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# Inflamm-aging microRNAs may integrate signals from food and gut microbiota by modulating common signalling pathways

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ABSTRACT

Human gut microbiota, which comprises an extremely diverse and complex community of microorganisms inhabiting the intestinal tract, may be associated with inflammation and age-related chronic health conditions. However, the mechanism underlying this association is only recently beginning to emerge. Transfer and modulation of gene expression by diet-derived microRNAs (miRs) in mammals might be involved in this communication. Through a bioinformatics approach, using on line tools and repositories, we searched for evidences that food-containing miRs, actually involved in the modulation of the inflammatory process, (inflamma-miRs), may contribute to mediate the anti-inflammatory effects exerted by some foods through the modulation of aging-related pathways and gut microbiota composition in a bidirectional communication. Supported by a "Pubmed" search and our previous research, a trio of experimentally validated inflamma-miRs were considered: miR-155, miR-146a and miR-21. Our *in silico* study supports the hypothesis that these inflamma-miRs could modulate some pathways, such as lysine degradation and lengthening of fatty acids which are involved in the modulation of microbiota composition, i.e. prevotella, ruminococcus and oscillibacter and *vice versa*. Food homologues to human miR-21, miR-155 and miR-146a were found in cow fat, cow milk, and eggs suggesting that they may be able of targeting, and probably exacerbating, inflammation related pathways. If these data will be experimentally validated, they will further support the relevance of a nutraceutical approach for a healthy aging.

## 1. Introduction

Although research on nutrition has focused on the interactions between nutrients and organism, it is becoming increasingly meaningful to study the effects of nutrient on host gut microbiota composition. Human organism hosts trillions microbial cells in a symbiotic relationship and, in the normal healthy state, they benefit from each other. Over 1000 different species of microorganism are making up the human microbiota. Ninety % of microbiota is concentrated in the gut, especially intestine. Emerging evidences indicated gut microbiota as an important component of human health preservation. The understanding the interrelationship among nutrient-host-microbiota may lead to the discovery of new mechanisms of disease onset and progression. Recent studies are indicating the microbiota as a principal key of healthy phenotype during aging (Franceschi et al., 2017; Claesson et al., 2012; Forslund et al., 2015). A new intriguing hypothesis of aging is that bacteria influence the degree of systemic inflammation through chronic, low grade endotoxemia, thus promoting and sustaining inflamm-aging (Zhang et al., 2013). Growing evidence suggests chronic low-grade inflammation (LGI) as one of the most relevant possible mechanism underlying the aging process (Custodero et al., 2018). A major negative consequence of aging is immuno-senescence, which can be defined as a decline in the functionality of the immune system (Gruver et al., 2007), causing a chronic low-grade inflammatory status in the gut. Immuno-senescence can therefore cause unfavourable changes in the composition and structure of the gut microbiota in older people (Neish, 2009).

Gut microbiota can modulate the host gene expression, primarily the innate immune response (Tomkovich and Jobin, 2015). Recent evidences suggest that communication between the gut microbiota and

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host may in part occur via microRNAs miRs (Williams et al., 2017; Dalmasso et al., 2011). MiRs are a class of short (18–24 nt) regulatory RNAs that are widely evolutionary conserved among many species. These single-stranded, non-coding molecules mediate gene regulation at different levels. The best characterized function of miRs is the post-transcriptional repression of the targets mRNA by promoting cleavage or inhibiting its translation. In this way, miRs negatively regulate target genes expression, modulating all biological functions, including cell development, apoptosis, proliferation, differentiation and regulate inflammatory pathways (Cătană et al., 2015; Olivieri et al., 2013).

