic species (Supplement S5).

S4. Income of bacterial products into blood flow from small intestine.

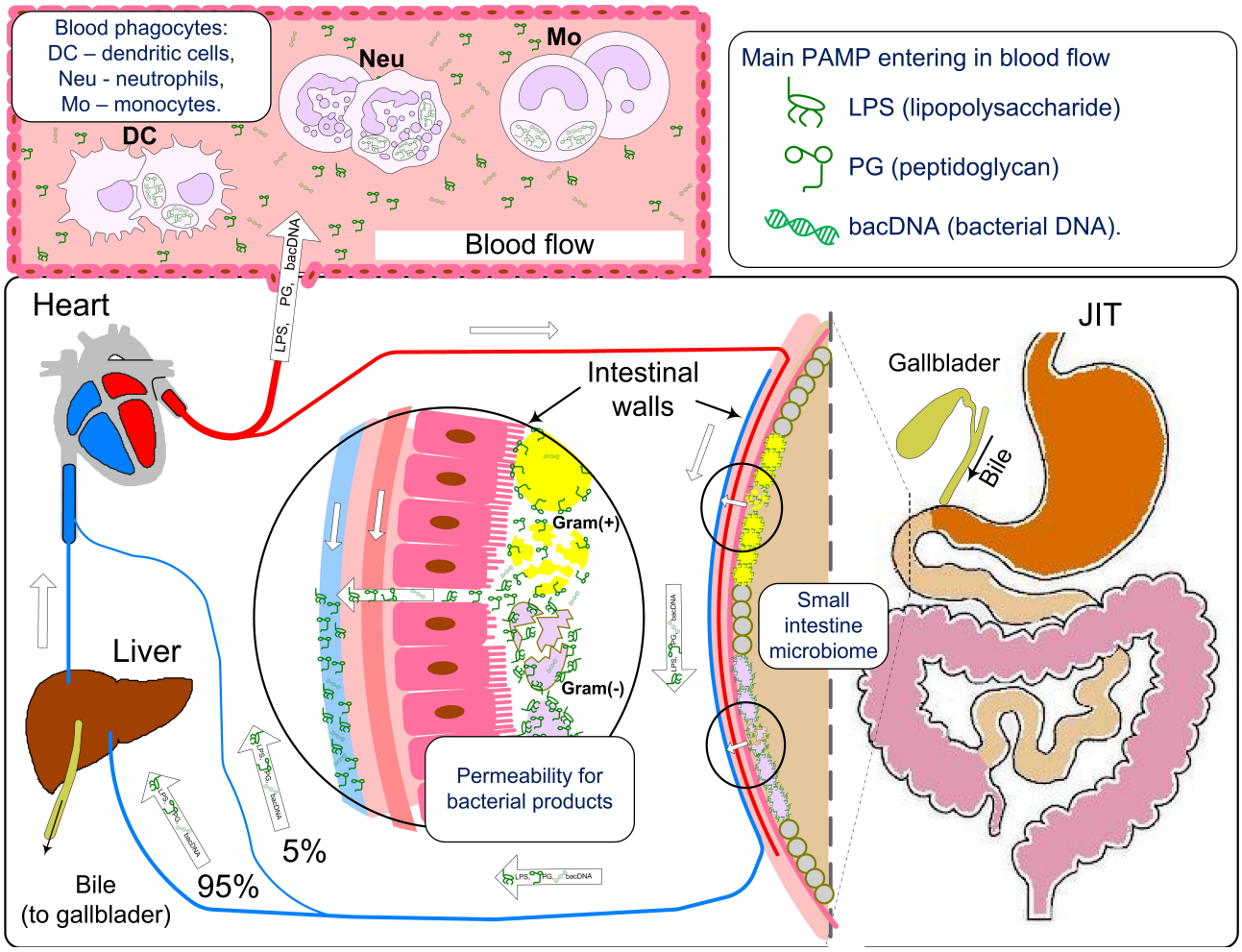

Fig. S1. Income of bacterial products into blood flow from small intestine.

Intestine microbiome self-renews; as a result of bacterial activity and death of bacterial cells, bacterial products develop, particularly LPS (lipopolysaccharide), cellular wall component of Gram(-) bacteria and PG (peptidoglycan), the main cellular wall component of Gram(+) bacteria, as well as bacDNA (bacterial DNA). At normal, and especially at increased small intestine permeability for bacterial products, their essential part gets into systemic blood flow.

At least 95% of venous blood from small intestine passes by portal vein through liver, where an essential part of bacterial products is degraded and filtered (and subsequently returns into small intestine together with bile). Due to porto-caval anastomosis, though, up to 5% of venous blood bypasses liver and gets directly into the system of superior vena cava, and then into systemic blood flow (including non-degraded bacterial products).

In systemic blood flow, bacterial products are constantly utilized, mainly with phagocyte participation (primarily neutrophils). The figure shows both young phagocytes (which have just left bone marrow and therefore do not contain bacterial products) and those which have already endocyted bacterial products. At each timepoint most non-degraded bacterial products in systemic blood flow are either bound by phagocytes through surface receptors or are endocytosed and located in phagocytes.

S5. YN-model of psoriasis pathogenesis. Partial description.

