Immune-mediated paraneoplasia

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ABSTRACT

Cancers induce a loss of homeostasis through the uncontrolled production and release of a variety of biologically active cellular products, natural compounds produced in unnatural quantities within abnormal anatomical locations. Often, there is an immune response to which the cancerous growth may succumb, or have the characteristics required to survive. If, during its proliferation, the cancer should coincidentally express a potent autoantigen then the organ in which that antigen is normally located may be damaged by the resultant immune response. Paradoxically, this aberrant immunological activity rarely has any appreciable inhibitory effects on the causal cancer. This inconsistency may result from the cancer's ability to block the host's immunological activity, while the affected organ situated elsewhere has no such capacity. Some predisposition, such as trauma to the affected organ, may prove a prerequisite that provides access to hitherto immunologically privileged sites. The effects of the subsequent loss of tolerance are often the first indication of a health problem, prompting the patient to seek medical help. Immune-mediated paraneoplasia is identified by antibody activity with any of a small but growing collection of organ-specific antigens demonstrated to have a distinct disease association and an apparent involvement in autoimmunity. Examples of the most common are described as introduction to this unusual collection of autoimmune diseases, for which in some cases the cause is known, and these may provide insight into the cause of those that are not.

KEY WORDS: Autoimmunity.
Gene expression.
Neoplasms.

Introduction

Immune-mediated paraneoplasia (IMP) is a collection of cancer-associated syndromes that involve pathological immunological activity.[1–3] Autoimmunity is implicated by reports of patients displaying abnormal antibody reactions focused on single antigens expressed within the affected organ. Evidence of cancer-induced autoimmunity accumulates from findings of malignancies expressing specific immunologically reactive epitopes, and sometimes the complete antigens involved in the patient's autoimmunity.[1,7–13]

The autoantigens are organ and cell-specific, and in some cases surgical removal of the neoplasm has resulted in amelioration of immune-mediated paraneoplasia.[2,14–18] Gammaglobulin treatment is reported to have beneficial results in some through processes that include anti-idiotype immunomodulation.[19] Plasmapheresis and immuno-suppression may provide symptomatic relief in others,[3,6,15,20] but no single immunomodulation is universally successful.

Acceptance of an immunological cause and effect led to the use of serological assays that detect abnormal antibody activity with a growing collection of paraneoplasia-associated antigens. As many are associated with a specific neoplasia, their recognition can lead to the identity of the type of cancer involved.[4–6] The individuality of the patient ensures considerable diversity of immunological activity with any given malignancy, but the same abnormal immunological reaction manifesting in different patients with the same type of cancer is indicative of a common pathway of sensitisation.

The possibility that IMPs may reveal the 'Achilles heel' of the cancer should not be overlooked. It is possible to use isotope-linked antibodies that react with the autoantigen to image the growth and locate metastases not recognised previously. The same process may also be used in targeting cancer treatment. While this possibility carries the risk of increasing the patient's autoimmune activity, suitably modified immunoglobulins can now be constructed that reduce the risk of harm to the host.[21]

Immune-mediated paraneoplasia commonly involves very few of the many antigens that compose the organ involved, a characteristic of autoimmunity in general that invites further inquiry into the therapeutic use of antigen-specific immunomodulations.

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Failure of some paraneoplasia to respond to treatment, even after apparently successful cancer treatment, may result from the unfortunate initiation of self-perpetuating immunological reactions involving specific host antigens to which tolerance has been lost. Successful treatment of IMP may require combination therapy aimed at eliminating the patient's cancer, and immunological desensitisation to address the abnormal hypersensitivity that may prove as debilitating and life-threatening as the malignancy.

Immune-mediated paraneoplasia

From the earliest published descriptions, the secondary effects of cancer were, and continue to be, found most often in patients with small cell carcinomas, which are the archetypical inducer of IMP.[22,23] Other neoplasia such as thymomas, lymphomas, adenomas, ductal carcinomas and

melanomas represent additional causes of cancer-induced immunological abnormalities, but the greater proportion of autoimmune reactions continue to be reported in association with, and sometimes preceding the recognition of, small cell carcinomas.[5,6] The high prevalence of neurological disorders occurring with this malignancy may result from its surmised neuroendocrine origins, the Kulchitsky cell.[24–28] Loss of control of such influential cells can have an immediate and deleterious effect on homeostasis, often inducing an impressive immune response as the transformed cells begin the inappropriate translation of genes not normally expressed in the organ in which the cancer develops.[29]

