



Consanguinity via Breastfeeding in view of Islam and Science of Epigenetics

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ABSTRACT

Background : One of the unique features of the Qur'an and Sunna is that never contradict the Science. Qur'an is not considered as a scientific book, however, includes many extraordinary signs and true scientific facts that have not been known at the time of the Qur'an revelation. Over the past few decades, several of them have been revealed, but many are still waiting to be uncovered.

Result : Breastfeeding is the most natural and safest way to provide nutrition, protection and unique bonding experience for newborn babies. The term "milk-kinship" is a kind of relationship via breastfeeding that was established hundreds of years ago via the Qur'an and Sunna. Recent study revealed that the life expectancy of the F2 offspring obtained from milk-siblings mating was much shorter than the offspring from control group. Which mean that there is period in which offspring are susceptible to breast milk induced epigenetic changes, especially in the first 2 years of life.

Conclusion : Latest research suggests that consanguinity via breastfeeding can be explained by heritable mechanism of epigenetic modifications.

Introduction

The Czech monk Gregor Mendel is considered as a father of genetics, one of the modern sciences that focuses on the heredity and variation. According to Mendel's simple model with a pea, each gene consists of two alleles, one dominant and one recessive. Human genome consists of approximately 22000 genes (Jackson et al., 2018). In autosomal inheritance, homozygous

recessive genotype means that organism carries two identical copies of the recessive allele that are expressed in the phenotype. Phenotypes involve any observable traits, including different abnormalities, and clinical features encountered in human disease. In dominant phenotype, one dominant allele is sufficient for the expression, (heterozygote dominant genotype). It means for example in a case of

genetic disorder, dominant allele hides recessive allele in one generation, however may “reappear” in a subsequent generation in a homozygote recessive genotype form. In fact, the reality of most human traits is more complicated, and the phenotype is usually determined by the interplay between genes and environment.

The concept of “reappearing” from Islamic point of view have been explained by using the hadith of the prophet Mohammed, peace be upon him (PBUH), who described this phenomenon several hundred years before Genetics was introduced (Ghareeb, 2011).

„There came a person to the Prophet, PBUH, from Banu Fazara and said: My wife has given birth to a child who is black, whereupon Allah's Apostle, PBUH, said: Have you any camels? He said: Yes. He again said: What is their colour? He said: They are red. He said: Is there a dusky one among them? He said: Yes, there are dusky ones among them. He said: How has it come about? He said: It is perhaps the strain to which it has reverted, whereupon he (the Holy Prophet) said: It is perhaps the strain to which he (the child) has reverted.“ (Sahih Muslim, 1500a).

Understanding genetic possibilities may prevent any false accusation of paternity or predict the probability of developing some inherited diseases caused

by changes in the DNA sequence known as mutation. Links between the Qur'an, hadith and ethical and genetic understanding of diseases have been already discussed (Ghareeb, 2010). In the present paper we focus on the implications of the recent epigenetic research which are in concordance with the signs from Qur'an and Sunna. Epigenetics that can be translated as being above or upon genetics explores heritable and stable alterations in the gene expression without direct change in the DNA sequence. It refers to the chemical modifications to the DNA or histones around which the DNA is packaged forming nucleosomes. Nucleosomes condense to make chromatin and remodelling the chromatin structure enables to understand how environmental factors including nutrition, stress, toxins and pollution, smoking, etc. may at any time of life span contribute to the development of many diseases including cancer. There are three main epigenetic mechanisms; DNA methylation, histone modification (acetylation, methylation, phosphorylation, deimination, ubiquitylation, sumoylation, and ADP ribosylation) and micro RNAs. Micro RNA (also miRNA or miR) are short non-coding functional RNA molecules that mediate gene silencing. They are transcribed but not translated into proteins. It can be microRNA (miRNA), short (less than 30

nucleotides) interfering RNAs (siRNA) and long (200 or more nucleotides) non-coding RNA (lncRNA).

Result and Discussion

Breastfeeding and Islam

The Qur'an appointed breastfeeding as a fundamental right for every newborn child and infant. It highly recommends completing a breastfeeding cycle of 2 years (Qur'an, 2: 233), and highlights the urgent need for mother milk's nutrition of the child.

“Mothers may breastfeed their children two complete years for whoever wishes to complete the nursing [period]. Upon the father is the mothers' provision and their clothing according to what is acceptable. No person is charged with more than his capacity. No mother should be harmed through her child, and no father through his child. And upon the [father's] heir is [a duty] like that [of the father]. And if they both desire weaning through mutual consent from both of them and consultation, there is no blame upon either of them. And if you wish to have your children nursed by a substitute, there is no blame upon you as long as you give payment according to what is acceptable. And fear Allah and know that Allah is Seeing of what you do.”

