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Theoretical-Scientific Foundations about the Use of Low-Dose in Oncology

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Editorial

Physiological regulating Medicine (PRM) is an innovative system based on the possibility of using LOW DOSES of biological compounds, which normally regulate human physiology, as a therapeutical mesaure. More and more experimental and clincal evidence of the efficacy of low doses (under minimal pharmacological effective dose) of hormones, citochines and neuropeptides is accumulating. Physiological concentrations, in the range of nano or picograms, are enough to activate membrane receptors and, by doing so, stimulate physiological response in target cells.

PRM reunites together the most modern knowledge in the fields of omeopathy, omotoxicology, psico-neuro-endocrine-immunology (PNEI) and nutraceutics.

The goal is to restore physiological balance by using compounds such as hormones, interleuchines, growth factors and neuropeptides in low doses. In normal physiology these molecules are found in the extracellular matrix and interact with transmembrane recptors. From an immuno-oncologic point of view patients suffering from solid tumors show an overexpression of Th3 lymphocytes, responsible (if expressed in the "right" physiologiical amount) for immune-tollerance.

This immune surveillance role is completed by producing a grow factor, TGF-β , which in turn downregulates Th1 and Th2. In different articles Th3 are referred to as T-reg or CD4/CD25/FoxP3.

Unfortunately in oncological patients Th3s are over-expressed leading to down-regulation of Th1 and Th2 lymphocytes; this is one of the mechanisms which underlies the severe immunodeficiency these patients experience. Down expression, and especially Th1 down expression, leads to a diminushed production of IFN-γ, which in turn is central in CD8+ generation. T suppressor lymphocyte production on the other hand is dependant on CD8+ generation and is fundamental in tumor cell proliferation control.

But this isn't all, the few Th1 also produce less IFN-γ, and this reduced quantity interferes with the expression of another vital set of cells that control tumor expansion, NK cells which are responsable for the lysis and death of tumor cells. An interesting theory is presented in the article published by the Journal of cancer therapy (Amico, Ruffini, Ferracini, Roato. IL-12 Stimulates T Cell Response in Cultures of PBMCs Derived from Small Cell Lung Cancer Patients. Journal of Cancer Therapy, 2012, 3, 337-342).

IL-12 is responsable for the down-regulation of Th3 lymphocytes. Since 1980's there have been many, promising attempts to take advantage of this physiological action. However, severe clincial (high fever, general malaise, nausea and vomiting) and immunological side effects , due to high concentrations, have prevented it's use. At high pharmacoligical concentrations, routinely used, ranging from ng/mL and higher, IL-12 does reduce not only Th3 lymphocyte population but also the other CD4+ lymphocyte populations (Th 1 and Th2).

By doing so, paradoxically, IL 12 causes severe immunodeficiency not mediated by overexpression of Th3 lymphocytes but by directly inhibiting Th1s and Th2s responsable for cell-mediated and umoral immune response respectively. IL-12 at the concentration of 10 ng/mL reduces Th3 and this is beneficial, in the meantime however it drammatically reduces CD4+ populations (Th1 and Th2). Furthermore the same 10 ng/mL reduce to a great extent IFN-γ production via Th1 lymphocytes by "blocking" them directly. On the other hand when IL-12 is used at the concentration of 0.01pg/ml, that is CH4 dynamiztion, the following observations can be made:

IL-12 4CH is capable of downregulating Th3 lymphocytes, which are over expressed in cancer patients, to a level which is lower than that found in controls. At the same time, however, it has the ability to elevate the CD4+ population (Th1 and Th2). Yet more interesting is data concerning the production of IFN-γ by Th1 under IL-12 4CH stimulating which was increased. Last but not least IL-12 4CH raises the production of lytic cells active against tumor cells.

