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ORIGINAL ARTICLE

Possible contribution of trained immunity in faulty hormonal imprinting and DOHaD: Review and hypothesis

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ABSTRACT

The faulty hormonal imprinting theory (published in 1980) and the DOHaD (Developmental Origin of Health and Disease theory (published in 1986) are twin-concepts: both justify the manifestation after long time (in adults) diseases which had been provoked in differentiating cells (e.g. during gestation). This was demonstrated using animal experiments as well, as comparative statistical methods (in human cases). However, there is no explanation for the tools of memorization (even after decades) of the early adversity and the tools of execution (manifestation) in adult age. It seems likely that immune memory is involved to the memorization of early adversity, up to the manifestation of the result (non-communicable diseases). Nevertheless, the relatively short timespan of adaptive immune memory makes this system insuitable for this function, however the newly recognized trained memory of the innate immune system seems to be theoretically suitable for the storage of the records and handling the sequalae, which is the epigenetic reprogramming in the time of provocation, without changes in base sequences (mutation). The flawed (damaged) program is manifested later, in adult age. Evidences are incomplete, so further animal experiments and human observations are needed for justifying the theory.

KEYWORDS

hormonal imprinting, DOHaD, immune memory, early-time-provoked adult diseases, innate immunity

INTRODUCTION

Up to the last decades in vertebrates two types of immunity were accepted: innate and adaptive immunity. The most prominent difference between them was their memory, as it was believed that only the adaptive immunity have immune memory (producing defense against the second attack by the same infectors), while innate immunity was believed more primitive with a general immune capacity, which can differentiate between self and non-self, without specifically recognizing the antigen. It is already characteristic to evolutionarily lower vertebrates, invertebrates, plants, bacteria and archea however, it is working also in higher vertebrates, which also have the adaptive immunity, with memory cells (B and T lymphocytes) memorizing the encounters with specific antigens. And reacting to them in case of a second encounter [1–5]. However, in the last time it was cleared that animals without adaptive immunity are also defended against secondary attacks (re-infection). This observation leads to the discovery of trained immunity (immune memory of innate immunity) which has many-sided evidences today [6]. This type of immune memory is represented by myeloid elements of the immune system: macrophages and monocytes as well, as natural killer cells (NKly) [7]. In the last time -first of all by the discoveries of M. Netea and co-workers it was justified that innate immunity also has memory and this type of immune-memory got the name, trained immunity. In addition to the special properties of trained immunity, it helps the memorizing actions of adaptive immunity, by controlling it [8].

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THE PHYSIOLOGICAL AND FAULTY HORMONAL IMPRINTING

In 1980 had been at first published the theory of hormonal imprinting [9, 10], which justified by animal experiments that a perinatal intervention (inside or outside the womb) by hormones or hormone-like materials provokes late manifested events in adult age of the offspring [11–13]. These events were alteration in the binding of hormone receptors and hormone synthesis as well as differences in sexual behavior and functions [14], bone composition [15], immunity [16] etc. Diseases freshly appeared or earlier present diseases are flearing up. This brought to the front the notion of the functional teratogenicity (which does not observable at birth, however appears at any period of life and could be as serious as morphological ones) and videned the teratogene zone beyond pregnancy [17, 18]. Later it was cleared that faulty imprinting could be provoked also in other periods of life, e.g. at weaning [19], during puberty [20, 21] adolescence and in any time of mammalian life in cells which are in the phase of differentiation, when the imprinter is active [22]. Considering this fact, immune system seemed to be the most vulnerable from this point of view however it is not only the target of the process, but could also be the executor of the harmful effects. The effect of faulty hormonal imprinting is lifelong, independent of the originating period of life.

THE DOHAD THEORY

Six years after the publication of the hormonal imprinting concept, in 1986, the developmental origin of health and disease (DOHaD) theory was published by David Barker and co-workers [23–25], which had an enormous publicity and popularity. This justified the possibility of manifestation in the adult human offspring: the effect of a perinatal disease or adversity. It was justified by using comparative statistical methods in human cases, demonstrating the relationships between weeds at birth (weights or death of the offspring), and cardial insufficiency in human adults.

It must be underscored that both concepts equally showed the interrelation between the developmental effect and late manifestation. However, there is not known the mechanism by which the developmental effect is fixed and memorized, even for decades. As animal experiments justified that the faulty hormonal imprinting was inherited to the cell line touched as well as transgenerationally [26–28], epigenetic changes were suspicious in the storage of the event.

