Clinical Nutrition 32 (2013) 460–465

Contents lists available at SciVerse ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Opinion paper

The conditional role of inflammation in pregnancy and cancer

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ARTICLE INFO

Article history:
Received 8 May 2012
Accepted 28 July 2012

Keywords:
Cancer
Fetal growth
Inflammation
Th1–Th2 ratio
Arginase
Anti-rejection effects
Cell proliferation

SUMMARY

Cancer growth is characterized by proliferation of tumor cells in conjunction with invasion of all different immune cells that also invade healing wounds. This inflammatory response is necessary for cell proliferation but a second purpose of the inflammatory process is so that a low Th1/Th2 ratio is present with overexpression of IL-10, TGF-β and IFN-γ. Down regulation of NO activity also shifts the balance between M1 and M2 macrophages. Both aspects allow the antigenous nature of the tumor to escape anti-tumor effects of the host. Support for this view comes from observations in pregnancy in which the placenta exhibits identical immune responses and downregulation of NO production to allow trophoblast cells to invade the uterine tissues without being rejected.

Cell proliferation requires a metabolic set-up in which the organism produces adequate substrate for growth. This also bears the characteristics of a systemic inflammatory response delivering a similar substrate mix required for cancer and fetal growth. This arrangement is clearly beneficial in pregnancy and therefore supports the view that cancer growth is facilitated by the organism: the cancerous tumor elicits an immunological response opposing anti-tumor effects and induces the host to produce building blocks for growth.

1. Introduction

Cancer ultimately leads, in a high proportion of cases, to severe malnutrition. The inflammatory state accompanying cancer is present in the tumor itself as well as systemically.[1,2] Systemic inflammation of any cause invariably leads to loss and compositional changes of peripheral tissues like skin, bone and muscle even when nutritional intake meets requirements. However, in addition to this catabolic influence of inflammation, many cancer patients also loose fat mass (and fat free mass) due to inability to maintain nutrient balance as a consequence of anorexia, intestinal obstruction and/or malabsorption. Consequently the typical presentation of cachexia develops, including both low fat free mass (FFM) as well as fat mass.

The question may be raised why the malignant tumor as well as precancerous lesions exhibit inflammatory symptoms and what the role is of the systemic inflammatory response accompanying cancerous lesions. Is inflammatory activity at the tumor site an endeavor of the body to heal the tumor and is, in a similar fashion, systemic inflammatory activity a (failing) effort of the organism to inhibit tumor growth despite paying the price of loss of FFM as happens in acute trauma or disease? Or is inflammation at the site of the tumor required to allow the tumor to grow and is therefore the accompanying systemic inflammation, induced by the tumor, necessary to create a metabolic environment that supports tumor growth? In other words is the inflammatory state present in cancer purposeful for the patient or for the tumor? In this opinion paper we will make a case favoring the last option. For this purpose we sought to compare cancer metabolism with metabolism in pregnancy in view of striking similarities, supporting this claim.

2. The origin and role of systemic inflammation

At present the view is shared by many workers in the field that systemic inflammation after acute trauma or disease is an adaptive phenomenon supporting the healing process in wounds and infection, as well as in growth.[3,4] Millions of years ago our forefathers (hominins, hominids, chimpanzees) were able to overcome minor or even intermediate size trauma and illness, testified by signs of broken and healed bones, and evidence of disease in fossils. At that time most if not all unhealthy states led to starvation, which caused healing to depend on the supply of building blocks from the body itself. These building blocks are largely derived from peripheral tissues like skin, bone and muscle, causing that part of the body to become catabolic but favoring healing. This process is steered by neuroendocrine and cytokine responses, although the exact

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0261-5614/$ – see front matter
http://dx.doi.org/10.1016/j.clnu.2012.07.010

orchestration is still a matter of debate: a combination of neuroendocrine impulses, cytokines, damage associated molecular patterns (DAMP's) or/and pathogen associated molecular patterns (PAMP's).[5,6] Thus in this historical context, individuals with a higher ability to mount a catabolic response would be more likely to survive.

It is questionable whether there is an all dictating signal which precisely determines the intensity and the art with which the organism responds to the primary insult (cancer, pregnancy, infection, and trauma) to cover its needs. It is much more likely that the multiple factors released by the primary insult (cancer, injury) as well as the neuroendocrine response induced by the insult, prime the organism to respond. This response is essential to adapt to all the dangers and life events to which monocellular as well as multicellular organisms, prokaryotes as well as eukaryotes are exposed. In view of their survival and the fact that many of the unsuitable genes did not survive, the response must have been successfully tailored by the threats imposed on their genomes during millions of years.

Summarizing this part, local trauma/healing processes require an adequate systematic hemodynamic response of the organism as well as delivery of building blocks: immune cells, fibroblasts, proteins to the primary inflamed or traumatized area to allow healing. Cell proliferation is an essential part of this response. This explains why growth of a fetus as well as of cancer requires a response of the organism with similar inflammatory characteristics which we will describe in this opinion paper.