Paraneoplastic cerebellar degeneration

Paraneoplastic cerebellar degeneration (PCD) was the first paraneoplasia to be described and occurs in a wide range of different types of neoplasia such as lymphomas, carcinomas of the ovaries, uterus, breast, in addition to the most frequently culpable small cell carcinoma. The pathological process involves the immunological inhibition and loss of specific brain cells. The selective destruction of Purkinje cells brought attention to the syndrome, but other brain components subsequently were found to suffer immune-mediated damage.[3,31,32] The resultant loss of cognisance initially may be confused with other diseases before the syndrome is recognised and the responsible cancer identified.[6,33–35]

When first recognised as a distinct clinical entity, PCDs were immediately suspected to involve autoimmunity,[30] and since have been shown to include abnormal antibody activity with a series of distinct neuronal proteins. With respect to the sensitisation process, the earliest immunological 'cancer connection' was established in paraneoplastic cerebellar degenerations when, in some cases, the cause of the unnatural hypersensitivity could be traced to small cell carcinomas expressing the autoantigens involved in the patient's pathological immunological activity.[36] Recognising this mode of sensitisation revealed a common theme in the pathogenesis of the IMP.

The brain proteins involved in PCD are identified by their relative mass observed in Western blot reactions of the patient's sera on an extract of brain. Examples include the Yo, Hu and Ri antigens but are not limited to these proteins as some cancer patients develop central nervous system (CNS) syndromes in the absence of immunoreactivity with either.[3,41,42] This immunological disparity suggests that those who react with the Yo, Hu or Ri antigens are experiencing the same antigenic stimulus, while those who do not may be reacting to closely related members of the same family of proteins, as clinical presentations are very similar.

The Yo syndrome may develop in association with breast, ovarian and transitional cell carcinomas, or adenocarcinoma. The Yo antigen is located in the cytoplasm of Purkinje cells, and in some cases is found expressed in the patient's cancer.[139]

The Hu antigen is a member of the family of RNA-binding proteins located in neurons of the central and peripheral nervous systems. Antibody reactions with this protein are associated with the appearance of paraneoplastic encephalomyelitis (PEM).[37] At autopsy, antibody complexes and activated lymphocytes recognising the Hu antigen are found in the brain of the affected individual.[38] In a few cases, response to treatment and survival is increased in those who produce high titres of antibodies to the Hu antigen.[39] It could be surmised that benefit ensues from an immunological inhibition of the carcinoma expressing the Hu antigen, a possibility that provides added incentive for continued efforts to develop new antigen-specific immune-mediated therapeutics.[4,40]

The immune response to the Ri antigen is associated with the induction of paraneoplastic opsoclonas-ataxia in breast and lung cancer patients. The antigen is also a member of the family of RNA-binding proteins located in the brain and spinal cord, and has been described as an aberrant expression in the neoplasia of affected individuals. As with many other suspected autoantigens, the Ri antigen is highly conserved in nature and even shares homology with components of yeast and retroviral proteins, a reminder that superimposed infections may occasionally be responsible for the induction of CNS hypersensitivity, and thus confuse the diagnosis.[140,150]

The list of immunoreactive neuronal proteins continues to grow but the Yo, Hu and Ri antigens represent recognised disease-associated cancer markers, and antibody reactions with either is reason to suspect occult neoplasia in a patient presenting with an unexplained CNS disorder and this type of immunoreactivity.

Although cytotoxic antibody activity is suspected in paraneoplastic brain syndromes, unlike the Lambert-Eaton myasthenic syndrome and paraneoplastic pemphigus, efforts at passive transfer to experimental animals with antibodies reactive with the Yo, Hu and Ri antigens have failed to reproduce the signs and symptoms of the disease.[43] Nevertheless, these antibody reactions have an immunological connection with cancer that serves to prompt appropriate screening when encountered in patients for whom no other explanation for a loss of cognisance is apparent.[6]

