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Lectures

Selected Lectures of the Meeting "Environment and Health: Messages from the Future"

CAGLIARI (ITALY) · OCTOBER 26TH, 2024

The Meeting "Environment and Health: Messages from the Future" is a Satellite Meeting of the 20th International Workshop on Neonatology and Pediatrics, Cagliari (Italy), October 23rd-26th, 2024.

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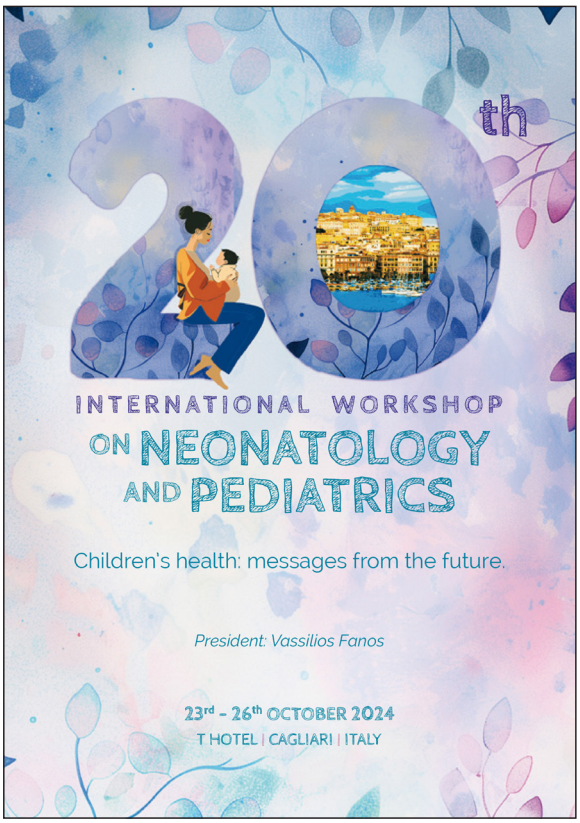

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LECT 1

MATERNAL MILK STEM CELLS: WHICH ROLE IN PERINATAL PROGRAMMING OF ADULT DISEASES?

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A new vision of maternal milk has emerged in the last years, moving from the theory of a peculiar mix of nutrients, towards a complex and partly unrevealed system, in which nutrients are associated to growth factors, microRNAs and multiple cell pools, with different functions. A cell pool, mainly formed by lymphocytes and monocytes, has an important function in protecting newborns from the huge amount of microbes they have to counteract after birth. According with recent research, breastfeeding protects lactating newborns from multiple infectious agents. This protection appears significantly more relevant in preterm babies, due to their immature innate and adaptive immune system. Another milk cell pool, mainly formed by stem/progenitor cells, may play a likewise important role in postnatal development. The huge amounts of stem cells present in maternal milk have the potential ability to differentiate into multiple cell types of ectodermal, mesodermal and endodermal origin, including neurons and glial cells. The huge amount of stem cells contained in the colostrum and in breast milk in the different lactation phases needs some answers to the following question: which role in the newborn development?

Stem/progenitor cells present in maternal milk may survive in the gastric environment, can cross the intestinal barrier, entering into the blood stream, and can be located into the breastfed newborn organs. In experimental animals, the presence of maternal cells has been demonstrated in multiple organs of the lactating neonates, in whom they give rise to a microchimerism. These findings allow a first answer to the question on the role of these progenitor cells sent by the mother to the son through breast milk. Given their ability to enter the newborn organs, the hypothesis that milk stem cells might be involved in postnatal development appears not only suggestive and intriguing, but also likely.

According with this new vision of maternal milk, stem/progenitor cells embedded in milk could represent the tool utilized by lactating mothers for continuing a "developmental training" even after birth. Preterm neonates could benefit particularly from this training, due to the immaturity of preterm organs.

The consequences of this hypothesis are many and all intriguing. First, breastfeeding appears as a fundamental step in postnatal development, due to the ability of maternal stem cells to integrate into the neonatal organs, boosting and propelling their development. This maternal developmental aid should be significantly higher in preterm and in low birth weight infants, in whom breastfeeding should be considered as mandatory. The second consideration regards the effects at long time of this "developmental training" exerted by milk stem cells. According with the J.P. Barker's theory on fetal programming of adult diseases, factors negatively influencing intrauterine and perinatal development of fetal organs should predispose newborns to the insurgence of multiple diseases later in life. In short, kidneys with a low nephron burden might undergo the insurgence of renal diseases later in life more frequently than infants with a higher nephron burden. Maternal milk stem cells might represent the physiological answer to an incomplete development of the newborn. Increasing the number of neurons and glial cells, thanks to breastfeeding, small-for-date and preterm newborns might escape the insurgence of neuropsychiatric disorders in childhood or in adulthood. These hypotheses are fascinating, but they should be confirmed by further studies. Given that nephrologists accepted the suggestion to ask their patients their birth weight, as a sign of intrauterine development, a second suggestion is to ask if they were breastfed and how long.