Several evidences showed that nutrients may modulate endogenous miRs (Carotenuto et al., 2016). In addition to endogenous miRs, recent fascinating results demonstrated that food-derived miRs enter the mammals' circulatory system and reach their target thus modulating specific mammalian protein expression (Wang et al., 2012; Sherman et al., 2015). This as an intriguing thesis that may pave the way for novel therapeutic approaches discovery. Recent studies confirmed this hypothesis demonstrating that miRs not only are synthesized endogenously, but also might be obtained from dietary sources (Philip et al., 2015; Baier et al., 2014). We hypothesized that ingested biological matter contributes directly to the miRs arsenal of body compartments or that the diet-derived exogenous miRs (referred as "xenomiRs") can affect total miRs profiles as part of a circulating miRs homeostasis that is altered in many diseases (Witwer, 2012). Epigenetic crosstalk between different kingdoms, has been extensively studied in the interaction between plants and bacteria, while evidences in humans are emerging only recently (Williams et al., 2017; Liu et al., 2016; Hua et al., 2018; Qin and Wade, 2017). Increasing evidence suggests the existence of a miRs-based crosstalk between microbiota, the host, and food (Witwer, 2012; Liu et al., 2016; Philip et al., 2015).

Beyond opposing arguments regarding the cross-kingdom regulation of gene expression by plant miRs, concern on how these molecules can access the gastro-intestinal (GI) tract, enter the circulation and transport to cell have also been raised. Several endogenously originating miRs intercellular carriers have been identified, including microvesicle (MV), which are membrane-derived vesicles released from various cell types (Valadi et al., 2007; Zernecke et al., 2009; Zhang et al., 2015; Turchinovich et al., 2012). Encapsulation of miRs in exosomes and exosome-like particles confers protection against RNA degradation and creates a pathway for intestinal and vascular endothelial transport by endocytosis, as well as delivery to peripheral tissues. Exosome-like nanoparticles present in edible fruits and vegetables can be phagocyted by intestinal macrophages and stem cells (Mu et al., 2014). Thus, considering the recent assumptions and evidences that exogenous miRs might be sufficiently stable to pass through the GI tract and enter circulation without losing functionality, we decided to study whether food-containing miRs, especially those that were identified in serum (exosome), can carry signals to host modulating immune system. For this purpose, we used a bioinformatics approach *(in silico)* that, through web-based tools and supplemental data available in literature, can predict the putative microRNAs involved in health microbiota. In this way, we were able to hypothesize new regulatory mechanisms associated to microbiota driven immune dysregulation and its implication with aging. Indeed, i*n silico* biology which refers to computational models and simulations applied to complex biological phenomena is a potent tool to obtain quantitative insights into regulatory networks and processes. Due to the vast amounts of data generated by molecular analyses, computational biology is increasingly exploited to filter big amount of data. *In silico* applied to vast amounts of biological data uses sophisticated algorithms to advance scientific understanding. The retrieved information can then be experimentally validated or serve as a guide for future investigations. We consulted different databases for microRNAs pathway prediction, microbiota integrated pathways, clusters % match with other species (Dietary microRNA Database) and to filter common pathways (SID1.0). The aim of our *in silico* approach is to study the possible miRs-mediated interactions between the healthy microbiota and host and to explore the impact of nutrition on maintaining the health status, with a specific focus on the inflamm-aging process.

## 2. Materials and methods

### 2.1. Data collection

We used PubMed free resource (https://www.ncbi.nlm.nih.gov/pubmed/) to collect papers from literature related to food and microbiota impacting to inflamm-aging. This data search helped us to collect miRs information contained in feces relevant for aging and inflammation. For this purpose, the combination of the following terms has been used in the search box: microbiota health interactions, immunity, inflamm-aging, microRNA, food and nutrition. We focused our attention on miRs able of shaping microbiota and of modulating inflamm-aging processes. These collected miRs were all experimentally validated in the papers we have selected.

### 2.2. Bioinformatics in silico analysis

We exploited different bioinformatics repositories and tools to analyze microbiota (Ruminococcus; Prevotella; Oscillibacter species) associated pathways, microRNAs modulated pathways, dietary microRNAs and common microbiota/microRNAs pathways. These tools are reported below.

