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SHOULD INTRACORPOREAL RESIDENT MICROBIAL ASSOCIATIONS BE VIEWED AS AN INDEPENDENT SYSTEM, ALONG WITH OTHER INTEGRATIVE SYSTEMS OF MAMMAL'S ORGANISM?

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ABSTRACT

Anaerobic microorganisms (saprophytes, conditionally pathogenic microflora) never existed and do not exist isolated in an animal organism, naturally they participate in formation of multicomponent associations that in addition to anaerobes include numerous representatives of mycoplasma, viruses and, most importantly, aerobic microorganisms. For this particular reason "microbe-host" relationships should be based on at least two cardinal principles:

Synergy and/or antagonistic relationships of microorganisms within a concrete association; inter-associative relations of microorganisms, persisting in various target organs are not excluded as well. Development of the infections process is a consequence of disturbed "dynamic" balance between evolutionarily formed relations in various inter-microbial associations. In its turn, initial changes of homeostasis caused by various exo- and endogenous provoking factors of non-infectious nature can lead to disturbance of symbiotic interactions both in microbial associations and at the level of micro- and macro-organisms interaction, which may also lead to induction of infectious process in a certain situation.

Biological expediency of "coexistence" between microbial associations and animal organism, developed in the course of micro- and macro-structures evolutionary development directed at the maintenance of optimal conditions for growth and vital ability of microorganisms, on one hand, and numerous integrative functions of the host organism, on the other.

As we described earlier, many bacteria that realize their existence and developmental cycle beyond the host organism are characterized by a rather difficult structural organization expressed in multidirectional activity of concrete micro-species within the "monoculture". This has even allowed some authors to consider the activity of those microorganisms that are capable to form original families-colonies from standpoints characteristic for highly organized beings.

Thus, the activity of resident microorganisms associations is based on the principle of mutually beneficial, expedient co-existence of micro- and macro-organisms.

Our hypothesis states that intracorporeal associations of resident microorganisms should be viewed as an independent system in the integrative activity of mammals' organism.

KEYWORDS: *microorganism associations, system of endogenous microorganisms, immunomodulatory effect, regulatory functions*

Many cellular associations of mammals' organism are endowed with multifaceted potencies dependent on the site of their application in the functioning of specific integrative systems. In our view, the concept "association", is exclusively arbitrary, since specific stages of their effects on target cells are singled out of the entire spectrum of polyfunctional activities of parenchymatous and stromal cells. Such analytical approach in biology and medicine can be rather justified, because it is aimed at identifying specific mechanisms underly-

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ing the formation and course of specific processes in specific organs and tissues.

Similar examples at the modern stage of development of various branches of fundamental medicine are more than enough. Several of them will suffice for elucidation.

As early as 1969, famous English pathologist A. Pearse proposed a concept about organism's "specialized, highly organized cellular system with a distinctive capability of producing peptide hormones and biogenic amines" [*Pearse A, 1969*]. According to this concept, certain cells throughout an entire organism are capable of synthesizing biogenic amines by preliminary uptake of their precursors. The author designated these cellular "associations" by the term APUD (amine precursor uptake and decarboxylation). APUD system includes over 60 types of cells localized in various organs and systems [*Andrew A, 1982; Raikhlin NT et al., 1993; Raikhlin NT, Kvetnoy IM, 1994; Kvetnoy IM et al., 1999*].

Kvetnoy et al (1999) rightly suggest that "accumulated data were largely beyond traditional concepts of hierarchic dependency within two major regulating systems: nervous and endocrine". In this regard, many authors [*Polak JM, Bloom S, 1986; Sundler F et al, 1989; Raikhlin NT, Kvetnoy IM, 1994*] believe that both of these systems should be united into "a universal diffuse neuroendocrine system", which should also include hormones and mediators produced within APUD system. Certain confusion arises with the aforementioned concepts, since one multicomponent (APUD system) is artificially integrated into another more multifaceted and more polyfunctional neuroendocrine system. Considering the significant role of serotoninergic processes in regulating the cardiovascular system, implemented at various levels of its structural organization, the very APUD system, in our view, can be considered "filial" – within the cardiovascular system.

Tissue basophils (mast cells) have to function, in our view, within the neuroendocrine system, and particularly APUD system. In particular, these basophils function as a source of the serotonin and melatonin synthesis. On the other hand, the same tissue basophils have been observed throughout many years as part of the functioning of "mast cells and eosinophil association". The activity of "mast cells and eosinophil association" is viewed as an extravascular factor in regulating transcapillary exchange in both directions of the blood-tissue interface functioning. Thus histamine and serotonin, produced in tissue basophils, exert a distinctive vasoactive effect on microhemocirculation pathways composite components. In the process of histamine efflux from tissue basophils, tissue eosinophils provide balanced supply of histamine to microvessels' walls by way of extra histamine "dose-dependent inactivation". Inactivation is achieved by histaminase that is produced in tissue eosinophils. That is exactly why the same "mast cells and eosinophil association" can be observed within the cardiovascular system as an important extravascular factor in regulating its final link – the microcirculatory stream. At the same time, the activity of tissue basophils is rather multifaceted due to their production of multiple biological factors of transmitter and hormonal spectrum of activity. In particular, there are data indicating that tissue basophils themselves act as a source of melatonin synthesis [*Kvetnoy IM et al., 1999*].

