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Developmental Progression of Remyelination as an Index of Activity of the Multiple Sclerosis Plaque

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Abstract: In terms of a realized predetermination of events of injury and of reconstituted remyelination within multiple sclerosis plaques, it is perhaps reasonable to consider demyelination as an endresult of various pathways of primarily developmental nature. In such a context remyelination rather than demyelination would characterize a disease process that is diffusely inflammatory in white matter but that is morphologically and pathologically definable as multifocal lesions of plaque type. It is further to be determined whether the blood brain barrier hyperpermeability constitutes a recharacterized series of pathways that transform interface reactivity with regard to T lymphocyte entry and reentry within a context of variable cytokine and chemokine effect. A strictly heterogeneous process of epitope spreading akin to possible viral transfer dynamics would implicate primary or secondary progression of a multiple sclerosis process both in established genesis and subsequent amplification. Inflammatory progression would evolve in terms particularly of a lack of growth factors that predetermine outcome of demyelination both as systems of injury to the axon and as a central process of neurodegeneration.

Key words: Sclerosis, plaque, remyelination, developmental, progression

INTRODUCTION

INTERACTIVE AND AMPLIFYING EFFECT

Interactivity of various primary pathogenic events, including genetic factors[1,2], in the development of multiple sclerosis would illustrate and also substantiate a pattern of evolution based on cellular reactivity. An autoimmune concept in the essential participation of various factors in the initial execution of injury to the myelin sheath and to the oligodendrocyte might indicate the subsequent development of secondary causes of cell injury.

In a sense, a first line series of injuries would amplify a secondary group of evolving injuries that further denote the complexity of multiple sclerosis as both a cellular and a primary membrane lipid disorder. Such a paradox might reflect in essential fashion a dual genetic and environmental pathogenic course of evolution based on etiologic considerations.

Associative factor evolution appears primarily to evolve not only as a mechanistic evolutionary series of pathways but rather to implicate an amplification of causative factors active as first, second and subsequent lines of evolutionary influence. One might specifically contribute towards the realization of events that both originate and evolve largely in terms of modes of amplification of effect.

On the other hand, chronically demyelinated axons appear to retain the potential for remyelination throughout life[3] .

EPITOPE SPREAD

The strict categorization of events in the development of autoimmune response might specifically involve the exposure of epitopes that subsequently promote epitope spreading superimposed on a series of secondary consequences. In such a scenario, anti-idiotypic reactivity would constitute a participating role in events that mirror faithfully or less faithfully events of pathogenesis that primarily characterize primary and secondary etiologic factors.

In a sense, one might speak of a series of pathways that self-amplify as different orders of magnitude in transformation of chemical and immunologic injury to myelin and to oligodendrocytes in a manner primarily characterizing autoimmune response. One might speak of how etiology arises as a genetic attribute of an individual driven by environmental forces of influence in an endless series of self-representations. One might further resolve events in multiple sclerosis largely in terms of how multiple sclerosis is multifocal beyond simple lesion infliction. Stem cell-based remyelinating therapies appear a potential mode of therapy in these patients[4].

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PATHOGENIC CASCADE

The nature of a pathogenic cascade in the evolution of a demyelinating event would represent the knowledge of how injury substantiates subsequent evolution in inflammation and repair of that myelin sheath.

Recognition of inflammation as a participating influence both in the injury and in the repair of that injury would reconstitute a series of pathways integral to representation of multiple sclerosis at multiple superimposed levels of pathogenesis and of causation. One might furthermore recognize a series of pathways that bespeak of a reactivity to injury as a primary event in subsequent causation of events of reparative reconstitution. Unlike in developmental myelination, adult expression of Notch 1 and Jagged I does not prevent or limit remyelinating attempts at repair[5].

REPARATIVE EVENTS

In a sense, a resolution of a subsequent reparative event secondary to primary injury to the myelin sheath and to the oligodendrocyte might constitute a further promoted series of pathways of interactivity between the genetic and environmental set of conditioning influence in pathogenesis. In such background noise one might recognize multiple pathways of induced amplification that both develop and transform beyond recognizable influence of demyelinating and remyelinating type.