DIANA tool (http://snf-515788.vm.okeanos.grnet.gr/) has been used for the prediction of the pathways modulated by microRNAs. Since DIANA can utilize experimentally validated miRNA interactions derived from DIANA-TarBase, we retrieved the KEGG Pathway IDs (strings) modulated by each miRNAs (Annex 1 in Supplementary data) and used them for SID1.0 analysis. MicroRNA nomenclatures used for the analysis were the following: hsa-miR-21-3p; hsa-miR-21-5p; hsa-miR-155-3p; hsa-miR-155-5p; hsa-miR-146a-3p; hsa-miR-146a-5p; hsa-miR-146b-3p; hsa-miR-146b-5p.

PATRIC (https://patricbrc.org/) tool has been used to find the metabolic pathways related to the genomes of Ruminococcus, Prevotella and Oscillibacter species. PATRIC puts together data from sources, data types, molecular entities and organisms. Data are collected from public repositories, for instance NCBI, the United States Department of Agriculture, the Centers for Disease Control (CDC) and other NIAID-funded projects, such as the System Biology for Infectious Disease Centers, as well as from studies published by researchers. The search tool was used to insert the name of each species and the KEGG IDs (Strings) has been used for SID1.0 analysis (Annex 2 in Supplementary data).

DMD database (Dietary microRNA Database: http://sbbi-panda.unl.edu:5000/dmd/browse) has been used to retrieve food containing microRNAs (miR-155, miR-146a and miR-21) with 100% clusters percentage match with human.

SID1.0 tool is a simple string identifier that has been used to filter the common microbiota/microRNAs pathways (strings of KEGG Pathway ID) obtained from PATRIC and DIANA tools retrieving common strings (Annex 3 in Supplementary data). All the information regarding the tools and repositories we used are reported in the webpage of the tools/repositories quoted. In the flow chart in Fig. 1 the followed road map is reported.

## 3. Results

### 3.1. MicroRNAs involved in the crosstalk between microbiota and host

From our data search we observed that feces contain miRs relevant for aging and inflammation processes. Based on our previous experiences we selected from the literature three miRs, namely miR-155, miR-21 and miR-146a as markers of inflamm-aging sensing. From the data

