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Spotentiality for Induced Inflammatory Exposure of Antigenic Epitopes in Ischemia and Neoplasia

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Abstract: Failed activation of the immune response to neoplastic cell proliferation and spread would implicate systems of exposure and of presentation of antigenic epitopes on cells. Such failure in antigenicity of tissue components would characterize primary inception of the lesion as a neoplasm that subsequently increases in size and progresses. It is with reference to inflammation as a mechanism of exposure and of presentation of antigen that one might envisage neoplastic and ischemic tissues as a dual coupling potentially related to both immune stimulation and activation of clones of lymphocytes, inflammatory cells and macrophages. Such cell components of tissue would participate in the realization of various compounding pathways of propagation involving cytokines and chemokines in inducing further progression of the neoplasm or in suppressing tumor growth and spread. Ischemia and post-ischemic perfusion injury of tissues appear applicable in inducing a coupled inflammatory and immune reactivity in various tissues including neoplasms.

Key words: Inflammatory exposure, ischemia, neoplasia

INTRODUCTION

A prominent feature in peripheral neuritis is the relationship of a purely inflammatory component with the immune response. Both these response types are closely interactive in their genesis, evolution, action on tissues and eventual resolution. They appear to constitute two integral components of one essential phenomenon.

Various chemokines, cytokines and inflammatory cells appear central to the elicitation of a truly effective immune response. The macrophage may be essential in combining such components within one integral system of immune and inflammatory reactivity. The inflammatory reactive processes are important in stimulating the local immune response in terms particularly of exposure of antigenic sites. Dendritic cells play a central role in T-cell-mediated immunity to tumor cells[1] . Direct stimulation and modulation of responses of the Schwann cells would be operative in attracting a macrophage cell population locally in peripheral nerves.

The inflammatory response and the reactive changes it induces would modulate the immune response that is centered mainly on local tissue homeostasis. Localization of focal immune reactivity would appear resolved in terms of a local inflammatory reaction that is coupled to a concomitant accumulation of macrophages. Macrophages as antigen-presenting cells would be instrumental in further stimulating and activating T lymphocytes locally in a setting of an evolving inflammatory response. By stimulating the immune response, neutrophils accumulate to suppress tumor growth as a surface phenomenon, with diffusion at the surface as the determining factor[2].

Such a mutually integral involvement of the immune and inflammatory response might prove essential for the successful mounting of a potentially effective response against neoplasms. A purely immune response would be expected to be ineffective in terms of the elicitation of a powerful local inflammatory reaction within neoplastic foci that subsequently evolve as suppressed tumor cell proliferation and elimination.

The whole range of adhesion molecules and receptors such as integrins would be associated with endothelial cells and with cell membranes and Schwann cells in peripheral nerves.

These would modulate the extracellular matrix in concert with agents such as metalloproteinases in eliciting also a systemic component to the inflammatory and immune reactivity.

Various such mechanisms would result in focal patterns of distribution of lesions leading to rejection of tissue components, the elimination of micro-organisms and the development of patterns of response including granulomatous inflammation. The latter may incorporate an immune response as cell-mediated mechanisms distinguishing native from foreign tissue components. In tumors, cross-presentation of antigen from tissue cells to antigen presenting cells might promote the establishment

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of protective immune responses. Cell death favors cross-presentation of antigen[3].

The inflammatory response is inherently excessive and induces pathology in its own right: The precise role of the inflammatory response in terms of resolution of the tissue damage and as a reparative series of pathway responses would also implicate much residual tissue damage.

This inherent response that damages tissues in terms of subsequent possible reparation of the damage would depend on a paradoxical over-activity of the inflammatory response.

Indeed, it would appear that much of the focal parenchymal and stromal damage elicited by the inflammatory response would operate in a context of subsequent better execution of the reparative response. With regard to suppressed anti-tumor immune reactivity, neoplastic cells might downregulate MHC Class I molecules and also the antigen-presenting mechanisms. Optimal anti-tumor immune responses require reactive CD4(+) T cells[4].

Such a basic phenomenon of tissue damage leading directly to the activation of the reparative processes would prove central to recovery in cases of trauma, tissue infarction and infection of major organs including the central nervous system.