LECT 2

MICROPLASTICS, ENVIRONMENT AND CHILDREN HEALTH

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In recent years, there has been a marked increase in scientific publications on microplastics (MPs) generally defined by their size (less than 5 mm). It should be emphasized that this definition does not consider some significant characteristics, such as shape, chemical composition, and color.

The increased interest is due to various factors, such as: their widespread diffusion in the terrestrial, aquatic [1], and atmospheric environment (widely justified by the fact that in most cases they are secondary to the fragmentation of plastic objects, which is known to be the element of greatest environmental pollution); the recognized damage that they can cause in various ecosystems by altering flora and fauna; and more recently the demonstration that they can penetrate the human body especially through the respiratory and gastrointestinal tract, spreading and accumulating in various organs and systems.

It follows that the fundamental question to which we are trying to give an answer today concerns the possible damage to human health.

Most researchers agree that there are not yet definitive elements to give a scientifically robust answer to this question. However, it should not be forgotten that numerous *in vitro* and *in vivo* studies on experimental animals (which require further evidence and more shared and homogeneous methodological approaches) have highlighted various mechanisms through which biological damage can be achieved. MPs can in fact determine alterations through three modalities (physical action, release of additives used for the production of plastic objects, release of exogenous pollutants) with consequent cytotoxicity, inflammation, endocrine disruption, oxidative stress, and genotoxicity. It is therefore advisable, especially in the pediatric field due to the known greater sensitivity of the fetus and child to toxic elements, to use a precautionary attitude, by limiting as much as possible contact with plastics during fetal life (MPs can cross the placenta and reach the fetus) and the first postnatal years [2]. Finally, the relationship between researchers, clinicians, and the mass media should not be overlooked, considering the conclusions of a recent review on this important aspect [3]: the representation of plastic and MPs pollution in the media has increased over time, influencing the perception of this risk; the study posits the necessity for accurate and balanced media reporting on MPs to prevent the dissemination of misinformation and ensure that people have a clear understanding of the risks associated with MPs; furthermore, a more detailed examination of people's perceptions lends support to the design of appropriate interventions to reduce plastic consumption, thereby decreasing the risks of MPs pollution, which in turn offers benefits for human health and the environment.

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LECT 3

ENDOCRINE DISRUPTORS (EDs) AND PERINATAL PROGRAMMING

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Endocrine disruptors (EDs) are represented mainly by chemicals that can act within the body mimicking or inhibiting hormones. Contact occurs through inhalation, skin contact and ingestion, and prenatally through placental circulation. Once in the body, they react with the internal chemistry that will largely depend on the presence of chronic diseases, drugs, inflammatory conditions, oxidative stress, etc., giving origin to different metabolites and individual responses with a measurable exposome [1]. The latter interacts with the individual's genomics, and depends on the individuals' transcriptomics, giving origin to a resposome. The latter can lead to disease or health can be maintained [1].

Whereas exposure to EDs in early childhood and adolescence is related with developmental changes, and later in life one observes the endocrine effects mainly on the hypothalamus-pituitary-gonadal and -adrenal axes, prenatal exposure is related with epigenetic changes that can predispose to disease

by modifying genetic programming. This provides a molecular explanation to the Developmental Origins of Health and Disease (DOHaD) theory put forward by J.P. Barker in the eighties. Epigenetics refers largely to DNA methylation, histone acetylation and to non-coding RNAs, including the miRNA network that throughout life turns on and off genes. We currently know that there is an enormous difference in the genes expressed from early childhood with respect to puberty and adulthood [2]. Exposure to several different EDs has been reported to affect bone growth and metabolism [3]. Recent studies have shown how exposure of human mesenchymal cells to mixtures of chemicals found in the urine of pregnant mothers can cause the accumulation of intracellular lipids and modify DNA methylation status. Most of the scarce studies showing a relationship between exposure to EDs (mainly phthalates, parabens and bisphenols), in humans, come from studies that use biological samples from adults, and concern mostly DNA methylation. Mitochondrial DNA methylation and histone modifications are also reported. In the fetus, more recent studies have shown changes in the expression of non-coding RNAs causing thyroid dysfunction. Interestingly, in medaka fish, exposure to triclosan a few hours after fertilization is associated with developmental changes and DNA hypomethylation. Extracellular vescicles are of increasing interest as carriers of important epigenetic material; however, it is largely unknown how EDs affect number, size and content. A few *in vivo* studies have shown that epigenetic changes are found mainly in gametes and are passed on to further generations (transgenerational effect).