Muscle

The Lambert-Eaton myasthenic syndrome (LEMS) is one of the most frequently studied paraneoplasia and is linked with small cell carcinomas expressing the specific neurotransmitter protein involved in the myasthenia.[44] Current doctrine advocates that the ectopic appearance of immunological epitopes of the voltage-gated calcium channels prompts a related and pathological immune response that cross-reacts with the corresponding component in the muscle presynaptic nerve terminal.[2,45] The clinical significance of autoantibodies in the production of LEMS is supported by passive transfer experiments in which antibodies from affected individuals were shown to produce similar transient myasthenic effects in neonatal mice following intraperitoneal infusion of the patient's immunoglobulins.[46]

Thymoma-associated myasthenia gravis

A variant of the phenomenon of 'ectopic expression' occurs in some rare malignant thymomas shown to express neurofilaments sharing antigenic epitopes with the acetylcholine receptor (AChR), a key component of the

autoimmune reactions of myasthenia gravis (MG), and titin, a muscle-specific protein.[47–49] However, these observations invite further inquiry into this coincidental expression as the mode of sensitisation because laboratory animals given transplants of thymomas have failed to produce antibodies that typify either paraneoplastic or classic MG.[51] This paradox should be addressed because it is essential that the mode of sensitisation in paraneoplasia, and indeed all autoimmune diseases, be identified if successful immunomodulations are to be developed.[144,145]

In the case of thymomas, the expression of only an epitope of the suspect autoantigen contrasts with that described in small cell carcinomas, in which the whole molecular autoantigen appears in the cancer. The recognition of immunologically cross-reactive epitopes requires an appreciation of the need to closely match epitopes, as those expressed by the malignancy may not be exactly those involved in the patient's pathological immune activity; hence the need to consider 'molecular mimicry'.[47,49–51] Epitope differences are not always readily apparent in Western blot analyses, as they require the more sensitive technique of molecular matching using specific synthesised epitopes to uncover any appreciable sequence and immunological relationship.[52]

A spectrum of severity of thymic transformations occurs in thymomas, ranging from gross to barely recognisable; a situation that has provoked supposition that classical MG evolves from the benign, less-recognised thymic changes that almost always accompany this disease.[48] In this respect, similarities are recognised and the nature of paraneoplastic and classical MG tend to converge.

The production of autoantibodies that react with key muscle components has in some cases diminished following early and complete surgical removal of the thymoma; a result that coincides with the increased survival rate of MG patients following thymectomy.[2,50] However, this does not exclude the occasional example of the appearance of MG following thymectomy.[14,15] The immunological complexities of the myasthenias slowly unravel as pieces of information on the pathogenicity of each fall into place, and more of the workings of this collection of autoimmune diseases is understood.

Paraneoplastic stiff man syndrome

Rheumatological disorders are sometimes the first indication of occult cancer in patients who present with unclear rheumatic complaints.[55] Those that characterise paraneoplastic stiff man syndrome (PSMS) are precipitated by noise, fear or touch, and initially may be confused with other diseases involving muscular rigidity.

Antibody production to amphiphysin was originally thought pathognomonic for PSMS.[56,57] Amphiphysin is a neuronal protein associated with synaptic vesicles and found in different isoforms in the nodes of Ranvier of the brain and around tubules in skeletal muscle. Expression of amphiphysin by small cell and breast carcinomas indicates one possible pathway leading to loss of tolerance, and complies with 'aberrant ectopic expression' as the sensitisation process.[1] However, more recent studies reveal immunoreactivity with this potential autoantigen can develop in association with breast, ovarian and small cell carcinomas in the absence of stiffness.[58,59] The same abnormal hypersensitivity also occurs in association with many other paraneoplasias such as sensory neuropathy, encephalomyelitis, cerebellar degeneration and the LEMS.[3,58,62] This apparent confusion may result from varying genetic susceptibility and/or the need for secondary complications such as trauma or infection that expose target tissues.

There is little doubt that immunoreactivity with amphiphysin is abnormal and sufficient reason to arouse suspicion of an underlying neoplasm, but it is not representative of any specific type of malignancy. The implication of amphiphysin as an autoantigen in paraneoplasia continues and is strengthened by recent demonstration of passive transfer of neurological symptoms to rats by antibodies that react with this 128 kDa protein.[151] These findings prompt the need for further studies of the predisposition to amphiphysin sensitisation to identify the factors that lead to a loss of tolerance to this important and widespread tissue component.

