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Science, innovation and society

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Abstract

This session focused on emerging areas in biomedical research that are of key relevance to toxicology and, therefore, may influence EFSA's work. The impact on the way risk assessment is conducted in the area of food may be through the identification of novel ways through which chemicals affect human health or through the provision of novel tools that could support regulatory assessment methods. Four topics were presented in this session. These covered areas such as epigenetics, proteomics, metabolomics and microbiomics, which are currently the subject of major research and development in systems biology and are beginning to impact on regulatory assessment approaches and methodologies. One emerging concept common to all four presentations was the importance of epigenetic changes, irrespective of whether development, neurodegeneration, ageing or cancer is considered. The epigenetic modulation of gene expression has profound effects on health and lifespan. Indeed, disruptions caused by environmental, dietary, pharmaceutical, microbial or lifestyle agents during pregnancy are key determinants responsible for major quantitative and qualitative changes in the epigenetic control of health and disease, either directly or indirectly through modulation of our gut microbiota. Although gut microbes provide energy to the body by helping in the breakdown of dietary components that are not degraded by our own digestive system, the intestinal microorganisms also produce important signalling molecules that regulate our systemic immune and metabolic responses and hence the microbiome can profoundly affect human physiology and health. A better knowledge of the different layers of information (genome, transcriptome, epigenome, proteome, metabolome and microbiome) will be paramount for our understanding of how environmental factors can impact on health and disease and will contribute to the regulatory assessment approaches and methodologies of the 21st century.

Keywords: genomics, epigenetics, proteomics, metabolomics, microbiomics, neurodegeneration, reproductive endocrinology

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1. Aim of the session

This session addressed emerging areas in biomedical research that are of key relevance to toxicology and therefore may influence the European Food Safety Authority's (EFSA's) work, in particular, the identification of novel ways through which chemicals affect human health and the provision of novel tools that could support regulatory assessment methods.

The four presentations in this session covered areas such as epigenetics, microbiomics, neurodegeneration, cancer and the endocrinology of the reproductive system. All of these topics are currently the subject of major research and development in systems biology and are beginning to impact on regulatory assessment approaches and methodologies.

2. Scientific background

The impact of the intestinal microorganisms in human health is an area of extensive research. The human gut is the natural habitat for a large and dynamic bacterial community, yet a substantial part of these bacterial populations is still unknown. The intestinal microorganisms encode our 'other genome' with millions of genes, vastly surpassing the coding capacity of the human genome. Gut microbes not only generate metabolites from the breakdown of plant-based complex polysaccharides and phytochemicals to provide energy but also to act as signalling molecules that generate systemic immune and metabolic responses, and hence can profoundly affect human physiology and health.

Another actively researched area is that on disorders of the nervous system, both in children and in the elderly. In recent years, scientists have made great strides in understanding the genetic and environmental multifactorial aetiology of neurodevelopmental and neurodegenerative diseases. Specifically, the healthy vs diseased state may not only depend on the genetic information provided by the genome but also on epigenetic mechanisms that reflect the interactions with the environment through the covalent modification of DNA, protein or RNA. Epigenetic regulation can adapt faster and be inherited. Epigenetic changes have also been implicated in serious adverse health effects, including cancer. While the initiation of most cancers is an irreversible step occurring most likely by a mutation, the promotion of the cancer is an epigenetic mechanism, which is threshold-dependent, species-, gender- and organ-specific, and which is also a consequence of our lifestyle.

Finally, the endocrinology of the reproductive system is relevant to most biological disciplines, particularly biomedical sciences, ecology and chemical risk assessment. The development and function of the reproductive system in both sexes is coordinated and integrated with all bodily systems to ensure that reproduction is optimally timed and executed.

3. Summary of presentations

3.1. Food and health: the role of intestinal microorganisms in human health (Anne Salonen, University of Helsinki, Helsinki, Finland)

Microbes are an essential part of the human body. While the human body is composed of around 1,013 cells containing about 25,000 genes, the human gut is inhabited by around 1,014 microbial cells covering 103 or 104 species (the intestinal microbiota[1] or normal gut flora) and more than 5 million genes (Qin et al., 2010). The intestinal microbiota lives at the interface of the host and the environment. The intestinal microbiota is currently acknowledged as a third factor in the aetiology of many diseases, including obesity and other metabolic diseases (Salonen and de Vos, 2014). The gut immune system has evolved to live with the symbiotic microbes and food antigens while remaining responsive to pathogens (Maslowski and Mackay, 2011). The many functions of the intestinal microbiota identified so far include the digestion of food to produce energy and bioactive metabolites, the production of vitamins, the metabolism of xenobiotics and the training of the immune system. For example, colonic fermentation of dietary fibre results in the production of short chain fatty acids (SCFA), of which butyrate and propionate have well-documented beneficial effects on the gut and systemic health. Other bacteria may have adverse effects, such as those that convert dietary protein into metabolites increasing the risk of atherosclerosis and colorectal cancer. Hence, intestinal bacteria appear pivotal in mediating the health effects of foods. In addition, the intestinal microbiota has a protective function with respect to maintaining the integrity of the intestinal barrier and preventing colonisation.