Thus, an example of only one cell of a tissue basophil and its role in implementing specific functions utilized in the neuroendocrine, cardiovascular and APUD systems seems highly debatable. As a result, some confusion occurs not only in the terminology for specific links of structural organization of cells, functioning within association and/or systems; at the same time, more importantly, "hierarchic structure" is affected, within which, in our view, "associations and filial systems" must be functioning. Similar examples where this principle is affected are abundant. Here are some of them. It is not clear how such concepts are related to each other:

- Nervous system and neuroendocrine system
- Neuroendocrine system and APUD system
- Serotoninergic system and APUD system
- Parasympathetic system and GABAergic system
- Cardiovascular system and catecholaminergic system
- Digestive system and hepatobiliary system
- Genitourinary system and reproductive system

The term "system" is also used in microbiology, virusology, bacteriology, mycoplasmology in "classification" of different microorganism associations. In a very informative report of G.G.

Miller (2000), the author touches upon this subject. Here are the author's literal statements:

"So, in summarizing literature data from the beginning of the century and spontaneous findings in biological and clinical materials and laboratory experimental designs in recent years, at least eight distinct systems of microorganism associations at different levels of organizations can be singled out. In this context, we once more face the irrefutable fact of the globality of this phenomenon.

- System of protozoa-protozoan parasites-eukaryotic cell
- System of bacteria-bacterial viruses-eukaryotic cell
- System of rickettsia-viruses-eukaryotic cell
- System of mycoplasma-mycoplasma viruses-plant or eukaryotic cell
- System of mycoplasma-infectious or oncogenic viruses-eukaryotic cell
- System of two or more infectious viruses-plant or eukaryotic cell
- System of infectious virus-oncogenic virus-eukaryotic cell
- System of two or more oncogenic viruses-eukaryotic cell"

Finally, association links of microorganisms both with each other and host cells are described as at least eight "independent systems":

In our view, these are not separate systems. They should be more correctly described as "association relationships". For instance, item two can be explained as association relationships: bacterium -bacterial viruses-eukaryotic cell. The other seven items should be corrected exactly by this principle. In this particular case, the term "system" should apply in the totality of association activity of intracorporeal microorganisms within a macroorganism, indicating the pattern of association relationships mentioned in the eight specific items.

I find it necessary to draw a reader's attention to the following circumstance. The concept of "the system of intracorporeal resident microorganisms" we have proposed is not random or dictated by someone's whims, not to mention priorities.

By meeting all the requirements of known functioning systems in an organism, the "system of intracorporeal resident microorganisms", in our opinion, should be viewed not in terms of application, being the prerogative of only microbiologists, virologists, infectious disease specialists, but also in a biology-wide aspect. Firstly, we deem it necessary to review the dogmatic, and sometimes faulty scientific and methodological approach when analyzing the entire multifaceted "microbe-host" activity, in which randomly pathogenic intracorporeal microorganisms were considered only as potential induction factors of pathologic processes in the presence of infectious and other somatic diseases.

The term "system of intracorporeal resident microorganisms" should be understood as association activity of persisting microorganisms in a host's econiches. These persisting microorganisms function by the only validated, evolutionally justified mechanism – existence by using energy resources of macroorganisms with simultaneous participation in the activity of an organism's integrative systems at all levels of their structural organization.

The basic provisions of our hypothesis are set forth in greater detail in the monograph of this article "The System of Intracorporeal Resident Microorganism Associations", published in 2014 in the Armenian, English and Russian languages.

It is known that populations of living beings are formed and function through interaction of numerous functional systems [*Sudakov K, 1997; 2007*].

In this regard, our proposed concept "the system of intracorporeal resident microorganisms" [*Zilfyan AV, 2014*] fully fits in with the concept of "functional systems" proposed by L. Bertalanfy [*Bertalanfy L, 1967*].

While relying on the tenets of L. Bertalanfy, P.K. Anokhin (1967, 1978) "precisely determined a system forming factor represented by adaptive results beneficial both for functional systems themselves and unifying their integral organizations in the formation of various functional systems".

According to abovementioned authors, "functional systems are dynamic, self-organized and self-regulated formations whose components unite in order to achieve adaptive results beneficial both for system itself and organism as a whole".

The concept of "system of intracorporeal resident microorganisms" meets all the constituent parameters-criteria, described in this definition of functional systems:

Resident microbial associations are undoubtedly "dynamic, self-organized and self-regulated formations". In this particular case, the concept

"dynamic" reflects all the evolutionary stages of coexistence of microorganisms within a macroorganism. These are permanently occurring processes of their reproduction and death, secretion and spread to organism's internal environment (blood, lymph, regional lymph nodes, target organs) bioactive compounds.

The concept of "self-organized and self-regulated formations" should be understood as intermicrobial relationships primarily based upon the peculiarities of their metabolism in the process of coexistence within unitary econiches of a host of resident aerobes and anaerobes, saprophytes and opportunistic microorganisms, including viruses, mycoplasmas and others. Continuity of specific microbial associations is due to evolutionally developed mechanisms in the host's organism, which underlie their internal self-regulation.

And finally, regarding the last tenet of the functional systems theory, "… all the community components unite in order to achieve adaptive results beneficial both for system itself and organism as a whole".

In our opinion, endogenous resident intermicrobial associations are communities whose activity, on the one hand, is aimed at sustaining bacterial homeostasis in host's organism, and on the other hand, their activity in normal organism is highly beneficial, and more specifically, necessary both for the microorganism itself and the host's organism. This activity is carried out by participation in maintaining organism's many integrative functions, primarily implemented at the level of immune, endocrine and cardiovascular systems. In its turn, the host provides all necessary conditions for optimal activity and permanent reproduction of microorganisms functioning within intermicrobial associations in strictly determined econiches of a macroorganism.

Our hypothesis states that intracorporeal associations of resident microorganisms should be viewed as an independent system in the integrative activity of mammals' organism.

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