14

Transgenerational Effects of Maternal Nicotine Exposure During Gestation and Lactation on the Respiratory System

G. S. Maritz
Department of Medical Biosciences,
University of the Western Cape, Bellville,
South Africa

1. Introduction

Both genetic and environmental factors affect an individual's risk for chronic obstructive lung disease [1]. Air pollution continues to be a major public health concern in industrialized cities throughout the world. Recent population and epidemiological studies that have associated ozone and particulate exposures with morbidity and mortality outcomes underscore the important detrimental effects of these pollutants on the lung. Inter-individual variation in human responses to air pollutants suggests that some subpopulations are at increased risk to the detrimental effects of pollutant exposure, and it has become clear that genetic background is an important susceptibility factor. Environmental exposures to inhaled pollutants and genetic factors associated with disease risk likely interact in a complex fashion that varies from one population to another [2]. Investigations have suggested an influence of age on genetic susceptibility to lung cancer and other diseases, which indicate that an interaction between age and genetic background may be important in air pollution disease pathogenesis [3]. Tobacco smoke is an important contributor to the factors in the environment that impact on the health of individuals, including the fetus in the womb.

Although cigarette smoking during pregnancy is associated with adverse fetal, obstetrical, and developmental outcomes, 15–20% of all women smoke throughout the duration of pregnancy [4, 5], despite intentions to refrain from smoking during that period [6]. Approximately 75% of pregnant smokers report the desire to quit smoking [7], but only 20–30% successfully abstains from smoking during pregnancy and half of these women relapse within 6 months of parturition [8]. In some countries nicotine replacement therapy is used as a strategy to assist smokers, including pregnant mothers, to quit the habit. However, several studies showed that maternal intake of nicotine have deleterious effects on the offspring.

2. Fetal onset of adult disease

In 1990 Barker [9] noted that "The womb may be more important than the home". Up to recently the old model of adult degenerative diseases, such as emphysema, was based on the model that link the interaction between genes and an adverse environment in adult life.

The new model that is currently being developed, based on environment-gene interaction, will include programming by the environment during fetal and neonatal life. There are critical periods during which the developing organs are very plastic such as when rapid cell proliferation occurs during growth, during which it is most sensitive to environmental stressors [10]. This is because during normal development precisely timed regulation of gene transcription is essential. Only genes that are: 1) specific to a particular cell type, such as epithelial cells, and 2) to a specific developmental phase, are transcriptionally active while others are silenced. The ability to modulate gene transcription results in plasticity during lung development [11]. It is therefore conceivable that interference with this process during a phase of high plasticity will result in various metabolic, structural and functional disorders in the offspring, or reduce the capacity of the offspring to protect itself against environmental insults [10]. The type of disorder is likely to be dependent not only on the type of insult but also the timing of the insult.

Apart from the various obstetrical and developmental complications in the adult and offspring, a wide variety of *in utero* insults, such as smoking and nicotine, are associated with an increased incidence of metabolic disorders in the offspring and in subsequent generations. Holloway et al [12] showed that fetal and neonatal exposure to nicotine results in endocrine and metabolic changes in the offspring that are consistent with those observed in type 2 diabetes and high blood pressure. Regular smoking increased the risk for asthma among adolescents, especially for non-allergic adolescents and those exposed to maternal smoking during the *in utero* period. It has also been shown that maternal and grand maternal smoking during pregnancy may increase the risk of childhood asthma [13]. Smoking during pregnancy changes the *in utero* environment within which the fetus develops and in this way induce changes to the program that control lung development, maintenance and aging in the offspring in such a way that these changes are transferred to the next generation. It is clear that certain conditions in the womb can lead to genetic or epigenetic marks that can persist for many generations [14].

It has indeed been shown that maternal and grand-maternal smoking during pregnancy is linked to an increased risk of childhood asthma which suggests that it is persistent heritable effect [13]. Alterations to the epigenome [15] and transcriptome [16] are mechanisms whereby prenatal exposure to smoke induce the development of diseases like asthma and emphysema later in life (Fig.1).

Although tobacco smoke contains numerous chemicals, many of the deleterious effects of smoking on the fetus and newborn arise are attributable to nicotine [17]. Nicotine replacement therapy (NRT) has been developed as a pharmacotherapy for smoking cessation and is considered to be a safer alternative for women to smoking during pregnancy. The safety of NRT use during pregnancy has been evaluated in a limited number of short-term human trials, but there is currently no information on the long-term effects of nicotine exposure of humans during *in utero* life. However, animal studies suggest that nicotine alone may be a key chemical responsible for many of the long-term effects associated with maternal cigarette smoking on the offspring, such as impaired fertility, type 2 diabetes, obesity, hypertension, neurobehavioral defects, and respiratory dysfunction [18]. It is therefore conceivable that exposure to nicotine during fetal and early neonatal development may contribute to the development of these diseases later in the life of the individual. This is conceivable since nicotine does induce epigenetic changes as well as direct DNA damage [12].