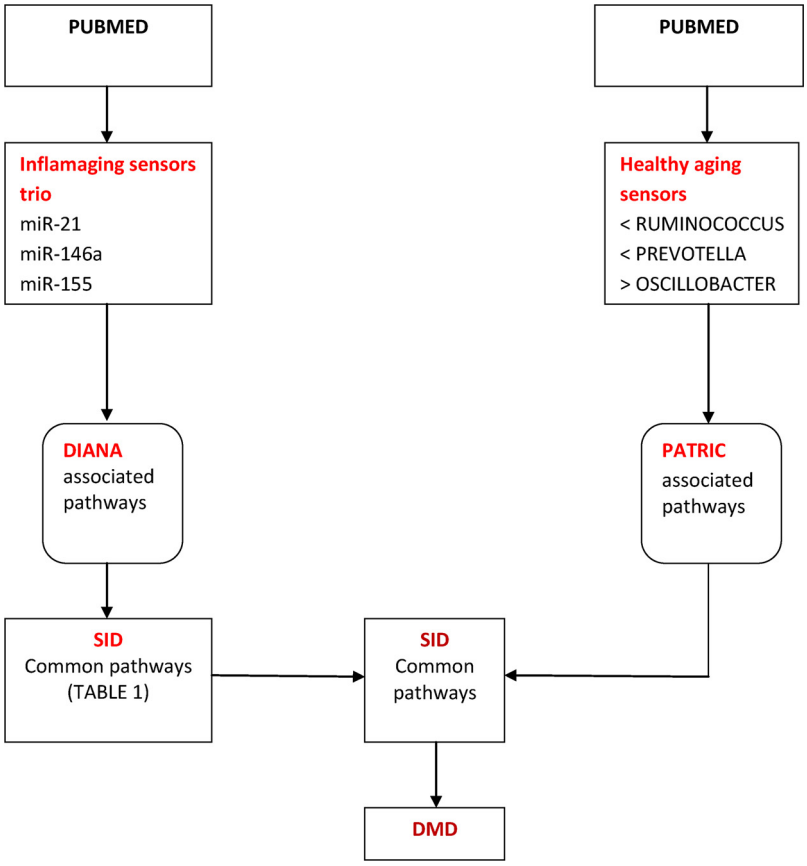


**Fig. 1.** Flowchart of visual representation of the sequence of steps applied to perform our *in silico* study.

**Table 1**
MiR-21, miR-155 and miR-146a common pathways analyzed with SID1.0 (the pathways have been retrieved with DIANA tool). Common pathways were found only with the combination of 2 miRs out of three, no common pathways between all the trio-miRs have been found.

| KEGG Pathway ID | Pathway name | Common microRNAs |
|---|---|---|
| hsa05142 | Chagas disease (American trypanosomiasis) | miR-146a; miR-155 |
| hsa05321 | Inflammatory bowel disease (IBD) | miR-146a; miR-155 |
| hsa04064 | NF-kappa B signaling pathway | miR-146a; miR-155 |
| hsa05161 | Hepatitis B | miR-146a; miR-155 |
| hsa05203 | Viral carcinogenesis | miR-146a; miR-21 |
| hsa04012 | ErbB signaling pathway | miR-146a; miR-21 |
| hsa04520 | Adherens junction | miR-155; miR-21 |
| hsa05223 | Non-small cell lung cancer | miR-155; miR-21 |
| hsa05219 | Bladder cancer | miR-155; miR-21 |
| hsa05212 | Pancreatic cancer | miR-155; miR-21 |
| hsa04110 | Cell cycle | miR-146a; miR-21 |
| hsa05210 | Colorectal cancer | miR-155; miR-21 |
| hsa00310 | Lysine degradation | miR-146a; miR-21 |
| hsa05220 | Chronic myeloid leukemia | miR-155; miR-21 |
| hsa00062 | Fatty acid elongation | miR-155; miR-21 |

collected, these three candidate miRs were found to be able of modulating inflamm-aging processes (Olivieri et al., 2013) and of shaping microbiota. The pathways associated to each miR of the trio were retrieved using DIANA tool. Subsequently, the search for common pathways was carried out inquiring SID1.0. This analysis demonstrated that common pathways were found with two by two miRs combination only. As indicated in the Table 1, many of the pathways regulated by these miRs are involved in immune system processes indicating that these processes are mainly involved in the crosstalk between microbiota and host.

### 3.2. Pathways associated to healthy microbiota, miR-21, miR-155 and miR-146a

Literature search evidenced that gut microbiota composition correlates with diet and health in the elderly and it is mainly associated either to a decreased amount of Ruminococcus/Prevotell and to an increased amount of the Oscillibacter as reported by Claesson et al. Thus, these three enterobacters have been taken as indicative of healthy aging.

By inquiring PATRIC tool we were able to find the pathways associated to healthy aging bacteria (Annex 2 in Supplementary data). We combined with that of Table 1 (pathways associated to each of the trio miRs) and inquiring SID1.0 analysis we, thus, retrieved the common pathways to bacteria and miRs as demonstrated in Table 2. As showed from the data reported in Table 2 common pathways to all of them were not found. We found the common pathways with the combination of 5 and 4 out of the six items (Annex 3 in Supplementary data).

Our results indicate that the miRs we selected, and the bacteria considered may modulate: Amino Acid Metabolism, Lipid Metabolism, Cofactors and Vitamins Metabolism, Glycan Biosynthesis and Metabolism.