One would go beyond simple characterization of events in demyelination to recognize remyelination as itself a primary series of events irrespective of dynamics of demyelination as an initial event of injury in multiple sclerosis. Indeed, in such further characterization of demyelination, subsequent events in patients with multiple sclerosis assume a primary role in evolving definition of both clinical and pathologic effect. Within such a context, Transforming Growth Factor beta 1, fibroblast growth factor 2 and Platelet derived Growth Factor AA modulate the myelinating phase in the presence of macrophages[6].

TRANSFORMATION OF INJURY

One might speak of how a series of amplifications is a true representation in transformation of injury as a reparative series of pathways superimposed on independently evolving demyelinating attacks. Action of growth factors appears implicated in myelination mechanisms[7]. One might speak of an uncoupling of both demyelinating and remyelinating waves of associative and interactive effect borne out by previous episodes of injury not only to the myelin sheath but also to the axon and the neuron as a whole.

In such a setting, one might reconstitute events as integral or less integral to the developmental constitution in terms of neuronal reactive patterns of injury and repair [8]

Understanding the evolution of a reparative process of response secondary to a primary event of injury to the myelin sheath might represent a faithful characterization of a disease process that both initiates and also subsequently progresses largely in terms of interactivity of genome and environment. Therapeutic agents target the blood brain barrier, systemic immune dysfunction, local inflammation and neurodegeneration[9].

MULTIPLICITY OF ORDERS OF MAGNITUDE

A duality and a subsequent multiplicity of orders of magnitude in the evolution of multiple sclerosis autoimmunity would represent the full characterization of a series of injuries that are dichotomous both in their representation of events and of derivation. In addition, neurotrophins may be implicated in such attempts at remyelination[10].

One might both call into question the development of demyelination as a primary injury and also recognize remyelination as an independent possible factor in pathogenesis[11] in further injury to the neuronal axonal segment. Recognition, in particular, of multiple sclerosis as a channelopathy would particularly emphasize events that develop primarily and secondarily to the demyelination of multiple axonal segments.

RECHARACTERIZATION OF EVENTS

It is only in recharacterization of events that repeatedly redefine the multiple sclerosis plaque beyond simple morphologic terms that there would be recognized a further series of pathways that invert pathogenic roles in subsequent disease course. An inappropriate cross talk between activated T lymphocytes and neural cells would sustain the progression of demyelination and axonal injury[12]. One might recognize remyelination not only as a reparative process but also as an exceedingly sensitive index of a responsiveness that is primarily injurious in its own right. One might realize a full characterization of events that both evolve and further propagate beyond simple dynamics of a postulated viral infection. Indeed, both involvement and subsequent propagation of events simply redefine multiple sclerosis at multiple different levels of both involvement and subsequent self-amplification of events.

MYELIN DYSREGULATION

The central concept of reactivity to injury inherent to the relapsing remitting course of classical forms of multiple sclerosis would typify further the evolution of primary and secondary cases of progressive injury as selective injury to the oligodendrocyte[13].

Indeed, the progressive nature of overall course in multiple sclerosis patients would arise primarily as a dysregulation of myelin synthesis by the oligodendrocyte and subsequently as a depletion of the same oligodendrocyte cell pool.

MYELINOGENESIS

In terms that arise largely as injury primary and also secondary to oligodendrocytes one would help characterize dysfunction in myelinogenesis and in myelination of axonal segments. Oligodendrocyte physiology represents a relapsing remitting series of reconstitutions of multiple axonal myelin sheaths that further more are implicated in subsequent attacks of multiple sclerosis. The common neutrophin receptor p75 (NTR), a stress receptor, can at times induce apoptosis of oligodendrocytes[14]. One might represent such characterization in terms of an overall view of events that both promote and further amplify different aspects of a dysregulation in reparation by remyelination.

Indeed, realization of events that constitute repair of the demyelinated axonal segment would implicate the emergent role of multiple factors involved in mobilization and subsequent deposition of myelin sheath determinants.

In terms that specifically evolve as defective reparative events due to dysregulation of myelin sheath genesis by an injured oligodendrocyte one might account for a responsiveness that is both repetitive and also subsequently defective in evolution.

EVOLVING INFLAMMATION

Multiple sclerosis plaque genesis is an event created within a context of evolving inflammation of the white and grey matter as an integral region. One might indeed implicate a whole series of possible consequences in the subsequent course of a multiple sclerosis process in terms largely of patterns of possible injury. Further injury to regions of demyelination might represent a full characterization of modes of pattern evolution based on multiple levels of possible execution and outcome of injury and of dysregulation.