3. Nicotine uptake and metabolism during pregnancy

Nicotine is arguably the major physiologically active component of tobacco smoke and is rapidly absorbed from the respiratory tract of smokers. The lung appears to serve as a reservoir for nicotine, which slows its entry into the arterial circulation [19]. This implies that the inhaled nicotine is gradually absorbed into the arterial circulation. It may require 30 – 60 seconds or longer for the nicotine to be absorbed. Once in the maternal circulation, nicotine readily crosses the placenta and enters the fetal circulation [20]. Once it entered the amniotic fluid it is absorbed via the skin of the fetus [21]. Nicotine enters breast milk, and can reach concentrations that are approximately 2-3 times that in maternal plasma due to the partitioning of nicotine into the high-lipid-containing [22], more acidic milk [23, 24].

Although nicotine readily crosses the placenta there, is no evidence that it is metabolized by the placenta. It is therefore likely that the blood concentrations of nicotine reached in the fetus are similar to those in the mother; however, there is no direct evidence supporting the notion. Peak nicotine levels in the pregnant mother's blood occur 15-30 minutes after it is administered [25]. Most of the nicotine that enters the fetus returns to the maternal circulation for elimination, although some enters the amniotic fluid via the fetal urine. Consequently nicotine and cotinine accumulate in the amniotic fluid of the pregnant smoker because the nicotine eliminated by the fetus is added to the nicotine coming from the blood vessels of the amniochorionic membrane [24]. The fetus is therefore likely to be exposed to nicotine even after concentrations in maternal blood have decreased. This means that the fetus is exposed to nicotine during phases of development that are characterized by high plasticity.

The clearance of nicotine and cotinine, the major product of nicotine metabolism, is increased in pregnant women [26]. This can be ascribed to an increase in liver blood flow and an increased enzymatic breakdown of nicotine and cotinine in the mother. Since the enzymatic protection mechanisms of the fetus are not well developed [27, 28], the metabolism of nicotine in the fetal liver is slow and a longer half-life of nicotine in the fetus can be expected. This is confirmed by the higher concentrations of nicotine in fetal tissue compared to maternal blood levels [29]. Consequently the cells of the developing lung and other organs are exposed to higher concentrations of nicotine for longer periods of time and thus to the adverse effects of nicotine on cell integrity. This is important as nicotine is genotoxic [30] and induces the release of oxidants [31]. Since rapidly dividing cells are more vulnerable to the effects of foreign substances such as nicotine [32], it is conceivable that nicotine exposure during gestation and early postnatal life via maternal milk may interfere with growth and development. This can be achieved in two ways: by having a direct effect on cells and/or by reducing the nutrient supply to the fetus during gestation and lactation. It has been shown that long-term nicotine exposure results in a predisposition for genetic instability [22, 33, 34]. This may result in changes in the genetic "program" that controls lung development, maintenance of lung structure and aging of lung tissue, which may render the lungs more prone to disease. Since nicotine is associated with DNA methylation [35], it is possible that it may change the program that is maintaining homeostasis in the developing lung in the long term and in this way contribute to the adult onset of diseases. In addition, a product of nicotine metabolism is nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) which induces DNA damage which is associated with an increase in mutational events [36]. It is therefore possible that nicotine affects cell growth

and proliferation as well as cell aging and death directly or via its metabolic end products. It may also act via other pathways such as oxidants.

4. Nicotine and oxidant/antioxidant status

It has been shown that maternal smoking is associated with increased levels of oxidative stress markers in the mother and offspring [37, 38]. There is also convincing *in vivo* and *in vitro* evidence suggesting that exposure to nicotine results in oxidative stress in fetal, neonatal and adult tissues [38, 39]. Reactive oxygen species (ROS) target mitochondria, and mitochondrial DNA has been shown to be more sensitive to the deleterious effects of ROS than nuclear DNA [40].

In addition to inducing overproduction of oxidants, nicotine exposure results in a decrease in the activity of SOD and catalase. It also results in a decrease in the levels of low molecular weight antioxidants such as vitamins C and E [41]. Along with the decrease in the antioxidant capacity of the body, concentrations of malondialdehyde (MDA) are increased, indicating oxidant damage to the cells [42, 43]. The increase in ROS levels, together with a decrease in the activities of enzymes with antioxidant function, results in an imbalance in the oxidant/antioxidant capacity. This imbalance is maintained long after nicotine withdrawal [43] and becomes worse with age [44]. Therefore, nicotine not only acts while it is in the system, but also act indirectly in later life, that is after its removal from the organs, through the disruption of the oxidant/antioxidant capacity of the individual later in life.

It is conceivable that the increased levels of nicotine-induced ROS in the fetus and suckling neonate, as a consequence of maternal smoking or NRT, will result in not only mitochondrial DNA damage but also methylation of nuclear DNA or direct DNA damage through point mutation. It is therefore likely that nicotine and ROS will result in a change in the capacity of the mitochondria to deliver energy and to participate in homeostatic mechanisms and in changing the "program" that controls growth, tissue maintenance, aging and cellular metabolism.