### 3.3. Food derived microRNA match with human microRNAs

Based on the fact that the analysis presented in Table 2 demonstrated that miR-21, miR-155 and miR-146a can probably modulate gut associated metabolism and could be involved in inflamm-aging process and on the observation that diet is emerging as the most critical determinant in human health and healthy aging, we inquired into the web platform DMD to retrieve information about foods containing such miRs. The results are reported in Table 3. As indicated in Table 3 cow fat/milk, chicken (and chicken egg), Atlantic salmon and pig possess

**Table 2**
MiR-21, miR-155, miR-146a, Ruminococcus, Prevotell and Oscillibacter common pathways analyzed with SID1.0 (the pathways have been retrieved with Diana tool, mirpath v.3 for miRS and with PATRIC tool for microbiota). Common pathways to all of them were not found. We found the common pathways with the combination of 5 and 4 of them out of 6 elements (trio-miRs and trio-bacteria).

| KEGG Pathway ID | Pathway name/Pathway class | Common microRNAs/microbiota |
|---|---|---|
| hsa00310 | Lysine degradation/ Amino Acid Metabolism | miR-21; miR-146a/ Ruminococcus; Prevotell; Oscillibacter |
| hsa00062 | Fatty acid elongation in mitochondria/ Lipid Metabolism | miR-21; miR-155/ Ruminococcus; Prevotell; Oscillibacter |
| hsa00670 | One carbon pool by folate/ Metabolism of Cofactors and Vitamins | miR-146a/ Ruminococcus; Prevotell; Oscillibacter |
| hsa00601 | Glycosphingolipid biosynthesis - lacto and neolacto series/ Glycan Biosynthesis and Metabolism | miR-146a/ Ruminococcus; Prevotell; Oscillibacter |
| hsa00290 | Valine, leucine and isoleucine biosynthesis/ Amino Acid Metabolism | miR-21/ Ruminococcus; Prevotell; Oscillibacter |
| hsa00071 | Fatty acid metabolism/ Lipid Metabolism | miR-21/ Ruminococcus; Prevotell; Oscillibacter |
| hsa00061 | Fatty acid biosynthesis/ Lipid Metabolism | miR-21/ Ruminococcus; Prevotell; Oscillibacter |
| hsa00100 | Steroid biosynthesis/ Lipid Metabolism | miR-155/ Ruminococcus; Prevotell; Oscillibacter |