3. How does the body tailor its response?

The systemic inflammatory response has similar characteristics in a multitude of differing events and therefore appears aspecific. The magnitude of the metabolic response matches the magnitude of the primary insult possibly with the exception of infectious disease, where some bacteria species have acquired or can quickly acquire genes smartly expressing mechanisms to overcome, increase or decrease the normal inflammatory and beneficial defense mechanisms of the host.

Much emphasis has been put on regulating factors that induce or block pathways. These indeed determine which pathways are upregulated or downregulated. But subsequently, the magnitude of the fluxes of substrates, leading to cell proliferation, must depend on the availability of substrate and on the requirements of the insult (growth, wound healing, disease). It is also evident that these two events are tightly balanced, the regulation of which is complex. Logic would lead to the view that the insult "pulls" substrate from the circulation as evidenced by the increase in posttraumatic uptake of glutamine and glucose by the spleen despite a low plasma concentration.[7] Signals from the insult must have been sent to the organism to increase production of the substrates required for local healing. Although much is known regarding the many regulatory factors that are operative, their exact orchestration is difficult to define exactly and is not the purpose of this review.

4. The role of the local inflammatory response

The inflammatory response in a fresh wound characteristically has been depicted as consisting of a pro- and an anti-inflammatory phase. This description is an (over)simplification because it focuses exclusively on the partially inhibitory effect of counter regulatory cytokines produced in the anti-inflammatory stage decreasing the influx of thrombocytes, polimorphonuclear cells, macrophages and lymphocytes and their initial effects.[8] These effects include removal of debris and extraneous material by pinocytosis and phagocytosis. Simultaneously growth factors are produced that initiate rebuilding and restructuring of the traumatized/infected area. Effects include angiogenesis, cell proliferation, collagen deposition and restructuring. The "anti-inflammatory phase" therefore only implies that the response changes from a successful completion of the preparative phase (elements of which need to be inhibited) to a regenerative/proliferative phase. Implicit in this description is that the inflammatory phenomena observed in wounds/infected areas represent a healing response.

This is not always appreciated by the medical community at large, who views inflammation as a deleterious process, which should be inhibited. It is clear that despite potentially relieving complaints like pain and fever the inhibition of the inflammatory response may be harmful, because of interfering with the healing effects of inflammation.[9] Many examples of NSAID's induced harm can be found in the literature like the disastrous effects on varicella in children receiving NSAID's,[10,11] on ulceration in the intestinal tract,[12,13]on bone healing in fractures,[14] on fetal development of gonads,[15] just to name a few examples of many.

One may conclude that inflammation is necessary to allow wounds to go through all the stages of successful wound healing and that it might be fruitful to view inflammatory events occurring in other acute states in the same light: an adaptive process of the body to deal with wounds, infections and non-infective inflammatory diseases. Considering the fact that the final goals of wound healing consist of cell proliferation and (re)building of tissue it is tempting to explore the role of inflammation in other conditions where rapid cell proliferation is required like in cancer.

5. Pathology of tumor growth

Tumors may cause obstruction, ischemia, atelectasis, malabsorption which may cause secondary inflammation. It is not the goal of this opinion paper to describe these secondary sequelae of tumors. However, (cancerous) tumors have been shown to be invaded and surrounded by many types of immunocyte that is also present during the first stage of wound healing, releasing a multitude of chemokines, cytokines and growth factors promoting growth of the tumor.[1,2] (Pre-) cancerous lesions are due to their abnormal protein structure in principle antigenic and elicit an anti-tumor response possibly through IL-2 and IFN-γ production by cytotoxic lymphocytes, Th1 and NK cells. On the other hand, tumor growth is very likely promoted by a B cell humoral response and a Th2 response promoting production of several cytokines including TGF-β and IL-10. In this process TGF-β has been shown to be tumor suppressive in the initial stages of tumor growth but to become tumor promotive at higher levels in later stages by regulating these inflammatory reactions and to create the microenvironment favoring tumor growth and allowing tumors to invade tissues escaping surveillance by the host.[1] The same has been shown to happen with IL-10 that is present in abundant amounts (higher than in clean wounds) in the microenvironment of tumors also inhibiting anti-tumor effects of the healthy tissues.[16] Therefore both IL-10 and TGF-β have been suggested to contribute to tumor resistance against anti-tumor effects of the host.[17] Also IFN-γ has been found to play this dual role, inhibiting tumor growth at low levels and promoting at high levels.[18] These findings have led to the claim that a low Th1–Th2 balance is required to allow invasive tumor cell proliferation without being rejected by the organism.[19] Ongoing tumor growth has therefore been called the "chronic unhealing wound" because it contains many of the elements of wound healing but fails to complete successful healing like production of a contracted metabolically inactive scar.

Another contributing mechanism for the inflammatory response seen in cancer, has been suggested to allow tumor growth