The above implies that the adverse effects of maternal smoking and/or nicotine intake lasts for a life-time in the offspring. Consequently the cells and DNA are continuously exposed to an unfavourable internal environment. This may induce changes in the epigenome and thus control of DNA, as well as changes in the DNA as such. This will increase the susceptibility of the offspring to develop diseases later in life.

5. Mechanisms of action of nicotine

It has been shown that long-term nicotine exposure results in a predisposition for the induction of genetic instability [32,34,45]. Gene amplification is a hallmark of gene instability. Gene instability requires two critical elements, namely an inappropriate cell cycle progression, and DNA damage. Long-term nicotine exposure, through the activation of Ras pathways and up regulation of cyclin D1, disrupts the G1 arrest. It also augments the production of ROS which may lead to DNA damage. This implies that exposure to nicotine via tobacco smoke or via NRT will make the lungs more prone to the development of cancer and other respiratory diseases, such as asthma and emphysema [46].

Various studies suggest that exposures during the intra-uterine period can increase the risk for developing diseases later in life [47]. Maternal smoking during pregnancy is associated with lower pulmonary function and increased asthmatic symptoms in childhood [13]. Studies which show that maternal as well as grand-maternal smoking during pregnancy is also associated with an increased risk of asthma in childhood. This suggests a persistent heritable effect [48]. An alterations to the epigenome is one way whereby exposure to foreign material affects disease risk later in life [49].

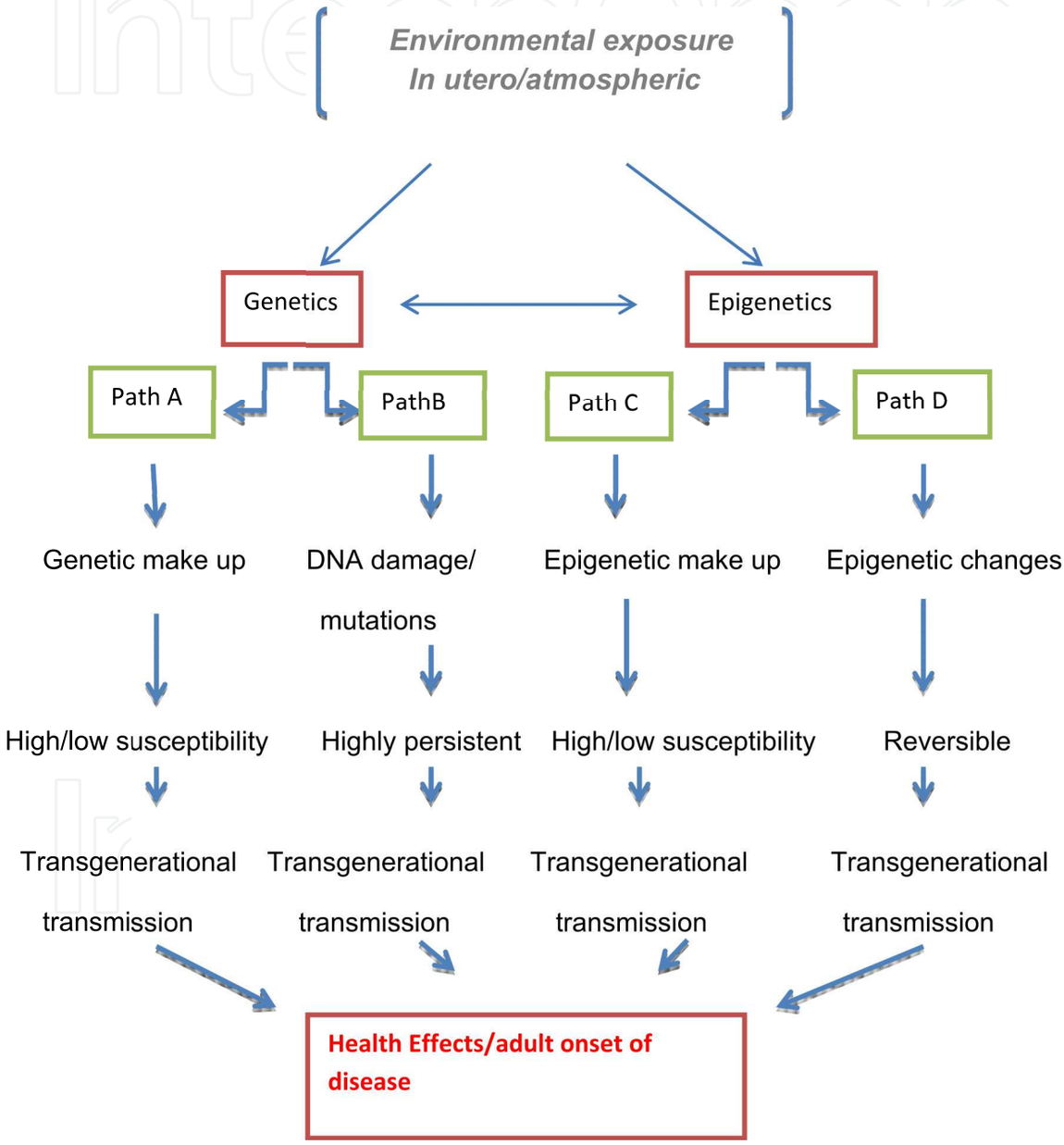


Fig. 1. The gene- vs the epigene-environment interplay. A model of possible genetic and epigenetic paths linking environmental exposures to health outcomes (Adjusted from: Bolatti and Baccarelli, 2010). [52]