**Table 3**
DMD has been used to find the percentage match between food and human miR-21, miR-155 and miR-146a.

| | miR-21 | miR-155 | miR-146a | % Match (Dietary species in DMD) |
|---|---|---|---|---|
| **Cow microRNA fat (bta-)** | bta-miR-21-5p | bta-miR-155 | bta-miR-146a | 95.65% gga-miR-155<br>**100 % hsa-miR-155-5p**<br>100 % ssa-miR-155-5p |
| **Cow microRNA milk (bta-)** | bta-miR-21-5p<br>bta-miR-21-3p | bta-miR-155 | bta-miR-146a | 95.65% gga-miR-155<br>**100 % hsa-miR-155-5p**<br>100 % ssa-miR-155-5p |
| **Orange microRNA fruit (csi-)** | – | – | – | – |
| **Chicken egg MicroRNA (gga-)** | gga-miR-21-5p | – | gga-miR-146a-5p | **100 % hsa-miR-21-5p**<br>100% ssc-miR-21<br>**100%hsa-miR-146a-5p**<br>100% ssc-miR-146a-5p |
| **Chicken MicroRNA (gga-)** | gga-miR-21-3p | gga-miR-155 | gga-miR-146a-3p | 95.45% bta-miR-155<br>**95.45%hsa-miR-155-p**<br>95.45% ssa-miR-155-5p |
| **Soybean MicroRNA (gma-)** | – | – | – | – |
| **Human MicroRNA, breastmilk (hsa-)** | hsa-miR-21-5p<br>hsa-miR-21-3p | hsa-miR-155-5p | hsa-miR-146a-5p | 100 % gga-miR-21-5p<br>100 % ssc-miR-21<br>100 % bta-miR-155<br>95.65% gga-miR-155<br>100 % ssa-miR-155-5p |
| | | | hsa-miR-146a-3p | 100 % gga-miR-146a-5p |
| | | hsa-miR-155-3p | | 100 % ssc-miR-146a-5p |
| **Apple MicroRNA (mdm-)** | – | – | – | – |
| **Banana MicroRNA (msp-)** | msp-miR-21<br>msp-miR-21* | msp-miR-155<br>msp-miR-155* | msp-miR-146<br>msp-miR-146* | –<br>– |
| **Rice MicroRNA (osa-)** | – | – | – | – |
| **Tomato MicroRNA (sly-)** | – | – | – | – |
| **Atlantic salmon MicroRNA (ssa-)** | ssa-miR-21a-5p<br>ssa-miR-21a-3p<br>ssa-miR-21a-2-3p<br>ssa-miR-21b-5p<br>ssa-miR-21b-3p | ssa-miR-155-5p | ssa-miR-146a-5p | 100% bta-miR-155<br>95.65% gga-miR-155 |
| | | ssa-miR-155-3p | ssa-miR-146a-3p<br>ssa-miR-146a-3-3p<br>ssa-miR-146b-5p<br>ssa-miR-146b-3p<br>ssa-miR-146d-5p<br>ssa-miR-146d-3p<br>ssa-miR-146d-2-3p | **100% hsa-miR-155-5p** |
| **Pig MicroRNA (ssc-)** | ssc-miR-21 | ssc-miR-155-3p | ssc-miR-146a-3p | **100% gga-miR-21-5p**<br>**100% hsa-miR-21-5p** |
| | | ssc-miR-155-5p | ssc-miR-146b | 95.24% hsa-miR-146b-5p |
| **Wheat MicroRNA (tae-)** | – | – | – | – |
| **Grape MicroRNA (vvi-)** | – | – | – | – |
| **Corn MicroRNA (zma-)** | – | – | – | – |

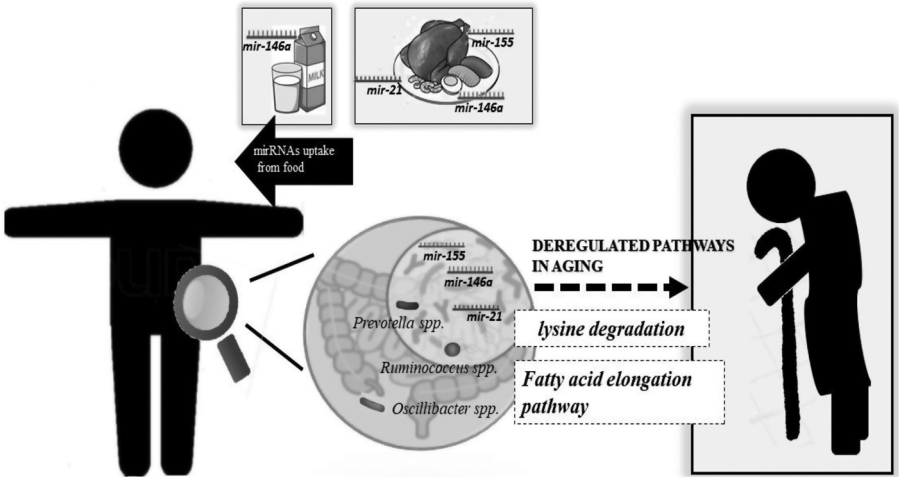


**Fig. 2.** Graphical representation of the results indicating an interaction among foods, host microbiota and aging through the common pathways lysine degradation and fatty acid elongation.

one or two inflamm-aging miRs with a 100% match with the same human microRNAs. All the other aliments indicated in the Table 3 do not have these microRNAs or do not matches 100% with humans. It must be noted that not many foods have been tested yet for miRs libraries. It's interesting to note that human breast milk used only by neonates, has 100% matches for the 3 inflamm-aging miRs from animal foods. The fact that breast milk is limited to weaning probably indicates that this aliment is not a suitable food for adults, and this represents an interesting observation.