THE IMMUNE MEMORY

In the vertebrate organisms two systems are believed for having memory "professionally": the nervous system and the immune system. In our case the immune system is more suspicious for contributing in the physiological and faulty hormonal imprinting as well, as in the manifestation of developmentally originated diseases. However, the immune system has two different parts, the innate immune system and the adaptive immune system. Considering the original belief, the adaptive immune system have memory cells (B and T lymphocytes, which are saving the reminiscence of a meeting with the antigen while the innate system seemed to be indifferent from this point of view. However, in the last time it was demonstrated that the myeloid cells of innate system (monocytes, macrophages) and NK-ly cells are also able to memorize the meeting with certain antigens and this was named by Mihai Netea trained immunity [7, 29–33]. The cells of innate immunity memory system has receptors for recognizing the education-executing cells [31] and can build cross-protection to secondary infections. It was not studied their role in case of non-bacterial provocations up to now however, it is likely that they have similar behavior. In contrast to the memory of adaptive immune system cells, trained immunity has longer life and by this property it could contribute in the storage of a developmental adversity for decades, and have the tools inside the system, by which it can realize a response to it, at any period of life. The "weapon" of trained (innate) memory is the epigenetic reprogramming, which does not change the sequence of nucleotid bases however, the changed program epigenetically inherited to the progenies (members of the cell line) and transgenerationally [30].

TRAINED IMMUNITY AND MEMORY OF ADVERSITIES

The epigenetic reprogramming

Genes bear and handle the information which characterizes a species and its individual members, and this genetic information is present in each cell of an organism. However, from this universal gene pool an epigenetic regulation chooses those genes which are manifested in a special organ or in a special occasion as well as their expression in a certain moment. This epigenetic regulation is arranged in a program which is assembled perinatally and theoretically valid for life. Methyl groups bound to DNA of promoters and histone tail metylation by methyltransferase enzymes and acetylation suppress the expression of genes and demethylatation of this latters is taking part in the promotion of genetic activity. These mechanisms are continuously working during life which epigenetically reprogram the whole original program or parts of it [34]. The previously mentioned methylation machinery (having the enzymes for methylation and demethylation) is working on the instrumental board, reprogramming the earlier settled program. There are such periods of life, which are outstandingly touched by reprogramming endogeneously or by external (environmental) factors. These are the perinatal period [35–41], weaning [16, 42], adolescence [21, 43], when hormones or hormone-like natural or man-made molecules (endocrine

disruptors) provoke faulty hormonal imprinting causing the developmental origin of health and disease (DOHaD), with life-long consequences, as functional alterations of the program, or inclination to diseases, manifestation of diseases etc. Sexual behavior is seriously altered [14], as well, as bone composition [15] however, the immune system seems to be the most vulnerable because of its continously differentiating cells in any periods of life. This vulnerability of the immune system also negatively influences different functions of the given organism and likely by trained immunity, is inherited to the cell line and the progeny generations.

How the memory to early adversities is working and how is it manifested later?

As between the early provocation of a late menifested disease and its manifestation could be even decades, somewhere in the organism the information of insult must be stored. This site could be the target itself or some memory-bearing apparatus. This latters are in vertebrates the nervous system and the immune system. However, in both systems epigenetic reprogramming is the tool, by which the change of program can be enforcable [44].

As long as it was believed that the immunological memory is present only in the adaptive immune system, this was believed incompetent for the function of storing information of adversities, as the information-storage for decades, would be above its abilities. Innate immunity seemed also not to be suitable, as it was accepted that this type of immunity has not memory at all. However, observations on the result of vaccination -which is an example of trained immunity call attention to the possible duration of it, permits the supposition, that training of innate immunity (trained immunity) is in connection with the storage of faulty imprinting information [45, 46]. At the same time, the immune system – its activation or deformation (into autoimmune events) could not only reactivate the memory, but to execute the realization of the -early-provoked-reprogramming [37]. This does not disclose the participation of non-immune cells in the storage of memory for early-life adversities, by other -even non-immune- cells, moreover by some opinions it is needed for the full memorization [47]. There is such opinion – and this seems to be real, considering developmental observations, that " every living cell might be capable of learning from experience, storing for a time by its own epigenetic reprogramming what has been learnt and display and use it when needed. The adaptive and innate immune system is only the highest efficiency of this property which "professionally practise" this process.

Primitive forms of trained immune memory can be observed already in invertebrates, however its well developed forms can be found only in mammals.