Studies by Jorgenson and his co-workers [50] showed that exposure of cells to cigarette smoke containing nicotine leads to formation of double-strand DNA breaks in A549 cells in culture. It is therefore plausible that nicotine can have the same effect on type II pneumocytes in lung tissue *in vivo*. Chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema, is commonly thought of as an adult onset lung disease most often seen in aging people with a tobacco smoking history [51]. On the other hand, only 20% of cigarette smokers develop full-blown emphysema. COPD may also be seen in non-smokers. The question is whether the latter group is not more susceptible to COPD due to changes in the program that controls lung aging and maintenance as well as its ability to protect itself against the onslaughts of the environment Therefore, genetic susceptibility is rapidly gaining ground in recent COPD research.

Apart from genetic alterations, genetic changes such as DNA polymorphism may have no or a very small immediate impact on developing organs such as the lungs with an apparent normal phenotype during the early developmental phases of the child. Although no clear differences are seen in the new phenotype, it may have reduced compensatory capacity

resulting in a poor response to injury imposed by other stress factors, including in the environment. This environment can be *in utero* or external. The latter implies that the lifestyle of the parents may actually increase the susceptibility of the offspring to COPD.

Changes to the epigenome is one of the mechanisms whereby exposures during gestation may affect disease later in life. DNA methylation is perhaps the most known type of epigenetic mark. In mammals there are at least two very important developmental periods namely, in germ cells and in pre-implantation embryos. During these periods of development the methylation patterns are reprogrammed genome wide and consequently results in the generation of cells with a broad developmental potential [53]. This period involves demethylation and remethylation in cells in a tissue specific manner. A basic premise of epigenetic processes is that once it is established, these marks are maintained through rounds of mitotic cell division and stable for the life of the organism [54]. Thus, maternal smoking during pregnancy and early postnatal life may have lasting effects on DNA methylation and as a result influence expression and disease phenotypes across the life time of the individual [55] or result in adult onset of disease [56].

In regard to the adult onset of disease, the most sensitive developmental periods to environmental exposures, are the period of fetal development as well as the early postnatal period [57, 58]. The reason for this is that various developmental processes are occurring that, when changed permanently, will alter subsequent organ development and function [59]. Alternatively, active organ development during late fetal and early postnatal life also undergoes critical programming of the epigenome and transcriptome that is associated with cellular differentiation and organogenesis. It has indeed been shown recently that exposures to environmental toxicants, such as maternal smoking during gestation and lactation, can modify the epigenome to increase the susceptibility to adult onset of disease [58]. This may explain the increased risk for asthma among adolescents and those exposed to maternal smoking during the *in utero* period of development [51].

Nicotine is also associated with DNA damage [60]. It also induces ROS production [61] which induce DNA damage [62]. It is therefore plausible that the irreversible adverse effect on carbohydrate metabolism of lungs of rats that were exposed to nicotine via the placenta

and mother's milk [63] is due to change in DNA or of the epigenetic control system. This is supported by the findings of Benyshek et al, [64] who showed that glucose metabolism of the ggrand-maternal offspring (F3) of female rats that were malnourished during development, is also adversely affected. It is likely that the structural changes that are getting progressively worse over time, were due to programming alterations during organ development *in utero* as well as during the early developmental periods. Adverse adjustment of carbohydrate metabolism may also impact negatively on the long-term maintenance of lung structure and function [65]. In addition the metabolic changes induced by maternal exposure to nicotine during pregnancy and lactation may induce premature aging of the lungs of the offspring [66] and consequently the increased risk of respiratory disease. It is therefore likely that maternal smoking, or the use of nicotine to quit smoking during pregnancy and lactation result in epigenetic changes in the lungs of the offspring which can be transferred to following generations and result in adult onset of respiratory disease.

6. Programming and future respiratory health

It has been shown that maternal nicotine exposure during critical windows of development result in offspring with a structurally and functionally normal respiratory system at birth [67]. However, as the offspring age structural changes become apparent. These include parenchymal changes that resemble emphysema and thickening of alveolar walls. The latter is due to accumulation of connective tissue in the extracellular matrix [68]. It was also shown that different structural changes appear in different age groups suggesting a programmed process [66]. This is likely due to altered gene expression in a time-specific manner. Such alterations are irreversible [69]. The data suggests that *in utero* exposure to nicotine resulted in an increase susceptibility to disease later in life. This programming is due to changes in gene expression due to altered imprinting. These changes appear to be heritable. The end result is an individual that is sensitized to be more susceptible to diseases later in life. The environmental insult could act via: 1) an *in utero* exposure that can result in pathophysiology later in life, or 2) an *in utero* exposure combined with a neonatal exposure, or 3) adult exposure that would induce the pathophysiology. The pathophysiology can lead to: 1) disease that would not normally have occurred, or 2) increase the risk for disease that would not normally have been the case or, 3) either and early onset of disease that would have normally occurred, or 4) an exacerbation of the disease [70]. Altered lung function, exacerbation of symptoms, and acceleration of disease processes seen with smoking during pregnancy might arise from direct injury suffered by the developing fetus by altering fetal gene expression [71]. It is also possible that the pathophysiology could have a long latent period from the onset during the perinatal period to the actual disease. These effects could potentially be transgenerational [72].