An immunological connection exists between PSMS, the classical stiff man syndrome[61,62] and that developing in some cases of insulin-dependent diabetes mellitus (IDDM).[63] All three involve endocrine imbalance resulting from autoimmune interference with different pathogeneses, but include the coincidental production of antibodies to glutamic acid decarboxylase (GAD). Although different epitopes of GAD are involved in each disease,[64,65] the commonality involving the same molecule may prove exceedingly interesting when the cause of the sensitisation process in these three different syndromes is finally identified. Until the aetiology of each is understood, the coincidence continues to represent another example of immunological overlap between paraneoplasia and diseases unrelated to cancer.

Skin

Skin disorders may be the most common form of paraneoplasia, and on first encounter can easily be mistaken for a multitude of other problems. However, the possibility of an occult neoplasia should be included in deliberations of the cause when bulbous pemphigus is diagnosed. This insidious syndrome has been described in patients with both malignant and benign neoplasia, with an obvious survival bias towards that induced by benign growths.[66–68]

The appearance of pemphigus ranks as one of the strongest stimuli prompting a patient to seek medical attention. Occurring most often in patients with lymphocytic leukaemia or malignant lymphoma, there is no known direct immunological connection between the patient's neoplasiam and the eruption of the dermatological disorder. The pattern of sensitisation may follow the path of other paraneoplasia and result from aberrant ectopic expression, but a thorough analysis of this possibility has yet to be undertaken.

There are several distinct skin-related immunological reactions associated with the appearance of cancer-induced pemphigus. Some of the antigens involved are recognised as the cytoplasmic components desmoplakin, envoplakin and periplakin, but also include members of the desmoglein family of cell surface proteins.[69,70] Antibody activity with these skin keratinocyte components is demonstrated classically by Western blot analysis, immunoprecipitation

assay and indirect immunofluorescence, in which antibodies of the IgG subclass predominate.[68,71]

Blistering oral lesions commonly accompany those of the skin and provide easily biopsied samples for direct immunofluorescence when abnormal antibody and aggregates of complement components are found to be localised in intercellular spaces. Confirmation can be made using the well-established technique of indirect immunofluorescence on sections of rodent urinary bladder, where related antibodies are found to localise on epithelial cell surface antigens.[68,72,73] Western blot reactions on extracts of normal human skin reveal antibody interactions with any or all of five paraneoplastic pemphigus-related proteins that have relative molecular weights of 170, 190, 210, 230 and 250 kDa.[74,75]

Tissue cultures of human keratinocytes labelled with any convenient isotope and mixed with serum samples from the PNP patient result in the immunoprecipitation of PNP-related skin proteins, demonstrable by polyacrylamide gel analysis and subsequent autoradiography.[70,75,76]

Passive transfer of comparable skin lesions to neonatal mice with antibodies from PNP patients provides another example of cytotoxic immunoglobulins encountered in paraneoplasia. As with other types of paraneoplasia, the pathogenesis of PNP appears founded in antibody-mediated autoimmunity resulting from cancer-induced sensitisation to specific disease-related proteins.[70,77]

Eye

Early enquiries into the immunological aspects of vision loss in cancer patients described the remote ocular effects of cancer as the 'visual paraneoplastic syndrome' (VPS), and included evidence of abnormal immunological activity directed at the various cell types that comprise the multilayered neurosensory retina.[78,79] Different immunological reactions reported by separate groups of researchers gave advanced warning of the need to organise continuing studies in order to understand the full scope of what were immediately suspected to be cancer-induced autoimmune retinopathies.[80–82] From the very beginning, the small cell carcinoma appeared to be the most frequently encountered cause of cancer-induced blindness.[23,35]

The implication of autoantibodies in the production of paraneoplastic retinopathies was first suspected when immunoglobulins that reacted with retinal ganglion cells were demonstrated in a patient with small cell carcinoma-associated retinal degeneration.[78,82,83] This aberrant immune response was shown to hold the potential for harm when it was demonstrated that an intraocular injection of rabbit antibodies that reacted with retinal ganglion cells produced experimental retinal ganglion cell ablation in cats.[84,85] The results of these experiments illustrated how the selective loss of specific ocular components can occur through antibody-mediated reactions in sensitised individuals.[85,86] Immunological similarities between host neurofilaments and antigens expressed by small cell carcinoma gave evidence of epitope cross-reactivity[87,88] comparable to that reported in the autoimmune reactions of patients with thymomas, in which parts of the autoantigen are expressed.[47,49,50]

