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Chapter 1

Introductory Chapter: The Biology of Reactive Species

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1. Main concepts

Reactive species are a relatively old topic in the field of biomedical research, and yet many aspects of their role have remained unclear.

The initial theory, still valid, considers reactive species to be involved in the phenomenon of cellular aging by assigning them an exclusively harmful role.

Current data indicate the involvement of reactive species in cell signaling, assigning them an additional role in the physiological process of adapting the body to stress factors.

Much more scientific evidence indicates that, similar to many other biological molecules in the body, the reactive species trigger different cellular responses depending on their concentration. It is now accepted that in physiological concentrations, reactive species exert a beneficial role by modulating a large number of processes, but both diminishing and accumulating their concentrations trigger pathological processes. That is why although the notion of reactive species is maintained today, there is much more talk about the biology of reactive species.

Until now, the mechanisms by which reactive species act in antibacterial defense and in some signaling processes such as nitric oxide (NO) activity in vascular relaxation have been fully elucidated.

Now, the most current researches pursue several directions such as:

- identifying the reactive species that could trigger the activation of specific proteins and the inclusion/exclusion of these species in the category of second messengers;
- identifying the cascade reactions that can cause cellular response under the action of reactive species and the mechanism of its regulation;

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- identifying the links between reactive species and the inflammatory and carcinogenic processes;
- identifying the mechanism by which reactive species influence epigenetics.

From the enumeration of these themes, it is obvious that research of reactive species is far from being elucidated and exhausted.

Survival of aerobic organisms depends on the presence of oxygen. The main use of oxygen is its participation in the energy generation process. In all processes using oxygen, reactive oxygen species (ROS) are constantly formed as secondary products. ROS are a group of compounds with increased reactivity including anion superoxide ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), singlet oxygen ($1O_2$), and hydroxyl radical ($OH^{\bullet}$), which can be formed in living organisms. In addition to ROS, cellular metabolites, generated by exogenous/endogenous nitrogen, can form reactive nitrogen species (RNS) that include nitric oxide, peroxynitrite, and nitrite/nitrate. The two types of reactive species, ROS and RNS, can act together generating the so-called nitrosoative stress ROS/RNS.

Thus, living organisms are continuously assaulted by reactive species from external to internal sources. The main problem is the concentration of reactive species and the time that their action lasts so that these two factors set the boundary between beneficial and negative effects of ROS. This boundary probably is the key to elucidating the mechanism of action of reactive species.

As for the role of reactive species, NO is the only reactive species that have been identified so far as a second messenger.

Regarding ROS, the debate continues, but from all ROS, only hydrogen peroxide appears to act as a second messenger.

Superoxide anion is a radical; however, it cannot diffuse remotely because of its limited lipid solubility and high reactivity. Hydroxyl radical ($OH^{\bullet}$) indiscriminately reacts with any structure in its path thus being devoid of specificity. Hydrogen peroxide, on the other hand, is lipid-soluble, diffuses through the lipid membranes [1], has a longer life span, and appears to be more selective in its reactions to biological molecules [2].

To meet the second messenger criteria, a structure must have a certain reactivity and specificity [2]. Hydrogen peroxide is less reactive than superoxide or hydroxyl anion, which allows it to have better diffusivity. This higher diffusivity makes hydrogen peroxide capable of reaching certain target proteins. Scientific data show that H_2O_2 has some specificity to oxidize cysteine residues belonging to specific proteins called protein-tyrosine phosphatases [3, 4]. Through this mechanism, H_2O_2 interferes with the known MAP kinase pathway that functions in cell signaling [5].

The possibility of reversing the oxidation of protein-tyrosine phosphatases under certain conditions makes this process suitable for regulation. But in the case of an intense oxidative process, the oxidation of protein-tyrosine phosphatases becomes irreversible, resulting in blocking the signaling process at a certain phase and thus triggering the pathological processes [3].

2. Reactive species in pathology

A subject of particular interest is inflammation. Inflammation is a complex process involving both a stage of destruction of damaged tissue and a repair stage to the initial structure. The complexity of this process is not only due to the large number of molecules involved but also to the mechanisms that must be perfectly correlated and synchronized. Shortening the global process leads to an inefficient repair or an irreversible damage to the affected area [6]. The prolongation of inflammation causes a large number of pathologies, some of which are moderate, chronic, and some lead to cancer. Scientific works demonstrate the links between inflammatory mediators and the emergence of tumor phenomena in various pathologies. This leads to the idea of a common mechanism that current research studies seek to elucidate, but the involvement of reactive species in cancer is far from being elucidated.

Recent data show that reactive species play a double role in cancer. On the one hand, ROS facilitate cell proliferation and adaptation to hypoxia; on the other hand, it can trigger the death of tumor cells by initiating autophagy [7]. Furthermore, tumor cells can themselves generate reactive species [8] and, at the same time, can increase their antioxidant activity to ensure their survival in the oxidation medium so formed [9].

Disrupting the balance of any of these mechanisms leads to various pathologies such as kidney disease, bladder cancer, hepatocellular carcinoma, male infertility, bone fragility, skin diseases, and cardiovascular system dysfunctions.

In an effort to limit the damage of reactive species, the administration of natural antioxidants is used in therapeutics. On the other hand, there are current approaches that envisage the use of reactive species to kill cancer cells. Therefore, there is a constant and high interest in the quantification of reactive species.

3. Perspectives in reactive species' research

At present, there is an increased interest in studying the action of reactive species in epigenetics. Recent data demonstrate that oxidative stress induces changes in chromatin by initiating histone methylation/demethylation processes. As these changes occur in physiological and pathological processes, reactive species open a new branch in biomedical research.

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