SUMMATION OF EFFECT

An integral composite of multiple sclerosis plaques and inflamed adjacent normal appearing white matter appears conducive to progression of injury of myelin sheaths. A combined myelin sheath and axonal segment injury on the other hand would imply a relative summation of effects promoting further injury in the form particularly of early transection of axons.

Composite injuries as combined myelin sheath and axonal injury would constitute the realization of pathways arising within a context of inflammation and attempted remyelination. It would appear significant that injury to myelin sheaths constitutes integral involvement of axonal segments subsequent to the demyelinating event. Conduction block to impulses along demyelinated axons would represent compromised viability of neurons.

INTEGRAL APPROACH

An integral approach to demyelination and to axonal injury promoting axonal transection would account for a heterogeneous but composite series of pathways that lead to resolved gliosis of burnt out plaques involving remyelinating features, and mature actively demyelinating plaques and to shadow plaques with remyelinating features. Progression of demyelination would promote a resolved pathway of events beyond simple recognition of modes or patterns of resolution of the demyelinating event itself. It is in the actual process of myelin sheath loss[15] that multiple sclerosis both arises and progresses as events borne out by vascular compromise or inflammatory reactivity.

Understanding how inflammation develops in white matter as discrete plaques might imply a reconstitution of events beyond simple delineation of origin and of subsequent progression of the lesion. In a sense one might recognize etiologic factors in the progression of demyelination that are permissive or actively conducive towards possible resolution of the inflammation. Only insofar as it is possible to recognize inflammation beyond just cytokine and chemokine production, one can a cellular composite of events redefine pathogenesis of demyelination in multiple sclerosis. The recognition of macrophage participation allows resolution of pathways that promote and further self-promote interactivity between demyelinating and remyelinating events in neuronal and axonal injury.

PREDETERMINED LESION OUTCOME

Inflammatory stimuli of reparative processes subsequent to demyelination would constitute complex

pathways due to the genesis of a heterogeneous system of lesion production.

Pathogenesis in multiple sclerosis is not only an amplifying series of mechanisms in the generation of demyelination but also a mode of transformation of such demyelination to a subsequent phase of remyelination of the involved axonal segments. One might speak of patterned loss of myelin spatially restricted to a large extent to the multiple sclerosis plaques.

Patterns of response to loss of myelin sheaths are strictly amplified in response to repeated episodes of demyelination but are self-limited particularly in the duration of the myelin ensheathment. Indeed, one might speak of how events develop largely in terms of onset and subsequent evolution of pathology of the parent neuron and its axon. In terms beyond simple categorization of events as inflammatory and reparative, one might implicate a whole constellation of responsive elements that both induce characterization of lesion production and also predetermine outcome of inflicted lesions such as axonal transection or the burnt out multiple sclerosis plaque.

HETEROGENEOUS CHARACTERIZATION

The repetitive episodes of demyelination are themselves a substitute system in the genesis of repeated attempts at subsequent remyelination borne out by a realized pattern of heterogeneity of lesion genesis individual to that particular patient affected by multiple sclerosis. In this regard, intravenous immunoglobulins may therapeutically interfere with the immune response at multiple levels[16].

Such a high degree of heterogeneous characterization of events in genesis of disease would perhaps be accounted for by the realization of pathways that originate largely as systems of predetermined outcome[17]

In such a fashion one might perhaps characterize inflammation itself in genesis of the demyelinating plaque as a system of attempted remyelination in its own right. In this sense phases of demyelination are direct determinants of a reparative wave of remyelination as predetermined by patterns of cellular interactivity and as networks of cytokine and chemokine effect.

Proinflammatory and anti-inflammatory classes of cytokines appear to reflect a constitutive series of pathways in the evolution of the multiple sclerosis plaque that is inbuilt beyond realization of either injury or repair of such injury[18].

PATTERNED INJURY

Antigen reactivity and antibody production are systems reflecting an inflammatory response built on a prevalent system of epitope exposure and a subsequent amplification of events. Indeed, one might speak of modes of response as interactive events that repeatedly recharacterize modes of participation of agonists in genesis and evolution of the transforming multiple sclerosis plaque.