Subsequent research uncovered a series of single retinal proteins involved in the antibody reactions of patients with small cell carcinoma-associated retinal degeneration. The first was that of the 23 kDa photoreceptor component, later identified as recoverin, essential to the functions of rhodopsin.[89] The recombinant equivalent of this protein, now used routinely as the test antigen in the serological identification of recoverin hypersensitivity, identifies a specific immunological subclass of paraneoplastic retinopathy and a clinically distinctive form of retinal degeneration.[141,142]

The signs and symptoms of retinal degeneration caused by cancers distant from the eye led to the designation cancer-associated retinopathy – the CAR syndrome.[35,90,91] The preponderance of cancer-induced vision loss in small cell carcinoma patients again demonstrates the relatively high frequency of paraneoplasia induced by this particular type of malignancy.

The pathological significance of antibodies in the pathogenesis of CAR was suspected from its first encounter.[92] Continuing findings emphasised the complexities of CAR and revealed that, in addition to the antiretinal antibodies that identify and participate in the retinopathy, the patient's serum contains factors and/or antibodies that react with and are detrimental to optic nerve functions.[93,94]

Ensuing enquiries into the damaging properties of antirecoverin antibodies illustrated an apoptosis-inducing activity on *in vitro* cultivated monolayers of rat retina cells,[95] and antibody-mediated retinal degenerations *in vivo* following intraocular injection of these immunoglobulins into the genetically prone Lewis rat. This animal is exquisitely sensitive to the induction of autoimmune reactions in the eye and provides a useful model to demonstrate the pathological processes involved in immune-mediated retinal degeneration[100,101] and the significance of inherited susceptibility.[96]

Entry of immunoglobulins to the inner workings of the neuronal retina may depend on leaks induced in the blood-retina barrier by the biochemical influence of the cancer, with subsequent access to the intracellular CAR antigen(s) through means comparable to those proposed to occur in other autoimmune diseases in which autoantibodies react with cytoplasmic and nuclear components.[97,98]

Reports on the pathological consequences of immunological reactions with the 23 kDa CAR antigen (recoverin) began to appear in the literature with mounting frequency as acceptance of the sight-robbing characteristics of the CAR syndrome increased. Correlation of the 23 kDa antigen/antibody reaction with loss of photoreceptor cells in which the antigen is located, and the coincidental expression of the same retinal protein by the patient's small cell carcinoma, was the first example of the immunological 'cancer connection' responsible for initiating the events that lead to an immune-mediated retinal degeneration.[7,10–13] Five additional retinopathy-related retinal antigens have since been discovered in this laboratory, with relative molecular weights of 20, 22, 40, 45 and 62 kDa, and undoubtedly there are more, each associated with different types of retinal degeneration.[164–168]

The 20, 45 and 62 kDa retinopathy-related antigens are all expressed in the outer segments of the photoreceptor cells of the retina, while the 22 kDa antigen is expressed in the nerve fibre layer. All four are also expressed in the optic nerve. Autoimmune reactions with such disseminated CNS

components may be responsible for the few reports of cancer-associated retinal degeneration accompanied by optic neuropathy.[102–104]

Although the 20, 22, 40 and 45 kDa reactions were found originally in cancer patients, retinal proteins sharing these same masses have since been described in the abnormal immunological activity of patients for whom no immediate explanation for the vision loss is apparent.[103] Such findings may illustrate the limitations of the Western blot method, as many proteins share the same molecular mass and a reaction at any given site on the blot could involve any of a collection of antigens of similar size, manifesting as a single band.

Conventional evaluation of a suspect autoantigen requires that Witebsky's postulates be addressed by demonstrating that the isolated antigen incites a related organ-specific autoimmune reaction, transferable by either immune cells or antibodies.[163] An animal model of experimental cancer-induced retinopathy, demonstrated in guinea pigs through the intraperitoneal propagation of viable small cell carcinoma cells, provides an alternative approach. This model is based on finding an American Type Culture Collection-derived small cell carcinoma expressing the 40 kDa CAR antigen located naturally in the outer plexiform layer of the retina.[99] Following intraperitoneal propagation of this culture in Pristane-primed guinea pigs, a 'quiet' retinal degeneration ensued, similar to that described in clinical observations of CAR syndromes, and was accompanied by the production of antibodies that reacted with the 40 kDa CAR antigen.[155,157]

However, attributing the retinal degeneration solely to the immune response is presumptions, as contributions from the many other cancer components and products the animals were exposed to cannot be excluded from the production of the experimental retinopathy. Propagating viable cancer cells in experimental animals results in a profusion of influences from the expression of a multitude of antigenic components and biologically active products, but the procedure has value. Although more difficult to interpret, investigating the influences of viable cancer cells *in vivo* permits an interesting replication to the complexities the patients experience.