Overall, the evidence is that modifications in epigenomic plasticity occur owe to ED exposure during fetal life, with subsequent reprogramming of gene expression. The effects of mixtures of chemicals and interactions with other contaminants as mycotoxins, effects of climate change, microplastics, particulate matter, etc. remain unknown.

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LECT 4

THE LIFE MILCH PROJECT: UPDATES AND PERSPECTIVES

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The Life MILCH ("Mother and Infant dyads: Lowering the impact of endocrine disrupting Chemicals in milk for a Healthy Life" [1]) project is a longitudinal study aimed at reducing the impact of endocrine disruptors (EDs) on children health, with breastmilk as a main biomarker of exposure. EDs are environmentally ubiquitous chemicals that can interfere with the hormonal system and induce adverse health effects in exposed populations and/or their progeny [2-4]. In the first phase, 689 pregnant women were enrolled in three obstetric centers (Cagliari, Parma, Reggio Emilia – Italy). They were recalled with their children at 1, 3, 6, and 12 months of age for assessing infant development and collecting urine samples and breastmilk. Biological samples were analyzed for presence and levels of different EDs (phthalates and their metabolites, bisphenols, polycyclic aromatic hydrocarbons, glyphosate, parabens, pyrethroid insecticides, heavy metals). At any timepoint, mothers filled questionnaires on their lifestyle and nutritional habits.

Preliminary results indicated that bisphenol A, phthalates, and parabens were present in over 50%

of urine and breast milk samples. When detected in mothers' urine during pregnancy, bisphenols were likely to be detected in their infants' urine. Parabens and phthalates detected in breast milk at 1 and 3 months predicted their presence in infants' urine. Infant neurobehavioral development and Bayley-III scores were within normal ranges, but significant negative associations were found between maternal bisphenol, parabens and phthalate levels and socio-emotional behavior and neurodevelopmental scores. Maternal lifestyle and nutritional habits were associated with ED levels in mothers, breastmilk, and infants, to establish a risk assessment model and identify possible main sources of maternal exposure to EDs.

Based on this evidence-driven model, the project has developed a prevention/awareness campaign and interventions for reducing maternal exposure to EDs. Our hypothesis is that a change in food habits and lifestyle would reduce the levels of some EDs in the mother, the breastmilk and, consequently, in the infant. These prevention activities are carried out in the three project locations and with three specific targets: first involving pregnant women and breastfeeding mothers, and then women of childbearing age and health professionals. The efficacy of the prevention campaign and intervention is currently under assessment by a subsequent biomonitoring of the levels of EDs in the breast milk of the women who have participated in the campaign during pregnancy/nursing, including an assessment of their infants' ED exposure levels and development at 6 months of age (ongoing 2nd screening). Eventually, we will compare the results obtained in the 2nd screening with those obtained in the 1st screening, to assess whether specific interventions could effectively reduce and prevent exposure to specific EDs.

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LECT 5

POTENTIAL OF TERPINEN-4-OL AS AN ADDITIVE FOR THE PREVENTION OF BACTERIAL INFECTIONS IN NEONATAL BREASTFEEDING

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INTRODUCTION

Food safety is particularly critical in the neonatal period, where infants, especially premature or less than 2 months old, are vulnerable to the onset of invasive infections caused by pathogens such as *Salmonella enterica* and *Cronobacter sakazakii* (formerly known as *Enterobacter sakazakii*). Although the World Health Organization guidelines recommend a preparation temperature of infant formula at 70°C, studies have shown that this temperature does not guarantee the complete eradication of these microorganisms.

OBJECTIVE OF THE WORK

To present the potentially antibacterial properties of terpinen-4-ol, a natural compound patented by the Istituto Superiore di Sanità (the main centre for research, control and technical-scientific advice on public health in Italy), and its applications as an additive in the water used for the preparation of powdered infant formula.

METHODOLOGY

Recent research has shown that terpinen-4-ol has significant antimicrobial activities.

