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Immunokinetics: a new approach to vaccines. A working hypothesis

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Abstract
This paper outlines the working hypothesis that immune response is triggered, beside antigenicity referred to by the two major theories of Burnet (1959) and Jerne (1974) by the kinetics of the antigen that enters the body or, in the case of an endogenous origin, there is released from compartments where it is normally sequestered. This hypothesis, for simplicity called immunokinetics, postulates that the intensity of the immune response grows with the increase of the rapidity of the above contact or release and, conversely, declines with its decrease. Sublingual administration allows, by speeding up the vaccines absorption, to optimize their efficacy, safety and uses. Kinetics is also discussed in connection with homeostatic and adaptive processes involved in evolution.

Key words
• immunokinetics
• vaccines
• sublingual administration
• adjuvants
• evolution kinetics

BACKGROUND

Vaccines are one of the cornerstones of medicine [1-3]. They have defeated debilitating and fatal diseases, such as smallpox, tetanus, diphtheria and polio. Vaccines could, if used to their full ability, fight many other illnesses, such as tuberculosis and AIDS. They are also effective against infections of domestic and farmed animals, some of which are transmissible to humans. They are characterized by a preventive action, but are also able to treat infections with slow progression, such as rabies and tuberculosis. The most common ones activate the immune system, but there are also those desensitizing, used against allergies. Vaccines open to research therapeutic perspectives concerning infections that still afflict humanity, such as malaria and leishmaniasis, as well as cancer and autoimmune and degenerative conditions. Vaccines have a valuable quality, which distinguishes them from antibiotics. The latter belong to antibiosis [4], an effective defensive system, but archaic and coarse, which uses little flexible arms, unable to adapt to the distinctive features of each pathogen. During the evolution, this system has been overtaken by the immune system, which produces the equivalent of antibiotics, but in a more advanced version, prepared "to measure" of the individual offender and often able to neutralize its counter adaptations resulting in resistance. While antibiotics and chemotherapeutic agents fight infection by adding a disease-fighting capability to the body, vaccines activate its internal defenses: the former can be compared to a mercenary troop, the second to the army that defends its own country and families. This is a biological lesson that applies to medicine, as well as to life in general: the best solution to the problems lies in the leverage of internal resources. The use of a mercenary aid, such as that provided by antibiotics, should be restricted to circumstances that can't be faced by the host per se.

Several problems, however, remain open. First, adjuvants and preservatives feed disputes and fears not wholly unjustified [5, 6]. Second, an obstacle to the widespread use of vaccines consists of injectable forms and syringes, which already themselves feed fears and concerns. Thirds, despite extensive research [7, 8] the majority of fungal and protozoan infections are still lacking viable vaccines. Fourth, the hopes of developing vaccines to prevent or combat autoimmune diseases and cancer have largely been disappointed.

THEORETICAL FOUNDATIONS

According to the theory of "clonal selection" [1], the immune system comes from a heterogeneous population of embryonic cells, originally able not only to distinguish "self" from "non-self" based on their antigenic properties, but also to attack and reject both of them. These cells are subjected, before and immediately after birth, to a selection of similar meaning to that which presides, in the Darwinian conception of phylogeny, the evolution of species [9]: those directed against the body of the host are eliminated, because harmful for survival, the others are preserved. The ability of living organisms have to defend what may harm would be bound, therefore, to this ancestral process focusing primarily, but not exclusively on T and B lymphocytes. Each clone of them is able to detect and reject, according to antigenic characteristics, only one

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of the multiple expressions of life that, being foreign to the body, could damage it.

The theory of "idiotypic immune netwo rk" [2] was drafted fifteen years after that of clonal selection. It provides the immune system with a negative feedback mechanism, in which antibodies behave as exogenous molecules, triggering an antigen reaction that slows their production. This response has the usual latency of 2-3 weeks, corresponding to the mobilization and proliferation of specific cell clone that there is involved. During this time interval, the antibodies remain active. The antibody against the antibody acts in turn as antigen, thus triggering a series of reactions of decreasing intensity, sinusoidal in character.

Despite extensive research, here again some basic problems remain open. As an example, there is no convincing explanation of why many endogenous macromolecules, which according to the theory of Burnet [1] should not be immunogenic, they become such as a result of events, traumatic or otherwise, able to bring about a rapid release into the circulation.