Several reports implicate immunological activity with the enolases in retinal degeneration,[153] and there is no doubt that some retinopathy patients do present with indications of a loss of tolerance to these components of glycolysis. However, as with reports implicating heat shock proteins in autoimmunity, it is difficult to attribute an organ-specific autoimmune disease to immunological activity with antigen(s) expressed in every tissue.[159]

The CAR and melanoma-associated retinopathy (MAR) syndromes are rare examples of autoimmune diseases in which the sensitisation process is traced to a cause. Sensitisation to the enolases and heat shock proteins could evolve from microbial infections because these proteins are expressed throughout nature. But the question remains: why the eye?

Retinal pigment epithelium hypersensitivity

The retinal pigment epithelium (RPE) may also be involved in adverse immunological activity, as it is in age-related macular degeneration.[146–148] The RPE is a highly specialised ocular tissue with its own peculiar immunological characteristics, some of which are known to preserve the integrity of the entire eye.[160,161] Evidence also implicates RPE hypersensitivity as an added complication in CAR, where its influence may be subtle and only inhibitory to cells that are required to function with a high degree of efficiency in the maintenance of the retina.[149]

Pigmentary changes occur in the extremely rare syndrome bilateral diffuse uveal melanocytic proliferation (BDUMP) in which the RPE is often lost. Most cases are traceable to malignancies that are found commonly after presentation and diagnosis of this syndrome. The few described in the absence of any cancer may have been induced by a tumour that regressed. Cellular damage may result from the biochemical influence of the cancer; however, immunological involvement remains a possibility, but is questionable due to the scarcity of patients to study.[169]

Retinal pigment epithelium cells can be propagated *in vitro* and provide the means to evaluate the effects of a patient's immunological activity directly on the viable tissue, in the presence and absence of complement.[149] *In vitro* and *in vivo* assays permit the antigenic dissection of the RPE and have led to the implication of specific antigens such as the 57 kDa and 65 kDa RPE proteins in adverse immunological activity.[156,162]

Melanoma-associated retinopathy

Intraocular melanomas are not included in MAR syndromes. These retinal degenerations develop as a remote effect of cutaneous malignant melanoma, usually many years after apparent successful treatment. Onset of the signs and symptoms that typify this syndrome suggest a recurrence and metastasis, if not already recognised. Electroretinograph (ERG) findings resemble those of congenital stationary night blindness,[105] with diminished b-wave activity. In some cases, this coincides with immunological findings of a focus of antibody activity on cells in the inner nuclear layer of the retina, where the nuclei of bipolar cells are located.[106–110] Immunological inhibition of bipolar cells could explain the decreased b-wave activity. No specific protein is associated with the immunological idiosyncrasy of the classic MAR syndrome that may instead involve lipid or carbohydrate antigens.

The MAR syndrome includes immunologically distinct subgroups, as is the case with the CAR syndrome. The 20 kDa retina/optic nerve antigen recently has been described in association with vision loss in a group of melanoma patients, but the same reaction appears in some patients with lupus-related retinopathies. This commonality may implicate an embryological cohesion that shows an immunological skin connection in patients with dermatological disease who suffer concomitant retinal degeneration.[152]

Visual fields in MAR, as with those in other types of paraneoplastic retinopathy, can resemble that of retinitis pigmentosa, sharing the same characteristic of a 'quiet' non-inflammatory and progressive degeneration.[111] Optic nerve involvement is common and could represent a major contributing factor to immune-mediated vision loss in the MAR syndromes, comparable to that reported in CAR.