### 3.4. Gut microbiota, inflamm-aging miRs, diet and signaling pathways

Lysine degradation pathway and fatty acid elongation pathways were the two most representative pathways (five out of six elements in common) as demonstrated in Table 2. Indeed, these pathways are found common to miR-21; miR-146a/ Ruminococcus; Prevotell; Oscillibacter. In Fig. 2 are graphically represented these converging routes, taking together the results from Tables 1–3.

## 4. Discussion

We demonstrated here, through a bioinformatics *in silico* study, that a cross-talk among i) gut microbiota, ii) human inflamm-aging miRs, and iii) foods might occur. This suggests that diet induces epigenetic modifications and these modifications work together in various combinations with gut microbiota and host, targeting signalling pathways relevant for contrasting or exacerbating inflammation associated senescence. The debate about gut microbiota miRs existence and their capacity to modulate human mRNA transcripts is a hot topic and a controversial issue. However, epigenetic crosstalk between different kingdoms, especially regarding exosome or vesicle like particles cross-talk between kingdoms is becoming more and more evident and it can be relevant for the aging phenotype outcome (Williams et al., 2017). In addition, recent studies suggest that miRs not only are synthesized endogenously, but also might be obtained from dietary sources (Quintanilha et al., 2017). We previously defined a set of miRs, namely: miR-146, miR-155, and miR-21, which play a central role in the interplay among DNA damage response, cell senescence and inflammation and yield a well-recognized role in aging and development of aging related diseases (ARDs) in humans (Olivieri et al., 2015; Carotenuto et al., 2016). We found here that this trio-miRs shows inflammation related pathways in common (Table 1). Noteworthy, the analysis presented in Table 2 demonstrated that miR-21, miR-155 and miR-146a share common molecular pathways with some of gut microbiota demonstrating that this trio-miRs can actually modulate the gut associated metabolism. Among the common molecular pathways, we found that lysine degradation and fatty acid elongation in mitochondria are the most represented being common to 4 out of the five items considered, namely: miR-21; miR-146a; Ruminococcus; Prevotell; Oscillibacter (for lysine degradation pathway) and miR-21; miR-155; Ruminococcus; Prevotell; Oscillibacter (for fatty acid elongation in mitochondria). Vital et al. (2014) demonstrated that acetyl-coenzyme A (CoA) is the microbiota most prevalent pathway (mean, 79.7% of all pathways), followed by the lysine pathway (mean, 11.2%). On the other hand, acetyl-CoA is a lysine degradation pathway product. Indeed, in mammals, lysine is metabolized to acetyl-CoA; an acetyl-CoA rise induces the increase of the overall acetylation of cytoplasmic proteins, as well as the impairment of autophagy (Mariño et al., 2014). Acetyl-CoA is a central molecule connecting the catabolism of glucose, fatty acids, and amino acids, thus it is a key metabolite at the intersection of catabolic and anabolic metabolism being a major acetyl donor in cells.

It is worthwhile to note that the mammalian degradation of lysine proceeds via two distinct routes, the saccharopine and the pipecolic acid route. In mammalian brain an age-dependent lysine degradative pathway occurs, and the pipecolate pathway emerged as the main catabolic pathways, whereas the saccharopine pathway prevails in developing brain (Hallen et al., 2013). Indeed, lysine degradation pathway dysregulation has been associated to neurodegeneration in elderly. In addition, lysine plays several others important roles in humans, like proteinogenesis, crosslinking of collagen polypeptides, uptake of essential mineral nutrients, production of carnitine, which is key element in fatty acid metabolism and elongation. The growing fatty acid chain is elongated by the sequential addition of two-carbon units derived from acetyl-CoAGenes of fatty acid elongation pathway were decreased in intestinal microbiome of patients suffering from neovascular age-related macular degeneration (Zinkernagel et al., 2017). Indeed, it has been suggested that fatty acid chain elongation is decreased with age (Jimenez et al., 1997).