The focal and systemic reactivity of the inflammatory response in patients with tissue or organ infarction would attest to an inter-reactivity of the immune and inflammatory systems. The reparative process originates focally and also systemically as significant stimulation of an inflammatory response that participates with the ongoing tissue injury.

AIDS-associated neoplasms of the anogenital region may respond to immunotherapy with novel vaccines in controlling human papillomavirus infection and associated inflammation[5].

Free oxygen-radical injury and hyperthermia affecting tissues in a patient with an infarct or an infection would contribute to the inherent excessive inflammatory response. Local tissue homeostasis would implicate injury and death of cells as related to the nearby foci of inflammatory and immune reactivity.

A whole series of primary and secondary waves of reactivity would be elicited as infarction of tissues that arises focally but subsequently implicates systemic responses of inherently progressive inflammatory and immune reactivity. Downregulation of transforming growth factor, on the other hand, might permit normal dendritic cell activation and maturation in inducing tumor immunity[6].

Oxygen-stress-related injury in cerebral ischemia as depressed systems of neuroprotection: Oxidative stress-injury to tissues appears central to the pathophysiology of an organ such as the central nervous system that depends on a highly constant supply of oxygen to neurons and cell components. The utilization of large amounts of oxygen is reflected in the very high percentage of the cardiac output that reaches the brain.

This would reflect the potentially large amount of free oxygen-radicals generated in ischemia or infarction of the central nervous system. Pathology such as trauma of inflammation or infection of the central nervous system would operatively induce mechanisms of protection and of modulated response to injury arising via multiple pathways of progressive tissue and cellular injury.

There would exist a close relationship between blood supply of an organ such as the brain and the tendency to develop oxidative stress injury. Brain ischemia would be particularly associated with significant oxidative stress arising as endogenously induced cell injury. The transcription factor DEC1 (Stra13, SHARP-2) is upregulated by hypoxia in tumors and may be implicated in cell death and tumor differentiation[7].

Neurodegeneration would also constitute a potential source of endogenously induced injury in terms of a subsequent neuroinflammation that progresses with reference to blood supply and systemic response. The penumbra around foci of cerebral ischemia would constitute evolving tissue damage arising as oxidative stress and inherently progressing inflammatory responsiveness.

The essential balance between excess free oxygen-radical production and a multitude of protective cellular mechanisms would be intrinsically disturbed in neuronal ischemia. Ischemia would appear to be particularly associated with oxidative stress in terms of a decreased blood supply followed by reperfusion of blood vessels primarily impairing neuroprotective mechanisms against induced inflammation.

Endogenously arising neuroprotective measures would often tend to be insufficient in preventing a combined form of injury arising as oxidative stress and inflammation to tissues in cases of reperfused ischemic tissues. Inflammatory cells may also contribute to the growth and spread of tumors by producing molecules that enhance neoplastic invasion of tissues, including high angiogenic activity[8].

Pathophysiology of cerebral ischemia as blood flow correlates of core temperature: The observed neuroprotective effect of hypothermia after an ischemic episode of the brain would attest to the important role of

a normal temperature range that is maintained as a function of the cerebral blood flow.

In normal individuals, the core temperature appears to correlate with several parameters associated with a normal blood supply to the brain.

Specific blood supply patterns would relate to a core temperature associated with maintenance of metabolic and other homeostatic functions of cerebral tissues.

Blood flow and core-temperature appear integrated as physiologic or pathophysiologic indices in suspected cerebral ischemia. The rate of blood flow to the brain may simply be an approximate index of the potential damage due to brain ischemia. Ischemia would activate various pathways related to elevated core temperature of the body.

In global ischemia of the brain, the core temperature is altered directly as a result of various deleterious effects on neuronal viability.

In the penumbral zone, the partly preserved neurons would appear implicated in the progression or nonprogression of further tissue injury arising as a result of reperfusion injury and oxidative stress and also of a raised core temperature of the tissues.

Core temperature and blood flow parameters fundamentally determine homeostasis of cerebral tissues and neurons in terms also of potential neuroprotective measures that are activated in cases of tissue injury.