Several clinical and laboratory studies are underway to evaluate the efficacy of this molecule in counteracting the growth of pathogens also in the preparation of aqueous solutions for infant formula.

RESULTS

Preliminary data suggest that terpinen-4-ol is effective in significantly reducing the bacterial load of both pathogens under controlled conditions. The use of this molecule could contribute to greater food safety in infants, especially in settings where hygiene and handling of infant formula are critical.

CONCLUSIONS

Although terpinen-4-ol is not yet certified as a food additive, its antibacterial properties, supported by emerging studies, could pave the way for new practices to improve the safety of infant formula. It is essential to continue research to validate the efficacy of the molecule in clinical settings and to promote its approval as a safe additive for food use.

LECT 6

KANGAROO CARE AND NEW HAND MANAGEMENT TECHNIQUES

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Skin-to-skin contact (SSC) is beneficial for the physiological and behavioral stability of preterm infants, for breastfeeding and bonding between the infant and parents and seems neuroprotective in the long term in this population. Kangaroo care (KC) is a method of care in which preterm or low birth weight newborn is positioned naked with only a diaper, prone, in SSC on the parent's chest, adequately contained and covered. It is considered a simple and effective method for promoting the health and well-being of preterm and also full-term newborns. This treatment modality was developed for the first time in Bogotá in the 1970s to address the problems of premature births in healthcare facilities lacking incubators, overcrowded and with high rates of infections and mortality. Subsequently, the practice of KC rapidly developed also in high-income countries (Europe, America, Australia); it is currently used in all Neonatal Intensive Care Units (NICUs) of industrialized countries, for example to promote the first experiences outside the incubator between the newborn and his parents.

Numerous studies have highlighted that KC facilitates the adaptation and stabilization of the newborn, reduces pain response in case of procedures, improves the thermoregulation, oxygenation, heart rate variability and stabilizes respiratory activity, reduces the frequency and severity of apneas.

The World Health Organization strongly recommends introducing the practice of KC, as soon as the clinical conditions of the newborn are stable, for as long as possible and for the entire period of hospitalization. Consider that the minimum recommended time for each KC session should not be less than 60-90 minutes and that to adequately promote KC, the opening of NICUs 24 hours a day is essential, without time limits and with the active participation of mothers.

Absolute contraindications are: unstable newborns, mechanical ventilation for respiratory pathologies in the acute phase, acute phase of sepsis, skin infection of the parent, therapy with vaso-active drugs, presence of umbilical arterial catheter, jugular or femoral catheter, thoracic drains, abdominal drains.

A Japanese observational study identified SSC as one of the risk factors for methicillin-resistant *Staphylococcus aureus* (MRSA) infection. In contrast, a *Cochrane* review found that the KC program significantly reduced the risk of severe infection/sepsis, but only 33 of the 745 children were from high-income countries in the review. Hand hygiene and the use of 2% chlorhexidine skin antiseptics are some of the strategies that prevent late-onset sepsis.

Before the KC session, the parent washes his/her hands antiseptically; with warm hands, the parent must support the newborn at the level of the head, shoulder girdle, and the podium. The bio molecule terpinen-4-ol extracted from tea tree oil, *Melaleuca*, has antiseptic properties and could be used in the future as a replacement for commercial disinfectants.

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LECT 7

POTENTIAL OF ESSENTIAL OILS IN THE MANAGEMENT OF MICROBIAL INFECTIONS

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The development of microbial resistance to various drugs represents a major challenge in the medical field for the treatment of infections. The pharmaceutical industry has shown a general disinterest in investing in research on new antimicrobials despite decreasing effectiveness

of those available, often preferring research on more profitable drugs, at least until the recent past. Therefore, the limited number of effective available antibiotics has stimulated research into different therapeutic approaches or those that can be integrated with antibiotic therapy. Recently, to overcome this serious public health problem, scientific research groups have shown interest in the enormous biodiversity of the plant world, since the latter represents an important source of potential anti-infective molecules and more. In particular, the scientific literature has reported extensive documentation on the biological properties of essential oils (EOs), complex biochemical mixtures extracted from aromatic plants. EOs possess, both as a phytocomplex and as individual volatile organic components, various bioactivities, including an antimicrobial and modulating activity against various virulence factors, but have some features that require specific measures to facilitate their applications.