In conclusion, it is clear that smoking and nicotine can affect the offspring phenotype via genetic and epigenetic adjustments with long term consequences, and is an illustration of the interplay between genetic, developmental and environmental factors. The gene-environment interactions may therefore, play an important role in the etiology of complex diseases where many of these diseases such as COPD may already be induced during *in utero* development of the offspring. It has been shown that oxidative damage occur even in ex-smokers. It is therefore plausible that the effect of nicotine and smoking during gestation and lactation may have a similar persistent effect in the lungs of the offspring. If this is so, it

implies that oxidants and nicotine induce irreversible damage to the epigenome and transcriptome of the lungs of the offspring. This will adversely affect the ability of the lung of the offspring to protect itself against environmental insults. Consequently the prevalence of respiratory diseases will be higher in the offspring of grand-parents or parents who smoked or used nicotine during pregnancy and lactation.

Despite a wealth of epidemiologic and experimental evidence, there is still resistance to the concept that environmental as well as other interference with early lung development have a profound effect on the vulnerability to disease later in life. Due to a lack of knowledge by health professionals and decision makers about developmental plasticity and intergenerational effects, they are not able to introduce or implement relatively simple approaches to reduce the burden of disease in particular in the low socioeconomic groups. It is, therefore, important to support approaches that will enable health professionals to introduce those who want to quit smoking to strategies other than nicotine replacement therapy; strategies that will not interfere with programming of the offspring in such a way that they may become more prone to respiratory disease later in life

7. References

[1] Mayer AS, Newman LS. Genetic and environmental modulation of chronic obstructive pulmonary disease. Resp Physiol. 2001; 128: 3-11.

[2] Kleeberger SR. Genetic aspects of pulmonary responses to inhaled pollutants. Exp Toxicol Pathol. 2005; 57 (Suppl 1):147-153.

[3] Kleeberger SR. Genetic aspects of susceptibility to air pollution. Eur Respir J Suppl.2003;40:52s-56s..

[4] Andres RL, Day MC. Perinatal complications associated with maternal tobacco use. Seminars Neonatol. 2000; 5: 231–241.

[5] Bergmann KE, Bergmann RL, Von KR, Bohm O, Richter R, Dudenhausen JW, Wahn U. Early determinants of childhood overweight and adiposity in a birth cohort study: role of breast-feeding. Int J Obesity and Related Metab Dis. 2003; 27: 162–172.

[6] Okuyemi KS, Ahluwalia JS, Harris KJ 2000 Pharmacotherapy of smoking cessation. Archives of Family Medicine. 2000; 9:270–281.

[7] Ruggiero, L., Tsoh, J. Y., Everett, K., Fava, J. L., Guise, B. J. The transtheoretical model of smoking: comparison of pregnant and nonpregnant smokers. Addict. Behav. 2000; 25: 239–251.

[8] Ebert, L. M., and Fahy, K. Why do women continue to smoke in pregnancy? Women Birth. 2007; 20: 161–168.

[9] Barker DJ. The fetal origins of adult disease. BMJ 1990; 301: 111

[10] Symonds ME, Sebert SP, Hyatt MA, Budge H. Nutritional programming of the metabolic syndrome.Nat Rev Endocrinol. 2009; 5: 604-610.

[11] Joss-Moore LA, Albertine KH, Lane RH. Epigenetics and the developmental origins of lung disease. Mol Gen Metab. 2011; doi: 10.1016/j.ymgme.2011.07.018

[12] Holloway AC, Cuu DQ, Morrison KM, Gerstein HC, Tarnopolsky MA. Transgenerational effects of fetal and neonatal exposure to nicotine. Endocrine. 2007; 3: 254-259

[13] Li YF, Langholz B, Salam MT, Gilliland FD. Maternal and grandmaternal smoking patterns are associated with early childhood asthma. Chest. 2005 Apr;127(4):1232-41.

[14] Heijmans BT, Tobi ZEW, Lumey LH, Slagboom PE. The epigenome: archive of the prenatal environment. Epigenetics 2009; 4: 526-531.

[15] Anway MD, Skinner MK. Epigenetic Transgenerational actions of endocrine disruptors. Endocrinology 2006; 147: s43-s49

[16] Skinner MK. What is epigenetic transgenerational phenotypes? F3 or F2. Reprod Toxicol. 2008; 25: 2-6.

[17] Petre MA, Petrik J, Ellis R, Inman MD, Holloway AC, Labiris NR. Fetal and neonatal exposure to nicotine disrupts postnatal lung development in rats: Role of VEGF and its receptors. Int J Toxicol. 2011; 30: 244-252.