It seems likely that the success of training (e.g. duration of the educated material) is dependent on the openness of a developmental window, similar to the case of faulty hormonal imprinting. However, the trained immunity concept is continuously developing and today there is also a form of it, named expanded trained immunity concept [48], which call attention on the possibility of a "unique, interactive, cross-talking: cellular organism sharing memories of previous microbial encounters". Replacing "microbial" to the more general "adversities" the contribution of this organism in memorization and evocation of a faulty imprinting event could be imaginable.

Dangerous trained immunity

The reprogramming as a consequence of training in the case of innate immune cells could reform the program of immune system hyperresponsive or hyporesponsive, provoking the immune response to secondary stimuli. Hyperresponsivity can lead to allergy or autoimmunity, which can be manifested in different diseases during or after the case of second encounter or after encounter with an otherwise indifferent stimulus. This fact is suitable to explain the manifestation of a chronic autoimmune, metabolic, and neuroinflammatory disease as well, as cardiovascular and cancerous diseases [32, 49–54], which are caused directly or translationally by faulty imprinting or DOHaD. This means that trained innate immunity can be useful or harmful with equal chance. The data are concentrated to microbial infections as early provocators however chemicals (e.g. endocrine disruptors) are likely able to provoke the later faulty response.

The diseases, which are manifested in adult age, after the perinatal or pubertal provocation seem to be spontaneous however, the early immunological attacks were not registered, as they are rather common, as intake of certain medicaments [55], mild bacterial or viral infections, an encounter with some unknown food or food components, and similar events, as provocators could be present also in adult age. If the innate immune system is hyperreactive, the process of disease-development starts co-operating with other factors destroying the organism (e.g. setting of lymphoid malignancies). This means that trained innate immunity not always amicable [56].

As the notion of trained immunity has been introduced and are used mainly by immunologists, bacterial cases are studied however, other factors (chemicals, hormone-like molecules as endocrine disruptors also can influence the innate immune system, producing trained immunity, the cells of which could memorize (likely lifelong) the attack in the developmentally sensitive periods of life. This memory could be raked up after a long time (even after decades) and a disease is manifested. This could be the explanation of faulty hormonal imprinting and the developmental origin of health and disease (DOHaD). This means that these pathological processes are sequelae (victims) of otherwise useful mechanisms, as well, as in many other built-in mechanisms, e.g. autoimmunity or rejection of life-saving transplants.

From evolutionary point of view immune system's development rather helped the defense of inner conditions than the fighting against outer attacks. Although trained immunity is demonstrated most often in cases of vaccination, its role in the regulation of tissue harmony can not be neglected. It is believed that "trained immunity is initiated

by extracellular signals, that trigger a cascade of events affecting many functions of the cells" and this process could be the provocator of the early-life induction of late-manifested responses (non-communicable diseases), from cardiovascular alteration to cancer development.

If "immunity" is not restricted to antibacterial meaning, a lot ot already above-mentioned non-infectious diseases can be listed as immune-problem-caused. The recognition of trained immunity and its combination with the faulty hormonal imprinting and DOHaD could give explanation to many problems in connection with diseases, the reason of which unknown up to now. The transfer of microbiological to immunocentral mentality could help the understanding of immune system in general and especially the outstanding role of faulty immune mechanisms in the emergence of diseases, beyond allergy and autoimmunity. At the same time it is not sufficient to explain why just the given disease appears, and how is this selected. It is also not known whether the execution of DOHaD or faulty imprinting is the original function of trained immunity, or this only a side-product.

There are no data on the inheritance of trained immunity. However, as faulty hormonal imprinting is inherited in the touched cell-line and transgenerationally, in all probability trained immunity, that is the results of innate immune cells' education could also be inherited. This means that a further factor makes the mechanism of faulty imprinting and DOHaD more complicated.

The innate immune memory in the early life is different from the adaptive immune memory, as it is developing following a stimulus, which is not specific to the original stimulus, as it is needed for the defense of immunologically unmatured immune system, and heightened vulnerability. The stimuli could be BCG vaccination, and beta glucan as well as a variety of other stimuli, as endocrine disruptors (e.g. bisphenol A), and infectious agents also can stimulate trained immunity, leading to epigenetic reprogramming of the earlier programmed immune activities. The results of these reprogrammings not always positive.

Hormonal imprinting, DOHaD as well as trained immunity are new approaches which help to decipher unsolved theoretical problems of immunology however, they also could help diagnosis and therapy alike. New data have to be collected and inserted into the well grounded knowledge of immune theories before the new notions rooted. Nevertheless, their presence must be considered as soon, as possible.

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