Recent studies have shown that EO-functionalized nanoparticles have significant antimicrobial potential against multidrug-resistant pathogens, both by increasing chemical stability and solubility and by decreasing the rapid evaporation and degradation of the active components of the EOs. However, little is known about interactions that lead to additive, synergistic, or antagonistic antimicrobial effects. Although the mechanism of action of some EOs components has been clarified in many pioneering works of the past, detailed knowledge of most EOs, their components and their mechanism of action is still lacking.

Considering these promising *in vitro* studies, future research should be encouraged to systematically study the mechanisms of action and synergy, also exploring new strategies for nanoencapsulation to reduce production costs. There are still few studies that explore the effectiveness of EOs or their components in the pediatric field. On the contrary, many herbal or cosmetic products are widely sold in pharmacies and/or herbalist's shops and recommended by pediatricians for the treatment or prevention of mild forms of pathologies, with special reference to microbial skin diseases or seasonal infectious pathologies.

To include EOs in the therapeutic armamentarium against microbial infections, inclusive of drug-resistant ones, further controlled clinical studies, to which the drugs are subjected, are obviously urgent and necessary to verify the safety of use and the effectiveness of these phytoextracts.

LECT 8

AFLATOXIN M1 IN MILK: SITUATION AND ANALYTICAL METHODS

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Aflatoxin M1 is a hydroxylated metabolite of aflatoxin B1 (a toxin produced by *Aspergillus flavus* and *Aspergillus parasiticus*) found in milk and dairy products. The presence of aflatoxin M1 occurs when dairy cattle ingest feed contaminated with aflatoxin B1.

The International Agency for Research on Cancer (IARC) has classified aflatoxin M1 as a class 2B carcinogen, and therefore monitoring it in milk and its concentration in the milk-to-cheese transition is of particular interest. This monitoring requires the possibility of capillary testing as many samples as possible in a short time, with simple methods and low cost. Immunochemical techniques such as LFD (lateral flow device) and ELISA (enzyme-linked immunosorbent assay) meet these needs in terms of both specificity and sensitivity. In contrast, a confirmatory analysis that achieves concentration levels well below the legal limits requires an instrumental type of analysis called HPLC (high performance liquid chromatography).

The maximum concentration in milk of aflatoxin M1 as far as the European Union is concerned is defined in Regulation (EC) No. 1881 of 2006. Currently, this limit is 50 ppt for the European Union and 500 ppt for the United States. Recital 21 of the aforementioned regulation states, "With regard to aflatoxin M1 in foods for infants and young children, a possible reduction of the current maximum level should be considered given developments in analytical procedures."

From the analytical point of view, it is important to remember that the validation of analytical methods based on an initial screening part and a subsequent confirmation allows a reduction in response time: a highly sensitive, but not necessarily specific, screening method allows the detection of definitely negative samples and the subsequent confirmation step only for uncertain presumptive positive samples, with important savings in reagents and human resources.

LECT 9

TOXICANTS AND TOXINS

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Toxic substances and toxins are ubiquitous in our environment, posing significant risks to human health and the ecosystem. We will explore the definition, classification, and mechanisms of toxicity, as well as the various routes of exposure and factors that affect the degree of harm caused by these substances.
Toxicants are substances that can cause adverse effects on living organisms, including humans, animals, and plants. They can be classified based on their chemical structure, source, or mechanism of action. Natural toxins (such as those produced by certain plants, animals, or microorganisms), as well as synthetic chemicals (like pesticides and industrial byproducts), are all considered toxicants.
Understanding the different types of toxicants is crucial in assessing their potential risks and developing appropriate mitigation strategies.
These metabolites can interfere with our molecular mechanisms causing metabolic, immune and endocrine damage.
In the diagnostics of monitoring toxicants and toxins, omics sciences, and especially metabolomics, play a primary role.
The examination of environmental toxicants and toxins is a fundamental step to direct personalized and targeted treatments, such as detoxification and nutritional pathways.

LECT 10

ONE HEALTH IN MEDICINE

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Proper management of Emergency Rooms is needed to improve healthcare and patient satisfaction, guiding resource allocation. Predicting access and hospitalisation rates through Machine Learning appears feasible and promising, especially when coupled with air pollution and weather data. This work further investigates, in a more detailed way, a previously presented approach that applied predictive algorithms to data related to clinical and environmental data in Brescia (Italy) from 2018 to 2022, to predict daily accesses or daily hospitalisations for cardiovascular or respiratory disorders. Starting from the previous work, that analysis was improved and widened to a greater geographical area. The applied algorithms' performances satisfactorily adhere to the actual data, especially when using the Support Vector Machine and Random Forest's models as regressors on daily accesses and respiratory disease-caused hospitalisations. Even if the specific value is not always correctly predicted, generally, the overall trend seems to be rightly forecasted, and performance metrics are rather satisfying. Although additional work could still be encouraged to improve the models' performances, results are rewarding and represent a new point of view on a complex and relevant matter. The real-life application of this One Health approach is now possible and could quite easily be adapted to other areas, too, with the final objective of improving the quality of healthcare and people's quality of life.