Chronic demyelinating polyneuropathy in melanoma patients has been attributed to immunological cross-reactivity between melanoma and Schwann cells, both of which originate from neuroectodermal cells. These immunological similarities are comparable with those of

other immune-mediated paraneoplasia and could involve antibody-mediated damage such as that associated with the vitiligo that may also complicate melanoma.[112]

Paraneoplastic optic neuropathy

Cancer-induced demyelinisation is another characteristic of paraneoplasia and may be the presenting sign in a variety of different malignancies.[113–115] That encountered in lymphomatous optic neuritis was among the first paraneoplasia to be linked with autoimmunity.[116,117]

Confusion may arise with that resulting from treatment,[118,119] but demyelination occurring as a remote effect of cancer can be identified by distinct immunological reactions such as those described in the 23 and 62 kDa CAR syndromes. The 'patchy' demyelination is comparable with that typical of multiple sclerosis.[92,102,104]

Cancer-induced demyelination can occur at any stage in the development of the malignancy. As with the majority of paraneoplasia, paraneoplastic demyelination develops primarily in association with small cell carcinoma,[92,104] but is reported in patients with a variety of types of neoplasia.[114,117,120–123]

Lymphoma-associated retinopathy

A rare form of retinal degeneration appears in some lymphoblastic, Hodgkin's and non-Hodgkin' lymphoma patients. The immunological reactions in Hodgkin's patients are unusual in that they include a focus of antibody activity on retinal cone pedicles, but the antigen(s) participating in this anomalous immunological reactivity remain unidentified. Detailed reports of the clinical features of each type of lymphoma-related retinopathy (LAR) have appeared in the literature, accompanied by descriptions of optic nerve involvement, but the events that initiate the immunological peculiarities of these syndromes are not understood and may differ from those attributed to ocular sensitisation induced by solid tumours. Viral agents suspected of causing some of these maladies eventually may be implicated as the source of sensitisation.

Onset of vision loss in paraneoplastic retinopathy can be sudden and rapid or delayed and slow; characteristics that appear dependent on the type of malignancy involved. It is significant that the antibody reactions so clearly defined in small cell carcinoma-associated retinopathy do not appear in the other forms of paraneoplastic vision loss. As each appears to present with distinct immunological characteristics, it can be predicted that in time the antigens involved in MAR, breast cancer-associated retinopathy (BCAR), LAR and paraneoplastic optic neuropathy (PON) will be recognised and provide clues to the events that initiate these pathological immune-mediated ocular degenerations.[143]

Breast cancer-associated retinopathies

The immunological features of BCAR develop late in the history of the cancer and may indicate a recurrence in an apparently 'cured' patient. The few that have been encountered exhibit a focus of antibody activity on retinal photoreceptors or the outer plexiform layer where the 40 kDa CAR antigen is expressed.[155] There is a clear need to learn more of the immunological nature of the BCAR syndrome because of the possibility that this immune-mediated loss of vision may be confused with treatment-related ocular toxicity.[118,119]

Vasculitis

Little is known about cancer-associated vascular disorders, which can range from mild, hardly noticeable lesions to the production of life-threatening emboli. In many cases these vasculopathies resemble those that appear in connection with other types of disease unrelated to cancer. Specific immunological characteristics are not yet recognised, so blockage and inflammation may result from cancer-induced biochemical imbalance such as the influence of cancer procoagulant or a direct immunological influence on the antigens peculiar to the retinal vascular endothelium.[124–126]

If recognised early, cutaneous leucocytoclastic vasculitis, which has a strong association with cancer, can prompt the search for occult neoplasia. However, attributing a patient's vascular changes directly to a malignancy is sometimes questionable, as an ageing individual may be suffering from a collection of unrelated diseases and present with different types of vasculitis emanating from superimposed health problems such as polyarteritis nodosa,[127] thromboembolism[128] and Henoch-Schonlein purpura.[129]

Most recognised cancer-associated vasculopathies are disseminated in both arteries and veins and are resistant to conventional therapy.[128,130–132] The 'cancer connection' is suspected in some cases by the correlation of disappearing vasculitis with successful cancer treatment, and a recurrence with reappearance of the growth. Paraneoplastic vasculitis illustrates a real cancer-induced pathological effect that in many cases involves inflammation, and the pathogenesis may be comparable with that seen in other types of cancer-induced immunological confusion. However, any such connection has yet to be demonstrated.

