Plasma Dose for Clinical Applications: New Considerations

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Abstract: When plasma is applied to target tissues, they are exposed to a unique cocktail of short- and long-lived reactive oxygen and nitrogen species, electrons, and electric and electromagnetic fields. The clinical effects of plasma are assessed by measurements of responses in tissues hours to days after plasma exposure. Among other approaches, incorporation of real-time monitoring of plasma effectors and tissue responses can assist in developing a definition for safe and effective plasma doses for use in medical applications.

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1. General

Since the discovery that non-thermal plasma (NTP) can be safely applied to cells and living tissues, tremendous progress has been made in the use of NTP to controllably achieve diverse biological effects ranging from the stimulation of cell division and differentiation to the induction of different cell death pathways [1, 2]. Based on these cellular effects, multiple medical applications of plasma are being explored, including disinfection, treatment of skin diseases, wound healing, and more recently, broad-spectrum anti-cancer therapies [2, 3].

Plasma medicine describes the delivery of partially ionized gas to target tissues using a variety of devices, each of which produces a unique cocktail of different short- and long-lived reactive oxygen and nitrogen species (RONS). The distinct effects of NTP are attributed to induction of different intracellular stress pathways triggered by the rich assortment of RONS produced in NTP [4, 5, 6]. Oxidative stress from low to moderate levels of RONS promotes immune stimulatory pathways, while higher levels induce cell death from oxidative destruction of cell structures [7].

Several investigators are attempting to identify cause-and-effect relationships between individual RONS and specific cellular outcomes to establish a definition of clinically safe and effective doses in plasma medicine. However, the definition of "plasma dose" remains elusive. One of the key reasons for this is that cells have mechanisms to create and destroy RONS. Cells produce a variety of RONS, including superoxide (O^{2-}), hydroxyl radical (HO.), hydrogen peroxide (H_2O_2), nitric oxide (NO.), and peroxynitrite ($ONOO^-$), as byproducts of cellular metabolism. In low quantities, RONS function as signaling molecules for many cellular pathways that are necessary for cell survival [8]. However, unmitigated accumulation of these molecules can be toxic to cells. To maintain redox balance, cells execute controlled destruction of RONS through an extensive system of antioxidant enzymatic machinery [9]. Many of the RONS produced by cells are also present in NTP and can become important players in the modulation of cell and tissue homeostasis by challenging the redox balance [7, 10]. These mechanisms can confound the experimental discrimination between biological effects that result from NTP RONS and the effects of cells on redox homeostasis and NTP-related chemistry. In addition, plasma physical components, such as electric and electromagnetic fields and surface charges can affect the properties of cells and cell culture medium and subsequent cell responses to NTP [11].

At present, the effects of clinical plasma delivery can only be assessed by measurements of secondary or tertiary responses hours or even days after a brief period of plasma exposure. There are presently no defined markers that can be monitored in real time as plasma is being delivered to achieve a desired clinical outcome. Another aspect complicating the definition of "plasma dose" is the differential effect of various cell types on plasma parameters and consequently the production RONS and the physical components of NTP that act on cells [12].

In this talk, we will examine the different methods being used to address this complex problem and discuss the importance of defining plasma dose, lessons learned from past and ongoing research, and the conceptual and technical challenges that need to be overcome. We will present our approach that encompasses *in vitro* and *in vivo* studies using diverse plasma sources that produce different cocktails of RONS. These investigations are being conducted in the context of normal cells, cancer cells, cells infected with viruses, cell-free viruses, and models of *in vitro* and *in vivo* wound healing. We will also explore reciprocal relationships in which cells and tissues are affected by plasma and are, at the same time, playing a role in changing the properties of the plasma.

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2. References

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