Intrinsic attributes of the immune system: The timing of stimulation of the initially present lymphocyte subset appears critical. Even postnatally, timing with regard to the stage of development of the particular subset of lymphocytes exposed to the antigen may prove significant.

Inter-relationships of various cellular components of the immune system would implicate relative capacity as a direct function of the timing of the activated immune response. This appears critical to the generation of a memory cell pool of lymphocytes with a given antigenic specificity.

The time interval between a primary stimulus and a subsequent re-exposure to the same antigen may possibly be of major importance in determining effective immune responsiveness.

Timing during development of exposure of the antigenic stimulus is probably also critical in terms particularly of possible immune tolerance. Stimulation or activation of lymphocytes would involve subsets and clones of lymphocytes that directly modulate inflammatory and immune reactivity in tissues. Immune cell activation involving time-dependent activation of macrophages and Natural Killer cells may contribute to anti-tumor activity of targeted liposome-CpG-myb-antisense oligonucleotides against neuroblastoma cells[9].

The developmental stage of the lymphocytes at initial stimulation would correlate with the time stage in the evolution of the immune response at a particular point in evolution of a given disease process.

Fundamental inter-reactivity of phenomena in evolving disease would prove significant with regard to an immune system that is well characterized mainly in terms of controlled timing and sequential evolution of antigenic exposure. In the progression of human cancer, chemokines and chemokine receptors play a critical role in interactions between immune reactivity, angiogenesis and cell survival cascades[10].

The evolution of B-lymphocytes to plasma cells, for example, would be one showing variable progression, depending probably on such factors as antigenic load and stage in evolution of the immune response.

The term evolution in development of the immune response would perhaps relate to actual dynamics of the immune system developmentally and as related to completion of an endstage of the immune reaction and its consequences.

The immune response would be considered an integral entity in its own right that arises and refers strictly to its directed evolution to a specific biologic endpoint.

This would give biologic and pathobiologic significance to the immune response that is inherently associated with inflammatory injury to tissues.

A whole series of mechanisms would incorporate inflammatory cells, cytokines and chemokines and also cell receptivity. Cell receptors, whether lymphocytic or macrophagic, would appear intrinsically a separate variable component in the immune reactions and a reflection of components of the inflammatory response to injured tissues. Targeting toxic therapeutics to tumors through receptors overexpressed on cancer cells carry a potential for better tumor penetration without neutralizing host immunity[11].

In this regard, the T-lymphocyte receptors are closely analogous to the immunoglobulins structurally, in terms particularly of fully complementary components of the immune response. It would appear that the intrinsic nature of the immune response is one conceptually based on immunoglobulin and lymphocyte receptor reactivity that evolves in compounding the effects of a system that biologically propagates and compounds influence within tissues and the body as a whole. Reduced leukocyte-endothelium interaction in neoplastic tissues appears to result from decreased expression of adhesion molecules such as ICAM-1 that induces effective immune escape for the tumor[12].

Autoimmunity versus neoplasia: Can genetic damage (germline or somatic) of antigen-presenting cells prevent activation of the immune response against a neoplasm?

Autoimmunity is primarily characterized as an immune system response against self-antigen. The lack of immune response to neoplastic cells appears to arise as a failure of immune mechanisms to altered self-antigen. Selenium, in particular, appears to downregulate proinflammatory chemokine production in cancer progression. Selenium may enhance lymphocyte progression through the cell cycle in these patients[13].

Central to both autoimmunity and failed immune response to neoplasia may be a functionally quantitative parameter determining immune reactivity to given tissue components.

An essential phenomenon of antigen presentation would lead to overstimulation in cases of autoimmune states, whereas understimulation of the immune response would participate in tolerance to neoplastic tissues. Both B cells and T cells would represent a qualitative rather than a primarily quantitative series of abnormalities affecting actual binding of antigen to lymphocyte receptors.

The lack of an immune response even in patients with widespread disseminated tumor would indicate a systemic disturbance.

Such systemic involvement would be consistent with a phenomenon of neoplasia that arises as a focal lesion in specific organs but one that primarily constitutes a systemic disease of spread within the body.