[1] Synonym of microbiome = microbiota and their collective genome/functions.

The extent to which the gut microbiota is responsible for human diseases is not well known due to experimental limitations (Salonen and de Vos, 2014). Nevertheless, researchers have documented animal models of diseases with an established role of the microbiota. The implication of gut microbes in diseases makes them potential druggable targets and therapeutic agents. The current challenge is to understand how different environmental and host factors modify the diversity of microbiota. The goal is to unravel how intentional modification of the gut flora can contribute towards health. The majority of gastrointestinal microorganisms remain uncultured and uncharacterised. Current experimental approaches are based on the sampling of entire microbial communities and their analysis by omics approaches. These studies have revealed a large degree of variation in intestinal microbiota between individuals due to different diets (Jalanka-Tuovinen et al., 2011). These variations, consequently, have an impact on the metabolic production of bioactive metabolites such as SCFA. Studies have also reported the impact of artificial sweeteners and emulsifiers on the microbiota. Further studies have shown that the microbiome can very rapidly change in response to changes in the diet (Salonen and de Vos, 2014). In short, we all have a personalised yet dynamic microbiome. This opens the possibility for new potential therapeutic approaches through tailored nutrition. A major challenge though remains that the data from current animal models are not easily extrapolated to reflect the human microbiome.

3.2. Epigenetic factors and ageing (Pierluigi Nicotera, German Centre for Neurodegenerative Diseases, Bonn, Germany)

Longevity has increased considerably over the past 100 years. The speed of this change rules out a genetic basis but suggests that epigenetic mechanisms, such as DNA methylation, histone acetylation or the expression of non-coding RNAs, may be responsible for the higher life expectancy. Studies in diverse species have shown that diet (in particular, dietary restriction), exercise, stress, inflammation and infections are major factors that contribute to the observed altered longevity and senescence through such epigenetic changes (Benayoun et al., 2015). In particular, dietary restriction, a regular circadian cycle and exercise have a positive effect on health and lifespan. However, an increased lifespan also increases the risk of genomic vulnerability to stress factors or random errors.

The effect of caloric restriction was recently studied in rhesus macaques where it was shown that caloric restriction not only delays ageing and extends lifespan but also delays the onset of age-associated pathologies such as diabetes and brain atrophy (Colman et al., 2014). Recent evidence has identified the importance of a mitochondria-dependent metabolic decline with a shift in metabolism towards lipid metabolism over carbohydrate metabolism as being responsible for the appearance of the pathologies associated with insulin resistance. This is supported by work in the nematode *Caenorhabditis elegans* where genetic models with decreased insulin/insulin-like growth factor-1 signalling present significantly increased longevity (Kenyon, 2010).

Recent work on learning and memory has identified a critical role in histone turnover in neuronal plasticity. Of particular importance is histone H3.3, which constitutes the predominant form of histone H3 in non-dividing cells. It is found at sites of transcribed genes and has been implicated in chromatin remodelling and transcription. It has been suggested that it represents an epigenetic imprint of transcriptionally active chromatin and cell type-specific gene expression (Lippi et al., 2011; Michod et al., 2012; Maze et al., 2014).

3.3. Key developments in the research into reproductive endocrinology (Richard M. Sharpe, University of Edinburgh, Edinburgh, United Kingdom)

Reproduction plays a key role in life because it enables us to pass on our genes to the next generation. Of crucial importance are the reproductive hormones that regulate or modulate body appearance; composition and growth; the development and function of many organs (including the brain); and puberty, sex drive/function and fertility. However, as a result of the male–female differences, the relative risk in males vs females for a number of diseases, including cardiovascular diseases, visceral obesity, most cancers and kidney disease, is substantially higher.

The commonest reproductive disorder of the developing and young adult male is testicular dysgenesis syndrome. Current evidence suggests that this disorder is caused by androgen deficiency in the 'masculinisation programming window', which is critical for determining normal reproductive development and ultimate reproductive organ size during gestation (Welsh et al., 2008). Lower

testosterone levels are associated with lower birth weight (in males) and, in turn, are associated with a higher risk of adult obesity and cardiovascular disease (Vanbillemont et al., 2010). Furthermore, intra-abdominal fat in men is associated with decreases in the levels of testosterone and increases in insulin resistance. In women, increased androgen exposure during fetal life leads to polycystic ovary syndrome and insulin resistance. Therefore, the disease risks associated with subnormal testosterone levels in adult men are similar to those occurring in women with supranormal testosterone levels. The same disorders are positively associated with dietary effects.