Apart from the above discussed cross-talk between microbiota and host organism, diet is the other key element modulating host response to inflammation. Diet is emerging as the most critical determinant in human health and healthy aging, thus suggesting that the study of the effects of food derived inflamm-aging miRs are urgently needed to elucidate whether some foods should be avoided in the aging people diet since they could harmfully regulate both inflammation related metabolism and healthy gut, thus contributing to unhealthy aging. With this in mind, we inquired the DMD (Dietary MicroRNA Database) web platform to retrieve foods derived miR-21, miR-155 and miR-146a that are 100% homologues to human (Table 3). Our results suggest that cow fat, cow milk, and eggs are rich in this trio-miRs (100% homologues to

human) and thus might target inflammation related pathways. Conversely none of the plant aliments in DMD yielded the inflamma-miRs trio. Thus, the information retrieved by enquiring the DMD repository would suggest restricting cow fat, milk and eggs and increase plant aliments which do not contain any of these trio-miRs. Of note is that human breast milk has 100% matches for the 3 inflamma-miRs from animal foods. Human breast milk is a particular nutrient used from birth to weaning only, and it is interesting that has a 100% match with animals (pig, caws, atlantic salmom, gallus) homologous miRs to be avoided in diet.

In order to uncover the network linking gut microbiota, inflamma-miRs, and diet we speculate on the possible converging signalling pathways. In Fig. 2 are reported some of these converging routes, crossing the results of Tables 1 and 2. As discussed above, lysine degradation pathway and fatty acids elongation pathways were the two most representative pathways (four out of six common elements). A cross talk between these two pathways is also evidenced from biochemical studies, as for example through carnitine production (lysine degradation) and fatty acids elongation (Longo et al., 2016).

Furthermore, some of the direct target of the inflamma-miRs trio are straightforwardly involved in the modulation of oxidative stress and autophagy. As for example miR-21 has as direct target BCL2 an antioxidant proteins family. A reduction of this protein suppresses mitophagy.

## 5. Conclusions

We demonstrated here, through a bioinformatics *in silico* research, that a cross-talk among gut microbiota, humans inflamm-aging miRs, and foods may occur through the sharing of signalling pathways. These pathways are relevant for contrasting or, *viceversa*, exacerbating inflammation associated senescence. Indeed, we postulate by this computational study that a putative multi-directional communication among i) microbiota; ii) dietary metabolism and iii) host metabolism exists. Dietary microRNAs affect pathways that regulate microbiota composition and gut microbiota affect these pathways as well. MicroRNAs act as a link between the two systems and both tune the host metabolism. Obviously, this observation must be validated experimentally, however we believe that this hypothesis is worthy and pave the way to the study of cross-talk among the systems.

Unfortunately, this scientific approach is still in its infancy, not many nutrimiromics studies are yet carried out and some show contradictory results. In addition a very few miRs food repositories are available as yet (Quintanilha et al., 2017). DMD for example contains miRs library for 15 aliments only. This fact highlights the urgent need for more research devoted to the study of the epigenetic role of foods and microbiota and the importance of nutrition for inflammation related aging.

## Ethical statement for solid state ionics – diffusion and reactions

All the authors: Laura Teodori, Ilaria Petrignani, Angelica Giuliani, Francesco Prattichizzo, Felicia Gurău, Giulia Matacchione, Fabiola Olivieri, Sofia Coppari, Maria Cristina Albertini

Testify that:

1) This material has not been published in whole or in part elsewhere.
2) The manuscript is not currently being considered for publication in another journal.
3) All authors have been personally and actively involved in substantive work leading to the manuscript and will hold themselves jointly and individually responsible for its content.

## Declaration of Competing Interest

The authors declare no commercial or financial conflict of interest.

Guardare se questa Rivista lo vuole scritto qui o su una dichiarazione a parte

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.mad.2019.111127.

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