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Opinion

Implications of Network Biology in the Understanding and Therapy of Cancer

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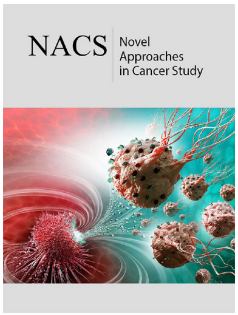

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Abstract

The complexity of the living world has only recently begun to unveil itself for scientists. Network-like chain of events,with multi-level regulation, build up an extremely complicated edifice, both in structure and function, that sustains life as we know it.The implications of this complexity for cancer are discussed in the present Opinion article.

Keywords: Network; Cancer; Immunotherapy; Targeted

Abbreviations: LT: Lymphocyte; MHC: Major Histocompatibility Complex; NK: Natural Killer Lymphocyte

Opinion

In the last few years, the network approaches în medicine have received increasing atention from scientists [1]. This was an expected development, as many studies in the fields of genomics, immunology, immunohistochemistry or computerized pathology showed a previously unknown complexity and multilevel structurality of the living world. Due to this extremely complex organization of molecular, cellular, tissue-level processes and not only, ordered chains of events take place, simultaneously or consecutively, at multiple structural levels, comunicating with each other in complicated loops, giving birth to an intricate network-like system which has as result the life of cells, organs and systems as we know it. In the meantime,when a disruptive factor modifies the operating conditions in a certain part of this complex system, this will result in the propagation of this disturbance along the biologic pathways, in a cause-and-effect manner, creating also a chain of events that often branches in a network-like pattern, which constitutes the pathophysiology of the respective disease.

Although it may seem an oversimplification , the study of such a system from the perspective of the network biology is necessary în order to have an accurate picture of what happens in the living systems, and, based on that, to design intervention strategies that correctly adress the events that happen.

How do these things apply to cancer? Very complicated chains of events occur în cancer, which were subject of much research, but in the end, as we and others have shown [2,3], all can be reduced to two main systems with network-like structure that are at work and interact in the cancer biology: the tumor development program and the immune system.

The development of cancer is believed to start with the occurence of oncogenic and supressor mutations [4]. The latter are usually congenital or acquired loss-of-function mutations in the genes that protect the genome or inhibit proliferation, so that the apparition or the action of the former becomes possible. These oncogenic mutations are believed to be the initiating event in the chain of phenomena that constitutes cancer biology, by the autonomous activation of the pathways that normally control proliferation. What happens next is the starting of a biologic program that was compared to a regenaration process [5]; the main

event is endless cell proliferation,but subsequent processes occur, which represent tissue capabilities that are normally activated when a tissue needs to regenerate: angiogenesis, recruitment of cells with regenerative potential and,very important for the events that follow, immunosuppression.

The observation that some events are systematically found în cancer has led researchers to characterize them as "hallmarks of cancer" [6] , traits that in a proportion or in another,are permanently present in cancer. Some of them are generated through the intracellular circuitry that is activated in proliferation, such as the inhibition of apoptosis and the metabolic reprogramming, and, given the stem-like character of many cancer cels, replicative immortality.The same is true about the cell adhesion, which is significantly down-regulated în tumor cells, making possible cell division, migration and invasion. Other cancer hallmarks like angiogenesis,cell recruitment and immunosuppression are,by contrast, manifested în the extracellular area or tumor microenvironment,being nonetheless cancer cell-derived.

What seems important to us is to observe that, although in some cases, there are mutations that can affect one or two of these hallmarks, such as mutations in E-cadherin or in the apoptotic pathway genes [7,8], these are rare events and cannot account for the widespread presence of these hallmarks în all cancers; indeed,it is highly improbable that these many traits arise independently in all cancers ; most likely, one or two of them arise through the action of carcinogens, and the others appear in a cause-and-effect manner, by the activation of the respective biologic pathways. The consequence is a network-like succession of events, in which the oncogenic mutation that provides the stimulus for proliferation occurs, with the support of the loss of suppressor genes, and all the other hallmarks are logically derived facts. Such a "network view" of the hallmarks of cancer has implications that will be discussed below.

In the meantime, the development of cancer is accompanied by many disorders, such as cellular stress, necrosis,surface cell modifications and apparition of antigenic structures; these constitute signals for the immune system, which will trigger an immune response, both innate, monocytes,neutrophils,eosinophils and inflammation, and adaptive, through Lymphocytes (Lts) of different types [9]. Each immune cell acts on its own stimuli, such as the down-regulation of MHC proteins for NK LTs, phospho-antigens for the γδ LTs or soluble antigens for B-LTs.

The resulting infiltration of tumors is composed by many immune "modules" that interact with each other, creating also a network-like structure on whose effectiveness the lifespan of the patient depends [10,11].It has to be said that immunocytes are versatile cells,acting on stimuli, the exposure to their specific stimuli making them tumoricidal cells, while exposure to the influence of the tumor cells turns them into cells with protumoral profile, or leads to their inhibition. By consequence, the multimodal and efficient immune response takes place in an hostile environment and loses much of its efficiency [12].

The therapeutic implications of the discussed facts could be the following:-regarding the tumor development program and hallmarks of cancer, attacking the different ramifications of the oncogenic program, like angiogenesis , immunosuppression or tumor-associated cells proved to be effective; approaching cell adhesion, for example re-expressing E-cadherin on the tumor cells, proved to diminish much of their invasiveness and to modify prognosis [13]; but if,as it was said, these all are derivates of the same oncogenic program, then the most reasonable thing to do is to atack this program at its roots,at the genomic level; indeed,some failures of the mentioned therapies coud be explained just by the fact that certain parts of the network were efficiently approached, while its main part continued to function;-concerning the immunotherapy,many approaches such as interleukins, adoptive therapies or immune checkpoint inhibitors are in use or in study; they have proven efectiveness in many situations,but had also limitations and failures; these may be explained,at least partially, considering the mentioned relation between tumors and immune response, because no matter which therapeutical mean is sent into the tumor, it will loose much of its efficiency in contact with the tumoral program. It results that while this program is going on, no maximally efficient immunotherapy is to be expected, and that to approach this tumoral program in every case becomes a reasonable, if not mandatory objective [14].

However, there is a difference between working with the "democratic" networks of the immune response and tumor microenvironment and with the much more "autocratic" networks of an activated tumor cell [15]. In the former case, where there are many immune "modules" with adaptable configuration, activating or polarizing stimuli like TLR agonists, bispecific antibodies or interleukins may be used to change the configuration of the immune response in the desired direction, while in the latter, where activation of certain key points leads to the activation of the entire subsequent signaling and transcriptional network, strategic points in this intracellular network may be found and adressed by actual means or by others that future research will uncover.

The knowledge of the biological networks, with all their branches, loops and feed-backs is a worthy objective in the effort to find efficient cures for cancer. Therefore,it is for future studies to shed light in this fascinating field, both by the understanding of the network structures in cancer, and by developing means to attack their key points.

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