(Sahih International translation of Holy Qur'an, chapter 2 (The Cow, Al-Baqara): 233)

The „complete“ cycle according to the Qur'an is a duration of two years which Ibn Kathir, highlighted as recommendation not obligation, depending on the personal choice of mothers, their circumstances and health conditions (Ibn Kathir, 1999). This explanation is in congruence with the World Health Organization's guidance that children should be breastfed for 2 years (WHO, 2021).

Another phenomenon known from the Qur'an and Sunna is relationship via breastfeeding another's child. According to the Islamic law (sharia) kinship is based on blood, marriage, or breastfeeding (Arabic: al-rida'a). The kinship, known as “milk-children” or “milk-siblings”, according to the Qur'an and Sunna does not allow a marriage between two people who were nursed from the same woman (“wet nurse”).

„Prohibited to you [for marriage] are your mothers, your daughters, your sisters, your father's sisters, your mother's sisters, your brother's daughters, your sister's daughters, your [milk] mothers who nursed you, your sisters through nursing, your wives' mothers, and your step-daughters under your guardianship [born] of your wives unto whom you have gone in. But if you have not gone in unto them, there is no sin upon you. And [also prohibited are] the wives of your sons who are from your [own] loins, and that you take [in marriage] two

sisters simultaneously, except for what has already occurred. Indeed, Allah is ever Forgiving and Merciful.“

(Sahih International translation of Holy Qur'an, chapter 4 (The women, An-Nisa: 23)

From the authentic narrations, Prophet's wife, Aisha, may Allah be pleased with her, reported that Salim was the freed slave of Abu Hudhayfa and lived with him and his family in their house. The wife of Abu Hudhayfa came to the Prophet, PBUH, and she said, “Salim has reached puberty as men do, he knows what they know. He enters our house freely, and I sense that this disturbs the heart of Abu Hudhayfa.” The Messenger of Allah, PBUH, said:

„Let him be fed with breast milk and he will be unlawful for you to marry, then the disturbance in Abu Hudhayfa's heart will disappear.“ (Hadith Ṣaḥīḥ, Muslim 1453b)

Ibn Hajar comments on this tradition, saying: Al-Qadi 'Iyad answers the question with the interpretation that the milk was put into a cup and he did not drink it from her breast. According to the Al-Nawawi this interpretation is the best. (Fath al-Bārī 4814, In: Abu Amina Elias, 2013)

It was also narrated that Aisha, may Allah be pleased with her, said: “One of things that Allah revealed in the Qur'an and

then abrogated was that nothing makes marriage prohibited except ten breastfeedings or five well-known“ (breastfeedings) (Sunan Ibn Majah 1942, authenticated by Al-Albaani). According to this hadith, the Qur'an initially stated that ten times of confirmed breastfeeding make the breastfed person unmarriageable (Arabic: Mahram) to those who shared breastfeeding from the same woman and their Mahram relatives. Yet, both the ruling and wording of this verse were abrogated and replaced with another verse stipulating five times of confirmed breastfeeding. Later, only the wording of the latter verse was abrogated while its ruling remained in force. As for Aisha's statement that the Prophet, PBUH, died while this verse was still being recited as part of the Qur'an, means that the abrogation came so late that news of it did not reach some people and, thus, they continued reciting the abrogated verse as part of the Qur'an due to their ignorance of its abrogation.

Abdullah ibn Abbas, may Allah be pleased with him, reported that the Messenger of Allah, PBUH, said about Hamzah bin Abdul-Muttalib's daughter: "She is the daughter of my brother through breastfeeding, and breastfeeding makes unlawful (for marriage) the same things that blood ties make unlawful" (Sunan Ibn Majah 1938).

This hadith is known also through another narrator, Ali ibn Abi Talib, may Allah be pleased with him, desired that the Prophet, PBUH, would marry the daughter of their uncle Hamzah, but the Prophet informed him that she is not lawful for him to marry because she is the daughter of his brother by breastfeeding (Musnad Ahmed 931).

The Prophet, PBUH and Hamzah, may Allah be pleased with him, were both breastfed by Thuwaybah, the maid servant of Abu Lahab. Therefore, Hamzah became his brother by breastfeeding and the Prophet is the paternal uncle of Hamzah's daughter and cannot marry her. In Islam, marriage that is permanently unlawful because of blood relationship is also permanently unlawful due to breastfeeding.