IMMUNOKINETICS

This paper outlines the working hypothesis that immune response is triggered, beside antigenicity at the center of the two major theories of Burnet [1] and Jerne [2], by the kinetics of the antigen that enters the body or, in the case of an endogenous origin, there is released from compartments where it is normally sequestered. This hypothesis, for simplicity called immunokinetics, postulates that the intensity of the immune response grows with the increase of the rapidity of the above contact or release and, conversely, declines with its decrease. While the theories of clonal selection and idiotypic immune network are largely based on experimental evidences described both in original papers and subsequent overviews [10, 11], the immunokinetics hypothesis is mainly supported by spontaneous natural phenomena, which anyone can verify. It takes into account that rapidly evolving infections, such as smallpox and typhus, elicit a stronger immune response than the slowly evolving infections, such as rabies, tuberculosis and AIDS. It also explains why passing from prokaryotes to eukaryotes, typically represented by malaria, leishmaniasis and tumors, the immune response is reduced in tandem with the increase of cell replication intervals, passing from less than 1 hour, with some viruses and bacteria, up to 12-24 hours and longer with protozoa and multicellular organisms. Finally, it takes into account and explains why many endogenous macromolecules, which according to the theory of Burnet [1] should not be immunogenic, they become such as a result of events, traumatic or otherwise, able to bring about a rapid release into the circulation.

More generally speaking, kinetics is the parameter that separates the two fundamental moments of life: homeostasis, which means the defense of "self" from anything that might alter it, and evolution, understood as an adaptation to the environment and circumstances. The more rapid is kinetics, the more intense is the homeostatic response. *Vice versa*, a slow kinetics facilitates a mutual adaptation, bringing about the changes associated with evolution. This problem has arisen with the transition from unicellular living organisms to multicellular organisms, combining quite different systems and functions. Their mutual adaptation and coexistence required the above mentioned increase of cell replication intervals, which passed from less than 1 hour, with some isolated viruses and bacteria, to 12-24 hours and more with both prokaryotic cells and viruses and bacteria that coexist in multicellular organisms. In the same way, immigrants are perceived as strangers and rejected not only because of the skin color and appearance, but also depending on whether their arrival is sudden or gradual. In the first case, they are perceived as a danger even when a few tens land together; in the second case, millions of them can be integrated.

SUBLINGUAL VACCINES

It is known that the sublingual administration involves a rapid absorption of many substances, from ethyl alcohol up to macromolecules that are present in vaccines [12-14]: hence it appeared a suitable mean for testing in practical terms the immunokinetics working hypothesis. The first clinical trial was carried out on patients who refused injectable vaccines, considering the extraneous substances forced introduction in body as contrary to their religious principles [15]. In those days there was a Law (DL 17 February 1998, coordinated with the Law of 8 April 1998 n. 94), which in paragraph 1 established that "A doctor may, under his direct responsibility, after informing the patient and after acquiring his consent, use an industrially produced medicinal for an indication, a way or an administration different from those authorized, supposed that the prescription is consistent with works appeared in scientific credited international publications in that matter." In that particular case, the reference was to credited publications referring to sublingual mucosa permeability of vaccines in man and laboratory animals.

Taken together with the immunokinetics working hypothesis, the sublingual administration opens new perspectives to vaccines, as to:

- improving efficacy, practicality and safety of the existing ones, with special reference to exclusion of preservatives and adjuvants;
- facing the slow progression viral, bacterial and protozoan infections, which are still without vaccine coverage;
- activating an immune response against cancer and, *vice versa*, disabling the autoimmune ones.

It is reasonable to assume that the sublingual administration of vaccines should not introduce toxicological risks other than those which appeared in previous therapeutic use; on the contrary, these risks should be reduced due to the exclusion of adjuvant and preservatives. Sublingual vaccines, therefore, should not be subjected to the long, costly and complex tests and procedures that are required for entirely new vaccines.

CONCLUSIONS

The immunokinetics working hypothesis incorporates the great clonal prenatal selection [1] and idiotypic immune network [2] theories, providing both of

them with kinetics, as an additional key of lecture of the immune system functioning. Moreover, it opens new perspective to vaccines and, more generally, to immune research. It's of note that this hypothesis goes back to the traditional scientific method, consisting of the experimental reproduction and confirmation of knowledge primarily derived by the study of naturally occurring phenomena.

Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

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