An absence of demonstrable perivenous demyelination in multiple sclerosis contrasts sharply with patterns of lesion infliction in acute disseminated encephalomyelitis.

In such a context, there might evolve patterns of responsive characterization of pathogenesis inbuilt within systems of how patterned injury constitutes well-defined demyelinating and subsequent remyelinating multiple sclerosis plaques[19].

Orchestrated events that self-amplify inflammatory lesions would further induce inhibition of axonal and myelin sheath repair within evolving consequences of either cellular or cytokine interaction[20]. Release of ATP might regulate remyelination in inflammatory demyelinating states, involving migration and differentiation of oligodendrocyte progenitors[21]. In terms beyond simple identification of the injurious event or of subsequent attempts at remyelination, the central role of patterned plaque genesis and evolution would attest to a centristic mode of orchestration that pathogenetically is predetermined by critical etiologic primacy of evolution.

One might perhaps recognize modes of patterned evolution that both develop and are in turn also recharacterized by dynamics of the remyelinating response to inflammatory events[22]. Indeed, inflammation is a constitutive characterization of the biology of the multiple sclerosis plaque and a representation of the integral multiple sclerosis disease process in that individual patient.

CIRCULATORY TRANSITION STEPS

Solubility of inflammatory mediators might implicate a circulatory series of transition steps in evolution of the plaque lesion borne out by the inflammatory milieu extending into adjacent normal appearing white matter. One might speak of events that recapitulate a developmental cascade pathway in white matter organization and repeated attempts at reorganization along patterned lines of injury and remyelination of given axonal segments[23].

Indeed, one might recognize a series of injuries to the axonal segment that are reparatively reconstituted largely in terms of only an attempt at remyelination without real resolution of the putatively primary axonal injury.

OLIGODENDROCYTE

Oligodendrocyte extension of the demyelinating process appears primarily characterized by a series of events initially involving a dying back phenomenon of outreaching processes of the cell. Such a dying back oligodendrogliopathy would represent events of transformation in further characterization of the primary genesis of the individual multiple sclerosis plaque. An inefficiency of oligodendrocyte precursor cells appears implicated[24].

Indeed, beyond real recognition of potential attributes of possible evolution of the demyelinating lesion one might further characterize multiple sclerosis as paradoxically a primarily diffuse rather than focal or multifocal lesion, particularly based on biologic markers of disease activity[25]. Platelet Derived Growth Factor and neurotrophin-3 may induce partial recovery and enhanced oligodendrocyte progenitor proliferation[26].

In such terms, amplification of events in reconstitutive pathways of genesis of various multiple sclerosis plaques is a misrepresentation of the true nature of a diffuse lesion that envelopes pathways of white and grey matter pathology. Viral infections constitute a possible representative pattern of prototypical evolution in demyelinating injury largely relevant to the oligodendrocyte, particularly in terms of activation of the Notch pathway[27].

VARIABILITY OF EXTENT AND SEVERITY

Prototypical demyelinating episodes in a patient suffering from multiple sclerosis would constitute only a progressive clinical course within a given context of injury to the axonal segment and beyond strict consideration of how severe such an axonal injury is initially determined[28] It might be significant to consider how realization of modes or pathways is patterned on a basic model of consequence outlining variability in extent and severity. One might recognize how pathogenesis is itself a reconstitution of events that primarily outline the initial event in establishment of an etiologic cause of the disease in that individual patient, particularly axonal injury and neurodegeneration[29].

The actual dynamics of mobilization of injured myelin sheaths would allow for a recategorization of modes of participation of the macrophage in further delineation of a disease process primarily limited by restricted remyelination attempts of an initially injured axonal segment.

PREDETERMINED EVENTS

Predetermination of events in reconstituting pathways that amplify the characterized patterns of evolution in multiple sclerosis appear largely a plaque delineating event integral to a diffuse inflammatory state of the white and grey matter. Axonal damage appears closely associated with inflammation[30] .

In thus defining multiple sclerosis one would recognize events largely in terms of how injury constitutes paradoxically a predeterminant in reparative events in multiple sclerosis plaque extension or maturation.