Composition of the human milk

Human milk is the most unique nutritional food for optimal infant growth, protection and development. This complex fluid is considered as a natural version of personalized nutrition and its composition vary depending on the infant age, gender, health status, etc. (Golan and Assaraf, 2020). Concentration of many macronutrients and micronutrients present in breast milk declines with the duration of breastfeeding, adapting to meet the child's needs. Interestingly, production of nutrient deficient breast milk, or genetic variations

that reduce breast milk quantity and quality in terms of nutrients are relatively rare and is against the evolutionary selection (Dror and Allen, 2018). Breastfeeding has been negatively associated with gastrointestinal tract infections or developing the type-2 diabetes (Horta et al., 2015). Protective effect of breastfeeding with some possible residual confounding has been shown in relation to the risk of obesity, high level of arterial blood pressure, high total level and LDL-blood cholesterol in adulthood (Horta et al., 2015). Protective effects of breastfeeding have been indicated also in autoimmune disorders including coeliac, diabetes type-1 or bowel inflammatory diseases. The n-3 long chain polyunsaturated fatty acids, the main components of breast milk, have been indicated to be involved in neurodevelopment and cognitive abilities of the child. Next to well-studied nutritional components of human milk such as mentioned fatty acids, immunological factors, growth factors, maternal cells, there are also abundant amounts of bioactive elements such as stem cells and miRNAs.

Stem cells in human milk and their therapeutic potential

Experiments in animal mouse models have shown that breast milk stem cells are able to migrate to the various organs of the

infant, such as heart, brain, thymus and pancreas (Kakulas, 2015) and potentially be able to differentiate into the tissues in which they will end up in the newborn child's body. In addition, stem cells found in human breast milk offer an attractive, relatively readily accessible alternative to the problematic embryonic stem cell research as they include cells exhibiting both multipotent and pluripotent capabilities. The moral implications of using an embryonic stem cell in research have sparked a discussion amongst the scientists, religious communities, and the wide public. Noteworthy, breast milk stem cells provide immense potential for developing new promising therapies that can treat, cure, or manage diseases such as hematopoietic, neurological, cardiovascular, and bone disorders (Peterson, 2016).

MicroRNA

Another valuable bioactive material present in human milk are microRNAs (miRNAs). These molecules play pivotal role in epigenetic expression and differentiation in phenotype between species and within human populations despite similarity in encoded proteins. The epigenetic consequences of miRNAs, transmission through maternal milk on future generations, are not yet understood.

Small non-coding RNA molecule have been demonstrated in all three fractions of breast milk and the levels of miRNAs and their expression are similar in colostrum and mature milk (Tingö et al., 2021). The richest in miRNAs are cells (leukocytes, lactocytes, myoepithelial cells, a hierarchy of progenitor and stem cells, and bacteria), in comparison to the fraction of lipids and skim milk. They are carried to the infant via the exosomal and cellular components of breast milk. Due to less acidic stomach environment of a child, miRNAs from human milk can survive, absorb and integrate in infant exerting gene regulatory function at the cellular level (Alsweed et al. 2016). miRNAs are resistant and stable when pasteurized by the Holder method (high pressure processing) of human donor milk at 62.5°C for 30 minutes (Smyczynska et al., 2020). An epigenome wide association study has shown association between breastfeeding duration and methylation level at 4276 CpG sites, corresponding to the 2635 genes (Naumova et al., 2019). Besides their job in cell-cell communication and regulation the immune system, miRNAs are likely involved in the epigenetic regulation of stem cells fate and function. In human milk have been abundantly discovered the following microRNA: miR-148a, miR-30a, miR146b, miR-200a, miR-21, let-7f, let-7i, miR-146b (Tingö et al., 2021) regulating

mainly DNA methylation by targeting DNA methyltransferases (Bodo and Melnik, 2017). MiR -148a is the most abundant microRNA in human milk extracellular vesicles and is involved in many cellular processes, such as suppressing tumour growth, metastasis, mitigating NF-kB mediated intestinal inflammation, exerting neuroprotective effect (Alzheimer's disease, epilepsy), or modulating angiogenesis (see cit. in Chutipongtanate et al., 2022). Dysregulation of miR-21 was suggested to be linked with the increased risk of hepatocellular carcinoma by changing mTORC1 signaling, such as PTEN expression (Meng et al., 2007). PTEN is also a direct target of miRNA-148a that was down-regulated following incubation with milk derived exosomes suggesting that miRNAs from human milk may protect children from cancer from birth to adulthood (Reif et al., 2019). Thus, understanding more about the communication between mother and infant may have key clinical impact and applications as a predictive marker and therapeutic agent.