[18] Bruin JF, Hertzel, Gerstein C, Holloway AC. Long-Term Consequences of Fetal and Neonatal Nicotine Exposure: A Critical Review. Toxicoll Sci. 2010; 116, 364–374.

[19] Brewer, B.G.; Roberts, A.M.; Rowell, P.P. Short-term distribution of nicotine in the rat lung. Drug Alcohol. Depend. 2004, 75, 193-198.

[20] Matta, S.G.; Balfour, D.J.; Benowitz, N.L.; Boyd, R.T.; Buccafusco, J.J.; Caggiula, A.R.; Craig, C.R.; Collins, A.C.; Damaj, M.I.; Donny, E.C.; Gardiner, P.S.; Grady, S.R.; Heberlein, U.; Leonard, S.S.; Levin, E.D.; Lukas, R.J.; Markou, A.; Marks, M.J.; McCallum, S.E.; Parameswaran, N.; Perkins, K.A.; Picciotto, M.R.; Quik, M.; Rose, J.E.; Rothenfluh, A.; Schafer, W.R.; Stolerman, I.P.; Tyndale, R.F.; Wehner, J.M.; Zirger, J.M. Guidelines on nicotine dose selection for in vivo research. Psychopharmacology (Berl) 2007, 190, 269-319.

[21] Onuki, M.; Yokoyama, K.; Kimura, K.; Sato, H.; Nordin, R.B.; Naing, L.; Morita, Y.; Sakai, T.; Kobayashi, Y.; Araki, S., Assessment of urinary cotinine as a marker of nicotine absorption from tobacco leaves: a study on tobacco farmers in Malaysia. J. Occup. Health 2003, 45, 140-145.

[22] Sastry, B.V.; Chance, M.B.; Hemontolor, M.E.; Goddijn-Wessel, T.A. Formation and retention of cotinine during placental transfer of nicotine in human placental cotyledon. Pharmacology 1998, 57, 104-116.

[23] Dahlstrom, A.; Lundell, B.; Curvall, M.; Thapper, L. Nicotine and cotinine concentrations in the nursing mother and her infant. Acta Paediatr. Scand. 1990, 79, 142-147.

[24] Luck, W.; Nau, H.; Hansen, R.; Steldinger, R. Extent of nicotine and cotinine transfer to the human fetus, placenta and amniotic fluid of smoking mothers. Dev. Pharmacol. Ther. 1985, 8, 384-395.

[25] Suzuki, K.; Horiguchi, T.; Comas-Urrutia, A.C.; Mueller-Heubach, E.; Morishima, H.O.; Adamsons, K. Placental transfer and distribution of nicotine in the pregnant rhesus monkey. Am. J. Obstet. Gynecol. 1974, 119, 253-262.

[26] Dempsey, D.A.; Benowitz, N.L. Risks and benefits of nicotine to aid smoking cessation in pregnancy. Drug Saf. 2001, 24, 277-322.

[27] Frank, L.; Sosenko, I.R. Prenatal development of lung antioxidant enzymes in four species. J. Pediatr. 1987, 110, 106-110.

[28] Hayashibe, H.; Asayama, K.; Dobashi, K.; Kato, K. Prenatal development of antioxidant enzymes in rat lung, kidney, and heart: marked increase in immunoreactive