Twin studies suggest that 40–70% of obesity is inherited, yet so far genetic explanations can only account for < 5% of obesity. While there is no denying that over-consumption of calories is what makes us fat, recent work has highlighted the importance of epigenetic changes and is suggesting that sperm (and/or seminal plasma) are transferring epigenetic information that may modify the function of DNA in the resulting offspring. Therefore, an over-consumption of calories may also negatively affect subsequent generations.

3.4. Understanding complex mechanisms in determining adverse and beneficial health effects with nutrition/diets: from basic Science of Hazard identification of the concept of 'one health-one planet' (James E. Trosko, Michigan State University, East Lansing, MI, USA)

In order to have a scientific explanation of how nutrition/diet affects human health, one must understand the fundamental mechanisms of toxicity and how they fit into the prevention of pathogenesis of diseases. There are three fundamental mechanisms of cellular toxicity: mutagenesis, cytotoxicity and altered gene expression or 'epigenetic toxicity' (Ledford, 2015). The term 'epigenetic toxicity' has emerged as a significant concept that must be integrated in the risk assessment process (Trosko et al., 1998). To understand 'epigenetic' mechanisms, the pathogenesis of human carcinogenesis can serve as a model. Most cancers are the result of a multi-stage, multi-mechanism process in line with the 'initiation/promotion/progression' concept. Initiation is an irreversible step taking place in a single cell of any organ, most likely by a mutation. With the exception of most ultraviolet light-induced skin cancers, cancers originate from 'bad luck mutations' or spontaneous mutations due to errors in the DNA replication of stem cells. By contrast, promotion is an epigenetic mechanism, which is threshold-dependent, species-, gender- and organ-specific.

Both acute and chronic diseases share a common underlying cellular mechanism, namely the modulation of the integrated extra-, intra- and gap-junctional intercellular communication. Chemicals can induce oxidative stress and reactive oxygen species but these are inducers of either receptor-dependent or receptor-independent intracellular signalling that alters gene expression and gap-junctional intercellular communications. Many natural chemopreventive chemicals, such as resveratrol, lycopene, genistein and lovastatin, are known to modulate gap-junctional intercellular communication (Upham and Trosko, 2009; Leone et al., 2012).

Major changes in our diets have occurred recently, with the modern diet being calorie unrestricted and typically consisting of processed food and grilled or fried red meat. The incidence of diseases such as colon cancer correlates with the exposure to the modern diet. The Barker hypothesis states that adult diseases are linked to prenatal and early postnatal life. Thus, early modulation of organ-specific adult stem cells can alter the risk of diseases later in life (Trosko and Kang, 2012). Experimental evidence is showing that chemoprotective agents such as metformin and melatonin can antagonise the growth effect of tumour promoters on stem cell growth (Jung et al., 2011).

In conclusion, human adult stem cells, which are naturally immortal, can be blocked from terminal differentiation (initiated) and then clonally amplified (promoted) by hormones, inflammatory cytokines, dietary factors and environmental epigenetic chemicals, which reversibly inhibit gap-junctional intercellular communication. This disruption can lead to either an increase or decrease in the risk to chronic diseases later in life. This disruption can be influenced by the interaction of genetic factors with environmental, dietary, pharmaceutical, microbial and lifestyle agents during pregnancy. Therefore, the term 'epigenetic toxicity' has emerged as a significant concept that must be integrated in the risk assessment process (Trosko, 2011).

4. Conclusions

The four topics presented in this session cover areas that are currently the subject of major biological research activities. One emerging concept common to all four presentations was the

importance of epigenetic changes, irrespective of whether development, neurodegeneration, ageing or cancer is considered. The epigenetic modulation of gene expression has profound effects on health and lifespan. Indeed, disruptions caused by environmental, dietary, pharmaceutical, microbial or lifestyle agents during pregnancy are key determinants that are responsible for major quantitative and qualitative changes in the epigenetic control of health and disease, either directly or indirectly through modulation of our gut microbiota.

If we are to understand health and disease phenomena in detail, a better understanding of the different layers of information (genome, transcriptome, epigenome, proteome, metabolome and microbiome) is needed. In the same way, the tools providing us with this information will be paramount for our understanding of how environmental factors can impact on health and disease. Together, this knowledge and the tools supporting it will contribute to the regulatory assessment approaches and methodologies of the 21st century.

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Abbreviation

SCFA short chain fatty acids