LECT 11

EPIGENETIC MODULATION OF INFLAMMATION IN THE AGE OF POLLUTION

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EPIGENETICS

In the prevention landscape, we have a need for more and more person-centered medicine, especially to know the causes of damage at the cellular level.
Epigenetics is the science devoted to the study of heritable genetic changes that, while not transforming the DNA sequence, cause alterations in gene expression. Therefore, it focuses on analyzing how factors such as age and exposure to environmental factors (e.g., diet, chemical and physical agents, physical activity) can alter the expression of an individual's genes.
What is the difference between genome and epigenome? The first and most important is related to the fact that the former remains constant in all cells and throughout life, while the latter changes with the passage of time and can change even between cells. The influence of the environment on these alterations in gene expression is extremely high, as our DNA reacts to numerous stimuli from outside. In practical terms, this means that the lifestyle and environment in which we live help

determine the expression of our genes through epigenetic mechanisms. Think, for example, of cigarette smoking, excessive alcohol consumption, air pollution, or, even better, food: the latter is by far the most recognized factor in its ability to influence our epigenome, because the decomposed molecules resulting from the foods we consume can alter the expression of our genes, and extremely rapidly, too! Epigenetic characteristics can thus change over the course of a lifetime, as environmental context, habits, and age change, and they can also be transmitted in two ways: from a cell to its daughter cells and from parents to their offspring. The set of compounds that can alter a person's epigenome is considered a very important topic of study in current science, especially from the perspective of the now well-known 4P Medicine, because it is now well established that epigenetics can influence an individual's risk of developing a variety of diseases, some of which very serious. However, although there are also very different epigenetic mechanisms that can alter gene expression, it is interesting to note that these changes can be reversible. This means that, by studying a patient's epigenome, it is possible to modulate treatment protocols specifically tuned to his or her unique characteristics, intervening in a precise and targeted way to reduce the risk of occurrence of certain diseases. In this context, the integration of a new technology, called S-Drive, capable of mapping epigenetic factors starting from the hair bulb, could be of interest. This technology offers the possibility of obtaining a personalized report, with indicators of epigenetic factors that could benefit cells (particularly vitamins, minerals, amino acids, antioxidant system, etc.), and especially highlighting polluting interference factors that could damage cells. This new device could be very useful to improve clinical and diagnostic accuracy and to support the instrumentations and analyses already in use in clinical practice.

EPIGENETICS AND PERINATAL PROGRAMMING

Epigenetics consists of all those modifications that regulate gene expression without altering the DNA sequence. Maternal characteristics (such as mitochondrial dysfunction and alterations of mitochondrial DNA, microcirculatory problems and constitution from birth, stress and nutritional status, BMI) and environmental factors (such as maternal smoking, smog, maternal sedentariness, etc.) can modify placental and fetal gene expression through epigenetic alterations (epigenetic inheritance), thus going to influence fetal programming. In particular, the maternal-fetal nutritional environment and pollution affect pregnancy outcomes by altering intrauterine development with effects that can become apparent at any time in an individual's future life. This is what the Developmental Origins of Health and Disease (DOHaD) theory describes, according to which the risk of disease in adults is modulated by factors *in utero* and since before conception. The epigenetic effect of many nutrients is well documented. Animal and, recently, human studies have reported how maternal intake of certain nutrients may or may not favor the placental and fetal epigenetic profile, leading to different pregnancy outcomes. Indeed, the diet of both parents affects the genetic modifications of the offspring, leading where incorrect (as in the case of maternal or paternal obesity) to the increased risk of developing cardiovascular and metabolic diseases, and affecting the plasticity of the central nervous system. Recently, it has also been reported that maternal diet and nutritional status can also induce modifications to the epigenetics of the fetus through changes in the fetal gut microbiome. Molecular characterizations that in recent years are elucidating the epigenetic mechanisms of fetal programming and metabolomics itself could be used in the future for early diagnosis and possible therapies for pregnancy diseases.

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