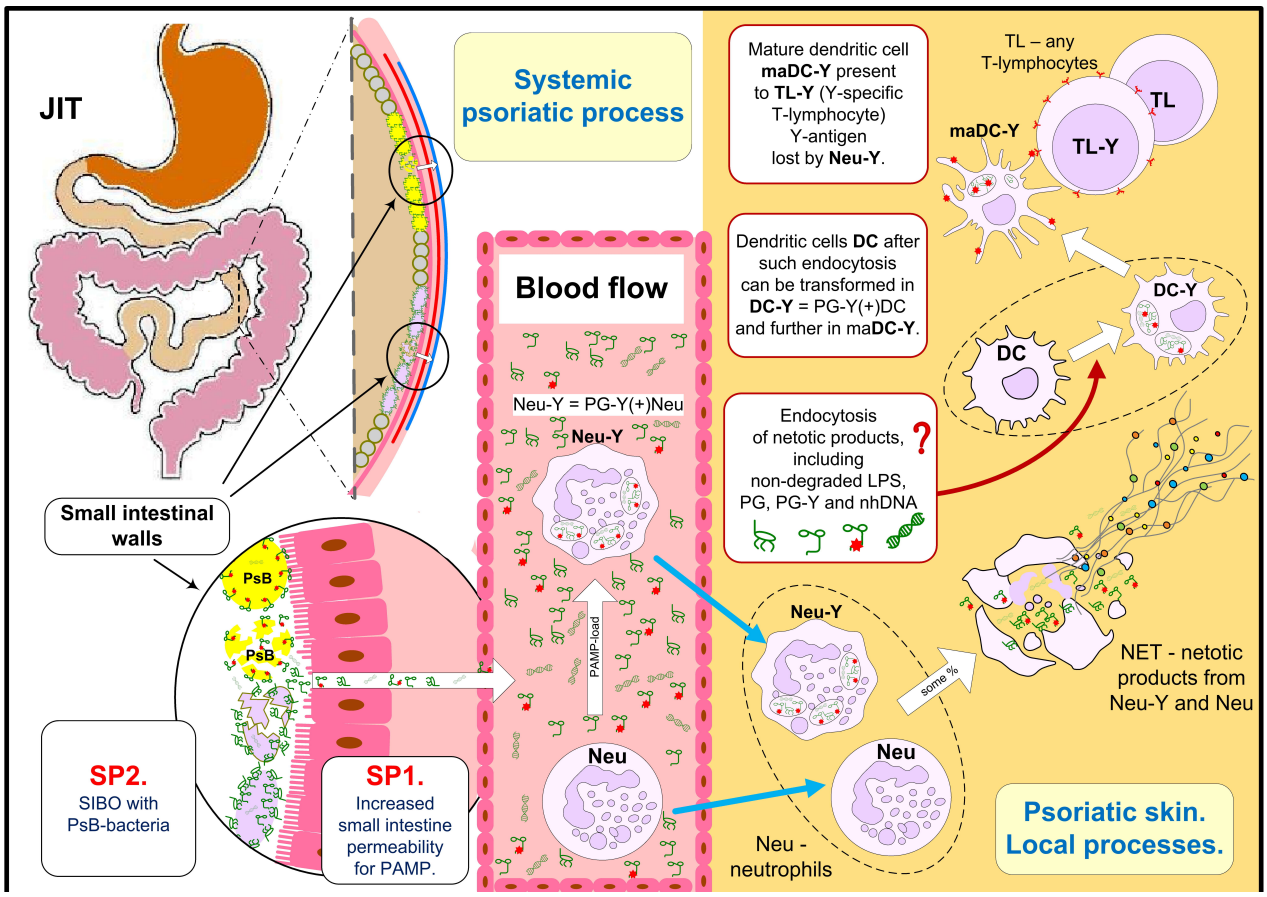

Fig. S2. YN-model of psoriasis pathogenesis. (Peslyak and Korotky 2019, part 5.2).

IB-Y	Interpeptide bridges of peptidoglycan *Str.pyogenes*: (L-Ala)-(L-Ala) or (L-Ser)-(L-Ala).
PG-Y	Peptidoglycan A3alpha with interpeptide bridges IB-Y (but can also contain others bridges)
PsB	Psoriagenic bacteria - species of bacteria presumed psoriagenic (with PG-Y peptidoglycan)
Y-antigen	part(s) of interpeptide bridge IB-Y
SIBO	Small intestine bacterial overgrowth. Excess of total bacteria concentration over norm and/or pathogens presence in biomaterial. Smears, scrapes from mucosa or aspirates can be used as biomaterial.

Systemic psoriatic process	**SP1.** Increased small intestine permeability for PAMP (including LPS, PG, bacDNA). **SP2.** SIBO with PsB-bacteria. SP1 and SP2 result in chronically increased - concentrations of PAMP (including PG-Y) in blood flow; - PAMP- and (PG-Y)-load on blood neutrophils; As a result, many blood neutrophils - become PAMP- and (PG-Y)-carriers; - pass into prenetotic state; - undergo netosis.

Local processes	In healthy skin neutrophils are practically absent. They are attracted from blood flow at the earliest stage of psoriatic plaque initiation (even before visible skin changes). Their intensive attraction continues as long as the plaque is present. In stable or growing plaque, neutrophils end their existence due to pro-inflammatory environment, mostly by netosis (or, at plaque remission, by apoptosis). Non-degraded PAMP (including PG-Y) brought from blood flow get into netotic products. They are endocyted by skin phagocytes, particularly by dendritic cells. Dendritic cells process PG-Y and present Y-antigen (contained in PG-Y) to effector T-lymphocytes. Other PAMP act as adjuvants. False adaptive response of skin immune system to false PsB-infection is formed. Psoriatic plaques appear and grow while **systemic psoriatic process** is going on, i.e. while neutrophils still attracted from blood flow are abundant in PAMP and PG-Y.

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