In conclusion IL-12 4CH, at a concentration in the range of picograms, shows the same efficacy in downregulating Th3 as the allopathic concentration (ng/mL) without downregulating the CD4+ and especially the Th1 population, which is a side effect. IL-12 4CH actually does quite the opposite enhancing IFN-γ production, crucial in the anti cancer response, by Th1. Summing all up it seems as if there were a biological intelligence connected with low physiological doses, capable of targeting only pathological changes without interfering on physiological mechanisms.

We now review the results of the study conducted by Radice, Miranda, Bellone. "Low-doses of sequential-kinetic-activated interferon-γ enhance the ex vivo cytotoxicity of peripheral blood natural killer cells from patients with early-stage colorectal cancer. A preliminary study, appena pubblicato su International Immunopharmacology, 19 (2014), 66-73.

From an immuno-oncological point of view NK cells play a central role in eliminating cancer cells (cell lysis). They play a crucial part in the immunesurveillance mechanism. IFN-γ has a primary role in regulating NK cells (by directly influencing these cells), but this isn't all as it promotes antitumor response mediated by type 1 T lymphocytes (Th1). This pressure towards Th1 differentian leads in turn to a potent CD8+ cytotoxic anti-tumor response.

Still, IFN-γ, by stimulating Nk cells, favours tumor invasion by these cells and by macrophages; as a consequence there is a rise in IL-18 and IL 12 levels. The latter is very important as, together with the higher IFN γ levels, and by the know cross reaction mechanisms it leads to downregulation of Th2 and up regulation of Th1, crucial point in giving rise to the CD 8+ anti tumor response.

This integration between natural and adaptive immunity is central in fighting solid organ tumors such as colon rectum cancer; sometimes however this sequence fails in it's task to control and prevent. When this is the case an insufficient immune-response and/or immune escape mechanisms arising an the tumor itself could be a plausible explanation.

Unfortunately in the cancer patient immune response is frequently compromised; as a result there is a downregulation in Th1 lymphocytes; this is one of the causes of the severe immune deficiency we find in these patients. Down expression, especially Th1 down expression, leads to decreased production of IFN-γ (mediated by this lymphocyte population), central citochine in activating CD 8+. Along the chain CD 8+ are fundamental for T suppressor production which in turn control cancer cell proliferation. Low levels of IFN-γ lead to a decreased presence of other cell types which are very important in controlling tumor cell expansion, such as aforementioned NK cells. This study aimed to underscore the central role of IFN-γ in the induction of immune response.

The mechanisms we have discussed led to realize that stimulation of the immune response by the use of high doses of IFN-γ could represent a promising therapeutic strategy when dealing with tumors, both solid and non-solid. Some clinical trials have been conducted to prove this hypothesis but all of them have faced serious side effects due to the intrisic toxicity of IFN-γ which is dose dependent.

The theoretical foundation of the ex vivo work in this paper summarised is to evaluate the lytic capacity of NK cells (isolated from patients with colon-rectal-carcinoma (CRC) with or without metastasis and from healthy donors) after apprpriate stimulation with IFN-γ using a conventional dose (1 ng/mL) or low-dose SKA IFN-γ (0.25 fg/mL).

In general we find a higher activity in NK cells from healthy subjects, a lower activity in cancer patients without metastasis and an activity which approximates none in patients with metastatic disease. The core of the work is that by administering IFN-γ 1 ng/mL or IFN-γ 0.25 fg/mL the number of NK cells grows in healthy controls, in non-metastatic tumor patients and in patients with metastatic disease.

Conclusions

The work clearly demonstrates that IFN-γ, because of it's usefulness at low doses (proved by the statistical analysis of the standard deviation to be non-inferior to the full dose of 1 ng/mL) is capable of stimulating NK cells in the healthy subject as in the cancer patients and by doing so is capable of strenghtening the cytotoxic response to the cancer cells, key point in the anti-tumor defense.

We must underscore how the positive proliferative response in the healthy control represents a potential opportunity. A prophilactic intervention could infact be conducted with the objective of raising the immune competence of NK cells in this population.