superoxide dismutases, glutathione peroxidase, and catalase in the kidney. Pediatr. Res. 1990, 27, 472-475.
[29] Lambers, D.S.; Clark, K.E. The maternal and fetal physiologic effects of nicotine. Semin. Perinatol. 1996, 20, 115-126.
[30] Kleinsasser, N.H.; Sassen, A.W.; Semmler, M.P.; Harreus, U.A.; Licht, A.K.; Richter, E. The tobacco alkaloid nicotine demonstrates genotoxicity in human tonsillar tissue and lymphocytes. Toxicol. Sci. 2005, 86, 309-317.
[31] Bruin, J.E.; Petre, M.A.; Raha, S.; Morrison, K.M.; Gerstein, H.C.; Holloway, A.C. Fetal and neonatal nicotine exposure in Wistar rats causes progressive pancreatic mitochondrial damage and beta cell dysfunction. PLoS One 2008, 3, e3371.
[32] Rehan, V.K.; Wang, Y.; Sugano, S.; Santos, J.; Patel, S.; Sakurai, R.; Boros, L.G.; Lee, W.P.; Torday, J.S. In utero nicotine exposure alters fetal rat lung alveolar type II cell proliferation, differentiation, and metabolism. Am. J. Physiol. Lung Cell Mol. Physiol. 2007, 292, L323-L333.
[33] Guo, J.; Chu, M.; Abbeyquaye, T.; Chen, C.Y. Persistent nicotine treatment potentiates amplification of the dihydrofolate reductase gene in rat lung epithelial cells as a consequence of Ras activation. J. Biol. Chem. 2005, 280, 30422-30431.
[34] Hartwell, L.H.; Kastan, M.B. Cell cycle control and cancer. Science 1994, 266, 1821-1828.
[35] Soma T, Kaganoi J, Kawabe A, Kondo K, Imamura M, Shimada Y. Nicotine induces the fragile histidine triad methylation in human esophageal squamous epithelial cells. Int. J. Cancer. 2006; 119, 1023–1027.
[36] Cloutier J-F, Drouin R, Weinfeld M, O'Connor TR, Castonguay A. Characterization and Mapping of DNA Damage Induced by Reactive Metabolites of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) at Nucleotide Resolution in Human Genomic DNA. J. Mol. Biol. 2001; 313: 539-557
[37] Noakes, P.S.; Thomas, R.; Lane, C.; Mori, T.A.; Barden, A.E.; Devadason, S.G.; Prescott, S.L. Association of maternal smoking with increased infant oxidative stress at 3 months of age. Thorax 2007, 62, 714-717.
[38] Orhon, F.S.; Ulukol, B.; Kahya, D.; Cengiz, B.; Baskan, S.; Tezcan, S. The influence of maternal smoking on maternal and newborn oxidant and antioxidant status. Eur. J. Pediatr. 2009, 168, 975-981
[39] Husain K, Scott BR, Reddy SK, Somani SM. Chronic ethanol and nicotine interaction on rat tissue antioxidant defense systems. Alcohol 2001; 25: 89-97.
[40] Droge, W., Free radicals in the physiological control of cell function. Physiol. Rev. 2002, 82,
[41] Zaken, V.; Kohen, R.; Ornoy, A. Vitamins C and E improve rat embryonic antioxidant defense mechanism in diabetic culture medium. Teratology 2001, 64, 33-44.
[42] Halima, B.A.; Sarra, K.; Kais, R.; Salwa, E.; Najoua, G. Indicators of oxidative stress in weanling and pubertal rats following exposure to nicotine via milk. Hum. Exp. Toxicol. 2010, 29, 489-496.
[43] Ozokutan, B.H.; Ozkan, K.U.; Sari, I.; Inanc, F.; Guldur, M.E.; Kilinc, M. Effects of maternal nicotine exposure during lactation on breast-fed rat pups. Biol. Neonate 2005, 88, 113-117.
[44] Bruin, J.E.; Petre, M.A.; Raha, S.; Morrison, K.M.; Gerstein, H.C.; Holloway, A.C. Fetal and neonatal nicotine exposure in Wistar rats causes progressive pancreatic mitochondrial damage and beta cell dysfunction. *PLoS One* 2008, *3*, e3371.

[45] Guo J, Chu M, Abbeyquaye T, Chen CY. Persistent nicotine treatmant potentiates amplification of the dihydrofolate reductase gene in rat lung epithelial cells as a consequence of Ras activation and antioxidant status. J Biol Chem 2005; 280: 30422-30431.

[46] Chu M, Guo J, Chen CY. Long-term Exposure to Nicotine, via Ras Pathway, Induces Cyclin D1 to Stimulate G1 Cell Cycle Transition. J Biol Chem. 2005; 280: 6369–6379.

[47] Holloway, A.C.; Cuu, D.Q.; Morrison, K.M.; Gerstein, H.C.; Tarnopolsky, M.A. Transgenerational effects of fetal and neonatal exposure to nicotine. Endocrinol 2007, *31*, 254-259.

[48] Whitelaw NC, Whitelaw E. Transgenerational epigenetic inheritance in health and disease. Gemetics and Dev. 2008; 18: 273-279.

[49] Waterland RA, Michels KB. Epigenetic epidemiology of the developmental origins of disease. Annu Rev Nutr 2007; 27: 363-388

[50] Jorgensen ED, Zhao H, Traganos F, Albino AP, Darzynkiewicz Z. DNA damage response induced by exposure of human lung adenocarcinoma cells to smoke from tobacco- and nicotine-free cigarettes. Cell Cycle. 2010; 9. [Epub ahead of print]

[51] Gilliland FD, Islam T, Berhane K, Gauderman WJ, McConnell R, Avol E, Peters JM. Regular smoking and asthma incidence in adolescents. Am J Respit Crit Care Med. 2006; 174: 1094-1100.

[52] Bollati V, Baccarelli A. Environmental epigenetics. Heredity 2010; 105: 105-112.

[53] Reik W, Dean W, Walter J. Epigenetic reprogramming in mammalian development. Science 2001; 293: 1089-1093.

[54] Jirtle RL, Skinner MK. Environmental epigenetics and disease susceptibility. Nat Rev Genet 2007; 8: 253-262.

[55] Morgan HD, Santos F, Green K, Dean W, Reik W. epigenetic reprogramming in mammalas. Hum Mol Genet. 2005; 14: R47-R58.

[56] Breton CV, Byun H-M, Wenetn M, Pan F, Yang A, Gilliland D. Prenatal tobacco smoke exposure affects global and gene-specific DNA methylation. Am J Respir Crit Care Med. 2009; 180: 462-467.

[57] Heindel JJ. Role of Exposure to Environmental Chemicals in the Developmental Basis of Reproductive Disease and Dysfunction. Semin Reprod Med 2006; 24: 168-177.