The blood brain barrier is a reliable indicator of conceptually implicated permeability factors in entry and reentry of T-lymphocytes within the central nervous system. One might recognize events largely in terms of mode of evolution of interactive pathways in further predetermination of the nature of subsequently induced lesions or plaques.

Molecular mimicry represents a characterization of possible significance in evolution of the immunologic response arising subsequent to vascular hyperpermeability.

One might further outline events in terms of binding dynamics of antigen-antibody profiles[31] in the recognized context of developmental change of the multiple sclerosis plaque. It is indeed in further characterization of such events as endothelial cell reactivity and permeability that there would arise dynamics of the demyelination of that axonal segment.

INTERFACE DYNAMICS

The interface between systemic circulation and the central nervous system implies a series of strictly definable interactive events that integrally predetermine attributes of the inflammatory processes within plaques and white/grey matter[32]. Such an interface might reconstitute events as best characterized by interendothelial cell reactivity in determining not only vascular wall permeability but especially attempts at reconstituted flow of blood within the microcirculation primarily supplying white matter of the central nervous system. Thyroid hormone in particular exerts a neuroprotective role with respect to axonal pathology[33].

Integral events of microcirculatory flow would represent a viable pathway in possible determined outcome of a multiple sclerosis process initially centered on a demyelinating plaque and subsequently progressing as a multiplicity of amplifying events in injury and reparation of axonal segments and of myelin sheaths. C5b-9 complement plays a dual role in neuroinflammation and subsequent remyelination in multiple sclerosis[34] .

DICHOTOMY OF EVENTS

A dichotomy of events in myelin sheath and oligodendrocyte injury would represent further

idealization of processes of etiologic significance and of pathogenetic consequence borne out in the realization of a diffuse process that manifests itself focally or multifocally largely or solely as multiple sclerosis plaques.

Morphologic and clinical correlates of disease are themselves divergent expressions of an amplifying series of events borne out as a unified process of injury to the initially definable axonal segment of a given neuronal cell.

DEVELOPMENTAL CONSEQUENCES

Basement membrane integrity reflects modes of interface reactivity in the promotion of the injury to the myelin sheath based on development of antigen epitope characterization or definition. It is significant that modes of evolution of events develop in terms of initially established injury to both the axonal segment and enveloping myelin sheath in multiple sclerosis. Heterogeneity in regulation of remyelination appears a centrally operative pathogenic series of mechanisms[35].

One further consideration relates to how injury is a predetermined outcome of processes borne out by pathways of resolved or partly resolved nature[36] . In this regard, failed remyelination attempts may largely result from failed oligodendrocyte migration or as a resulting inhibitory stimulation, rather than simply axonal injury [37].

In this sense, a partly resolved inflammatory reactivity constitutes only a process of potential hyperpermeability of the blood brain barrier and of consequences largely that further evolve developmentally rather than pathologically.

In such developmental terms it is to be realized that multiple sclerosis plaques are integral to processes that further promote multiple pathways of interactive response [38], including the inhibition of maturation of oligodendrocyte progenitors[39].

A mitochondrial defect in some patients with multiple sclerosis would represent a category of disease entities progressing as self-potentiating events inducing tissue oxidative injury.

The activity of multiple sclerosis plaques denotes a progression arising as a consequence of lymphocytic and macrophage infiltration of the parenchyma. The advancing edge of expanding plaques constitutes a progression borne out by the perivascular infiltration of the white matter. Perivascular zones of active response to injury indicate a primary cellular infiltrative phenomenon that promotes subsequent progression as demyelination, within a context of multifaceted immune reactivity[40].

Demyelination would constitute a primary perivascular origin to a process manifested both as cellular infiltrates and also as consequent injury to axons. Primary and secondary axonal injury would constitute a reflection of dynamics of involvement also of the myelin sheath simply as a result of perivascular origin of the inflammatory changes.

Perivascular consequences reflected in progression of inflammation and as plaque expansion might denote an aspect of progression of a lesion that is primarily constitutional. Tumor Necrosis Factor alpha and lymphotoxin-alpha are upregulated in the chronically inflamed and demyelinated multiple sclerosis plaque[41], A concept of degeneration arises as a realization of factors that prove progressive from the initial stages of an inflammatory reactivity borne out by perivascular infiltrates of lymphocytes and macrophages. Lymphocytic antigen reactivity constitutes a full participation of factors that heterogeneously progress beyond simple conceptual definition of strictly inflammatory change. Microglially secreted factors and expression of Golli proteins may mediate lipopolysaccharide induced proliferation of oligodendrocytes and subsequent remyelination of axons[42]. As a consequence, it is simply as a reflection of progression that multiple sclerosis proves invariably a disease of remitting relapsing or else progressive type.