In summary

The finding that some well-recognised autoantigens and/or component epitopes are actively expressed by dendritic cells in the normal thymic medulla is probably of great relevance to the induction and avoidance of autoimmunity.[53,54] As the centre of immunological instruction, the thymus is the locus of surveillance, where immune cell education occurs and autoreactive populations are depleted. The 'learning' process requires close contact with host autoantigens to induce the tolerance required for natural survival. Loss of tolerance is minimised in the normal individual where active immunological suppressor functions are intact. Accordingly, autoimmune reactions in cancer patients may be restricted to those with faulty suppressor function, making them genetically predisposed to succumb to sensitisations that lead to the immune-mediated paraneoplasia.[33]

In an increasing number of cases, aberrant immunological reactions in paraneoplasia are traced to the fact that the patient's cancer expresses the same autoantigen involved in the pathological response.[7–11,99] Sensitisation is proposed to result from such abnormal exposure, but this line of reasoning is not without flaws.[3,5] In the case of PEM, antibody production to the cerebral protein designated as the Hu antigen is used to identify the syndrome, and expression of the Hu antigen can be demonstrated in the patient's malignancy.[40,43] However, an immunological response to the Hu antigen can occur in cancer patients without symptoms of the Hu syndrome.[39] Why some

succumb and others do not is not understood, but it could involve the need for disruption in the blood/brain barrier such as that demonstrated in animal models of cancer-induced neuropathies.[39,43,99,133,134,154]

Small cell carcinomas are known to express numerous CNS components, but immune-mediated paraneoplasia has a low incidence relative to the total number of cases reported annually. Therefore, sensitisation cannot be attributed simply to exposure to 'sequestered' proteins, and other factors must be involved. If expression of neurological proteins in the wrong place at the wrong time is the mechanism whereby some individuals lose tolerance to specific cellular components, a predisposition to abnormal hypersensitivity may be responsible, similar to that recognised in other autoimmune diseases.[1,33]

The production of antibodies to the same autoantigen in different individuals with the same type of paraneoplasia supports the proposal of an immunological 'cancer connection' and suggests that the stimulus might be traced to the same site on the same chromosome in each patient. If the chromosomal location of the autoantigen is adjacent to a transformation site, expression could result from coincidental translation during tumourigenesis. This possibility has been addressed in relation to the expression of the 23 kDa CAR antigen, the retinal photoreceptor protein recoverin, with tantalising results.[158] Co-translation due to genomic proximity would ensure that specific transformation sites dictate precisely which potential autoantigen the host will be exposed to, should co-translation occur. Moreover, the co-translated 'paraneoplastic autoantigen' would probably be the product of a single gene, and all those are that have been recognised to date.

The scarcity of immune-mediated paraneoplasia could be due to the need for multiple transformation sites to be influenced, some being more likely than others to lead to cancer.[135] The transformation site associated with the gene encoding the autoantigen(s) could be of minor importance, not entirely essential to cancerous growth, and may not always be included in the conversion to cancer.[136,137] This may explain why cancers of the same type are not all found to be expressing 'paraneoplasia-associated autoantigens'.

If the theory of co-translation proves correct, immune-mediated paraneoplasia will provide an opportunity to learn more about the chromosomal transformation sites involved in carcinogenesis. Once the chromosomal location of the autoantigens involved is established, an upstream and downstream search of adjacent genes could identify a related transformation site, and possibly even the specific carcinogen required to influence its activity.[35] This pursuit is encouraged by the finding that the autoimmune response in LEMS involves the expression of an antigen encoded at a chromosomal region close to one that undergoes rearrangements in the transformation to small cell carcinoma.[138]

Paraneoplasia provides examples of autoimmune reactions for which the cause may be readily identified, which is a rare occurrence in immunobiology. Most recognised autoimmune diseases have no known cause, but some may emanate from a combination of genetic susceptibility and the appearance of 'transient neoplasia'. Short-lived neoplasia can appear and then disappear as they succumb to the actions of immune surveillance. Immunological confusion could occur and a key cellular component recognised as alien during the process of ridding the host of the transformed cells. Once tolerance is broken, the response might persist from continued exposure to the native tissue component involved in the autoimmune disease, or it could decline and disappear, as seen in infection- or vaccine-induced Guillain-Barre syndrome.

Studies of the immunology of paraneoplastic disease continue to reveal much about the events that occur in the production of abnormal hypersensitivity involving single proteins. The similarities between paraneoplastic syndromes and other autoimmune diseases sometimes are quite striking. Enquiries into commonalities may bring a better understanding of the means whereby specific antigens become the target of misdirected immunological activity in the majority of autoimmune diseases currently of unknown aetiology. □

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