[58] Bateson P. Developmental plasticity and evolutionary biology. J Nutr. 2007: 137;1060-1062.

[59] Ginzkey C, Kampfinger K, Friehs G, Köhler C, Hagen R, Richter E, Kleinsasser NH. Nicotine induces DNA damage in human salivary glands. Toxicol Lett. 2009;184: 1-4.

[60] Kajekar R. Environmental factors and developmental outcomes in the lung. Pharmacol. Ther. 2007; 114; 129-145.

[61] Zhao Z, Reece EA. Nicotine-induced embryonic malformations mediated by apoptosis from increasing intracellular calcium and oxidative stress. Birth Defects Res B Dev Reprod Toxicol. 2005; 74: 383-391.

[62] Wiseman H, Halliwell B. Damage to DNA by reactive oxygen and nitrogen species: role in inflammatory disease and progression to cancer. Biochem J 1996; 313: 17-29.

[63] Maritz, G. Pre- and postnatal carbohydrate metabolism of rat lung tissue. The effect of maternal nicotine exposure. Arch. Toxicol. 1986, 59, 89-93.

[64] Benyshek DC, Johnston CS, Martin JF. Glucose metabolism is altered in the adequately-nourished grand-offspring (F3 generation) of rats malnourished during gestation and perinatal life. Diabetologia 2006; 49: 1117-1119.

[65] Maritz GS, Windvogel S. Is maternal copper supplementation during alveolarisation protecting the developing rat lung against the adverse effects of maternal nicotine exposure? A morphometric study. Exp Lung Res 2003; 29: 243-260.

[66] Maritz GS, Mutemwa M, Kayigire AX. Tomato juice protects the lungs of the offspring of female rats exposed to nicotine during gestation and actationh. Ped Pulmonol. 2011; DOI: 10.1002/ppul.21462

[67] Maritz GS, Windvogel S. Does maternal nicotine exposure during different phases of lung development influence the progam that regulates the maintenance of lung integrity in the offspring? A comparative morphologic and morphometric study. Trends Comp Biochem Physiol. 2005; 11: 69-75.

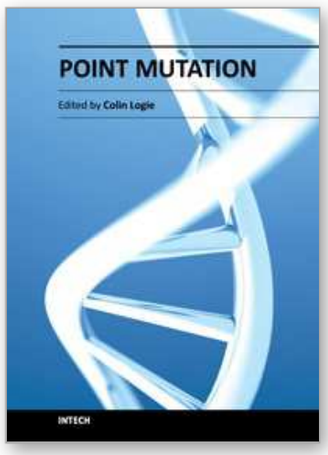
[68] Sekhon HS, Proskocil BJ, Clark JA, Spindel ER. Prenatal nicotine exposure increases connective tissue expression in foetal monkey pulmonary vessels. Eur Respir J. 2004 Jun;23(6):906-15.

[69] Gluckman PD, Hanson MA, Buklijas T, Low FM, Beedle AS. Epigenetic mechanisms that underpin metabolic and cardiovacular diseases. Nat. Rev Endocrinol 2009; 5: 401-408.

[70] Skinner MK, Manikkam M, Guerero-Bosagna C. Epigenetic trnsgenerational actions of environmental factors in disease etiology. Trends Endocrinol Metab. 2010; 21: 214-222.

[71] Rousse RL, Boudreaux MJ, Penn AL. In utero environmental tobacco smoke exposure alters gene expression in lungs of adult BALB/c mice. Environ Hlth Perspect. 2007; 115: 1757-1766.

[72] Asami S, Manabe H, Miyake J, Tsurudome Y, Hirano T, Yamaguchi R, Itoh H, Kasai H. Cigarette smoking induce an increase in oxidative DNA damage, 8-hydroxydeoxyguanosine, in a central site in human lung. Carcinogenesis 1997; 18: 1763-1766.



Point Mutation

Edited by Dr Colin Logie

ISBN 978-953-51-0331-8

Hard cover, 352 pages

Publisher InTech

Published online 21, March, 2012

Published in print edition March, 2012

This book concerns the signatures left behind in chromosomes by the forces that drive DNA code evolution in the form of DNA nucleotide substitutions. Since the genetic code predetermines the molecular basis of life, it could have been about any aspect of biology. As it happens, it is largely about recent adaptation of pathogens and their human host. Nine chapters are medically oriented, two are bioinformatics-oriented and one is technological, describing the state of the art in synthetic point mutagenesis. What stands out in this book is the increasing rate at which DNA data has been amassed in the course of the past decade and how knowledge in this vibrant research field is currently being translated in the medical world.

InTech Europe

University Campus STeP Ri

Slavka Krautzeka 83/A

51000 Rijeka, Croatia

Phone: +385 (51) 770 447

Fax: +385 (51) 686 166

www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai

No.65, Yan An Road (West), Shanghai, 200040, China

中国上海市延安西路65号上海国际贵都大饭店办公楼405单元

Phone: +86-21-62489820

Fax: +86-21-62489821

IntechOpen