Progression of injury to myelin sheaths might reflect a constitutional susceptibility that in turn is evidence of a reactivity of cellular infiltration of parenchyma. In this sense, the tissue matrix proteases identified in the cerebrospinal fluid of multiple sclerosis patients constitute a reflection of characterized influence borne out by progression of the pathologic severity of the lesions.

In this context, the axonal involvement also constitutes a progression of injury that permits such change due to inflammatory involvement to transform to an infiltrativeness of the myelin sheath itself. Blocking of oligodendrocyte progenitor cell migration may develop due to disruption of glial-neuronal signaling at synapses and paranodes[43] .

Axonal and myelin sheath combined injury constitutes different aspects of a single process of substituted change that progresses beyond infiltration of the parenchyma and perivascularly[44].

Stability of factors of synthesis and of maintenance of myelin sheaths reflects a propensity for determination of axonal integrity[45]. Also, the neurofascin isoform NF155 associated with microdomains on oligodendrocytes appear involved in intermolecular events in myelinogenesis[46], including the action of fibroblast growth factor 2[47].

Plaque activity constitutes an expression of modes of interactivity and progression as simple superimpositions of cellular and tissue damage. Different patterns of injury

would demarcate aspects of myelin synthesis that are dysfunctionally distinct from normal myelinogenesis.

An essential process of accumulation appears to arise as a consequence of events borne out by an interaction of antigen-antibody and cellular reactivity beyond the vascular wall of regional blood vessels.

Direct contact of macrophages with demyelinating axons appears to constitute a projected and targeted process of catabolized myelin. Myelinogenesis is a target for processes inducing progression. The role of macrophages constitutes a contact phenomenon that progresses along transformational change of antigenic determinants. Combination therapies, in this regard, would offer considerable potential to improve therapeutic yield[48].

In this sense, it appears that fundamental processes of determination of antigenic specificity are central to the progression of injury to the myelin sheath[49].

Meningeal infiltrates of lymphocytes and macrophages overlying plaques appear to represent a full characterization of events that progress as a complementary pathway of injury to tissue matrix and parenchyma. Cross-reactivity with progression of inflammation constitutes the biologic basis of development of injury to the myelin sheath and also axon[50,51].

Cross-reactivity pathways account for development of modes of subsequent change in reactivity of both lymphocytes and macrophages that breakdown myelin and also promote transection of axons.

A multiphasic progression constitutes a representation of events characterized primarily by cross-reactions between myelin determinants and axon determinants and matrix components in inflammatory change. CXC chemokine receptors on oligodendrocytes and their ligands on astrocytes around multiple sclerosis plaques may indicate immune systems of recruitment of oligodendrocytes and of remyelination[52].

A sharp distinction between central and peripheral myelin represents a compromised pathway of reactivity in the case of peripheral nerve myelin that prevents lymphocytes and macrophages from breaking down tissue matrix. In a fundamental sense, tissue matrix degradation is a fundamental biomarker in progression of injury to myelin sheaths and axons. Matrix metalloproteinase-9 enhances remyelination and involves processing of inhibitory NG2 proteoglycan[53].

The acute Marburg subtype may very well constitute a consequence of myelin injury that is progressive largely in terms of accompanying tissue matrix degradation. Ongoing autoantibody action with lack of CNS repair might underlie a primarily progressive form of multiple sclerosis[54] .

Similarly, a predilection for involvement of a combined optic neuritis and acute transverse myelitis might arise due to defined characterization of matrix degradation steps in progression of select areas of plaque genesis. Concentric (Balo type) plaques similarly are a primary expression of dynamics of matrix degradation due to the action of tissue proteases. In addition, the progression of lesions of injury in multiple sclerosis would be an expression of subsequent change or even necrosis of tissue components. Myelin preservation appears a representation of a number of processes determining outcome both in terms of substitute systems of altered identity as well as in terms of modes of progression of tissue damage.

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