It is conceivable that a basically systemic and acquired abnormality would develop with increasing age of the patient that is central to permissive tolerance of neoplastic tissue. Intrinsic alterations in antigen-presenting cells might derail the whole antigen-presenting mechanism, first as a focal phenomenon and subsequently as a systemic process in parallel with development of the neoplastic focus that metastasizes.

A dual phenomenon of mutability of the neoplastic focus and of the antigen-presenting cells would permit the subsequent development and progression of the neoplastic cell proliferation that involves an already stimulated immune system. Regulatory T cells indicate dominant tolerance and control of the antitumor response and the suppression of immune reactivity in the microenvironment of tumors such as metastatic melanoma[14].

Increasing age and primary tissue injury, as induced by inflammatory action, might act together in inducing genetic damage that is proneoplastic and also damaging to the antigen-presenting mechanisms in affected tissues.

Restorative immunotherapy with a corpuscular antigen may potentiate cell-mediated response or a stimulated cytokine network against tumors[15].

Is neoplasia a fundamental defect in antigen presentation to the immune system on an organ-specific basis?: A failed anti-tumor immunologic response against solid neoplasms appears suggestive of a fundamental failure of immune surveillance that at an early stage does not develop reactivity to various tissue components in the lesion. Immunogenicity of tumors and their ability to induce type 1 or type 2, CD4 or CD8 cell immunity are not primarily determined by signals associated with apoptotic or necrotic cells but appears an intrinsic attribute of the tumor itself[16].

Indeed, the clinical presentation of a neoplasm would implicate a failure to mount an immune response at any subsequent stage in progression of the lesion. The neoplasm may rarely arise as a response to an infection, requiring however specific cofactors for malignancy to develop. Patients who are immunologically impaired or on immunosuppressive therapy would be expected to suffer from a marked cancer incidence[17].

Neoplasia as a lesion type wouldclinicopathologically refer to a subset of failed instances in immune surveillance that implicate overt failure of immunological and inflammatory coupling and of antigen presentation.

Failed immune surveillance may determine incidence of neoplasms.

Such a process would perhaps help define neoplastic transformation as central to the intrinsic biology of immune cells and immune system reactivity.

Subsequent evolution of the neoplastic lesion would involve immune-related systems of response against tumor growth, proliferation and spread in the body, but not an age-related suppression of CD 8(+) T cell immune response[16] .

A primary failure of the immune surveillance system may involve a specific organ origin of the tumor that characterizes development and progression of the lesion. Also, age-related decline of immune surveillance to tumors may develop[18].

As the neoplasm develops in size, phenomena would further suppress an effective immune response to the lesion. This would be particularly significant in terms of an overwhelming suppressive effect arising as a result of sheer bulk of the antigen load concurrent with neoplastic cell proliferation.

Efficiency of presentation of self- or altered antigen might account for an anomalous system of development of neoplasia that implicates dendritic cells and macrophages. Toll-like receptor ligands may possibly stimulate dendritic cell presentation of antigen in tumors and result in a T-lymphocyte response[19] .

A particularly vigorous immune response would tend to develop in draining lymph nodes and yet the immune system would fail to prevent subsequent systemic spread of the tumor cells.

Such a phenomenon would be suggestive of an abnormality characterizing neoplastic cells as primarily developing altered self-antigen. A basic failure to activate the normal immune system would participate in the prevention of an induced modulation in subsequent steps of progression of the neoplasm. The antigenic stimulus appears to constitute a masked epitope that evolves with neoplastic proliferation and spread.

Effective isolation of the tumor cell pool from the immune system would contribute to prevention of tumor antigen presentation particularly to T-lymphocytes and to Natural Killer cells. Both the innate and adaptive immune systems interact with neoplastic cells, particularly with activation of genes related to inflammation and mononuclear phagocytes[20].

Neoplasia may be characterized as a primary failure of antigen presentation that is closely linked to the biology of an immune system modulation that evolves.

Essentially failed interactivity between antigen-presenting cells, lymphocytes, macrophages and inflammatory response may underlie neoplastic generation and progression.

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