Epigenetic mechanism of "Milk-kinship"

Milk-kinship according to the religion of Islam defines the consanguinity caused by breastfeeding genetically not related individuals by the same woman. To understand how milk-kinship marriage

maybe associated with risk of certain disorders in future generations, Ozkan and his research group set up an experimental animal model using a/a and Avy/a mice on C57Bl6J background (Ozkan et al., 2012; 2021). Since the genetic structures and environmental conditions of the crosssibling and control groups were the same in their model, breast milk was supposed to be the only responsible factor for existing epigenetic changes. Because of the similarity of the genetic backgrounds and environmental exposures of the two groups, posttranscriptional epigenetic mechanisms, especially through miRNAs, were investigated instead of DNA methylation patterns or histone modifications. Thus, randomly selected animals in the both F2 groups (milk-siblings vs control) were sacrificed for miRNA expression analysis and the remaining were screened for phenotypic features (coat colour, obesity, hyperglycemia, liver pathology, lifespan). Their study revealed that the life expectancy of the F2 offspring obtained from milk-siblings mating was much shorter than the offspring from control group (387 vs 590 days, $p = 0.011$). Offspring of milk-siblings were more obese during the aging period and histopathological examination of liver tissues displayed abnormal findings that have not been observed in the offspring from control matings, e.g., lymphoproliferative

nodules, abnormal iron accumulation, and fibrosis (Ozkan et al., 2021). The microRNA profiling identified particularly mTOR signalling, P13-Akt, ErbB, MAPK and insulin signalling pathways that were targeted by miRNAs differentially expressed in milk-siblings. These signalling pathways are associated with the development of the metabolic syndrome and its complications, fatty liver disease, respiratory disease, diabetes, cardiovascular disease, and cancer development (Templeman and Murphy, 2018). Moreover, miR-186-5p was downregulated and GSK3b upregulated in milk-siblings compared to control groups. Downregulation of miR-186-5p and upregulation of GSK3B have been reported in ovarian carcinoma (Hilliard et al., 2011; Templeman and Murphy, 2018). Overexpression of GSK3B has been implicated in insulin resistance, polycystic ovary syndrome, platinum-resistance in ovarian cancer (Hilliard et al., 2011).

Their finding have shown that there is period in which offspring are susceptible to breast milk induced epigenetic changes. The period that begins with conception and covers the first 2 years of life is suggested as the most active period in terms of epigenetic regulation, especially in terms of DNA imprinting. Therefore, this period is referred to as “1000 day period” (Linner

and Almgren, 2020). And this period is in agreement with the verse from the Quran:

„We have commanded people to honour their parents. Their mothers bore them in hardship and delivered them in hardship. Their ‘period of’ bearing and weaning is thirty months. In time, when the child reaches their prime at the age of forty, they pray, “My Lord! Inspire me to ‘always’ be thankful for Your favours which You blessed me and my parents with, and to do good deeds that please You. And instil righteousness in my offspring. I truly repent to You, and I truly submit ‘to Your Will’.”

(Sahih International translation of Holy Qur’an, chapter 46 (The Wind-Sandhills (Al-Ahqaf):15)

The Qur’an highlights a physiologic bond between a mother and child lasting 30 months. This has been interpreted as a period that starts during gestation and continues until weaning when the child is 2 years old (Subudhi et al., 2021).

Nevertheless, these remarkable findings open important bioethical problems and put new barrier in potential necessity of using human donor milk from the human milk bank where all donors are usually anonymous. It created uncertainty and serious concerns of Muslim communities because no single donor is identifiable or recorded. It should be standard norm to provide all necessary documentation about

donor woman and even all recipients of her milk to avoid marriage between individuals of these families. Ghaly (2018) recommended that newborn baby can receive milk from three to five donors with known identity and four feeding from one donor only. Another solution is suggestion of Daud et al. (2020) to introduce Sharia Compliant Human Milk with the option to establish milk kinship when the requirements are met (wan Yusoff and Abidin, 2022). For example, Human Milk bank in Spain has established mixing milk from only a single donor, allowing batches to be classified as female or male depending on the gender of the donor's child, "gender-specific donor milk". This solution was based on the interviewing different Muslim families, and developing a specific informed consent for Muslim families who preferred that their child could receive donor milk in case the gender of donor's child and theirs is the same. Furthermore, the donor milk has been pasteurized by high-temperature short-time that is thermal process in which milk is forced between plated or pipes and heated on the outside by hot water at the temperature 72 °C for 5-15s (Moro et al., 2019).

Conclusion

Recent research supports the idea of consanguinity via breastfeeding. It has been

indicated that factors modifying epigenetic mechanisms might be transmitted via breast milk to offspring and suggested the heritable unfavourable epigenetic effects of cross-fostering on future generations. However, further research in human model is required to verify and confirm these preliminary and undeniably impressive results which enlighten the superior wisdom of the Qur'an.

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