The ubiquitin–proteasome system and neurodegenerative disorders

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Abstract

As in all other mammalian tissues, the UPS (ubiquitin–proteasome system) is fundamental to normal brain function. A consistent feature of the major human neurodegenerative disorders is the accumulation of disease-related proteins, in non-native conformations, as protein aggregates within neurons or glial cells. Often the proteins in these aggregates are post-translationally conjugated with ubiquitin, suggesting a possible link between pathological protein-aggregation events in the nervous system and dysfunction of the UPS. Genetic evidence clearly demonstrates that disruption of ubiquitin-mediated processes can lead to neurodegeneration; however, the relationship between the UPS and idiopathic neurodegenerative disorders is less clear. In the latter cases, although a number of different mechanisms could potentially contribute to dysfunction of the UPS and promote the neurodegenerative process, whether UPS dysfunction is causally related to disease pathogenesis, or alternatively arises as a result of the pathological state, and indeed whether

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ubiquitinated inclusions are harmful or beneficial to cells, remains to be clarified.

**Introduction**

Human neurodegenerative disorders represent a clinically and pathologically diverse group of conditions, in which the selective loss of neurons in specific areas of the brain underlies the individual disease symptoms. Most are complex disorders in which genetic and environmental factors interact. A common feature seen in the majority of neurodegenerative disorders is the presence of abnormal protein aggregates within neurons (and sometimes glial cells), which are covalently and post-translationally conjugated to the protein ubiquitin. This commonality has focused attention on the role of the UPS (ubiquitin–proteasome system) in both pathological events within the nervous system as well as normal brain function.

**The UPS controls memory and learning**

Given the range of cellular pathways and physiological processes in which ubiquitin is involved, many of which are described throughout this volume, it is not surprising that normal function of the nervous system largely depends upon ubiquitin conjugation/deconjugation and the UPS.

Synaptic remodelling in response to activity and external stimuli is central to memory formation in the brain. Neuronal plasticity involves changes in the molecular and structural organization of the synapse, as well as neurotransmission. This remodelling of the synapse requires co-ordinated protein synthesis and proteolysis, and the UPS is increasingly acknowledged to play a critical role in regulating the abundance of key proteins at neuronal synapses and hence in normal brain function. The PSD (postsynaptic density) is pivotal to the learning-related synaptic activity within the brain. Recent work in primary rat hippocampal neurons shows that the UPS is integral in the functional and molecular reorganization of the PSD in response to synaptic activity [1]. Multiple classes of postsynaptic proteins were found to be involved in PSD remodelling, but only a subset of postsynaptic scaffold proteins, including Shank, GKAP (guanylate kinase-associated protein) and AKAP (A-kinase anchoring protein) 79/150, are ubiquitinated and targeted to the proteasome for degradation by synaptic activity. The enhanced turnover of other proteins in active PSDs may also be influenced by the ubiquitin-dependent degradation of the scaffolding molecules. Activity-associated proteasome-dependent postsynaptic modifications are accompanied by altered synaptic signalling to CREB (cAMP-response-element-binding protein) and ERK (extracellular-signal-regulated kinase)/MAPK (mitogen-activated protein kinase) pathways, each of which have specific roles in synapse dynamics involved in information storage and processing.
In addition to modulating protein turnover in the PSD, proteasome-regulated proteolysis also has a role in the presynaptic density. The levels of presynaptic DUNC-13 (Drosophila homologue of UNC-13), a protein that regulates synaptic vesicle priming to control synaptic transmission strength, is specifically regulated by the UPS in the Drosophila NMJ (neuromuscular junction) synapse, and the rate of degradation of presynaptic DUNC-13 modulates the strength of synapse neurotransmission by affecting presynaptic efficacy [2].

The concept that proteasome-mediated degradation is central to multiple levels of synaptic modulation is supported by work on sensory-motor synapses of Aplysia (a type of sea slug). The learning-related switch from short-term to long-term facilitation in Aplysia involves UPS substrates functioning in both the presynaptic and post-synaptic densities of sensory-motor synapses [3]. A ubiquitin C-terminal hydrolase [a DUB (deubiquitinating enzyme)] was previously found to be required for long-term facilitation, suggesting a role for the UPS in Aplysia neuronal plasticity [4].

Axonal regeneration is another major area of interest in the mature central nervous system. The formation of a new growth cone following axonal damage is necessary for extension of the axon and hence successful regeneration. It is understandable that remodelling to form this specialized structure at the tip of an axon is accompanied by the synthesis of new proteins and the regulated degradation of existing ones. Although local protein synthesis plays a significant role in this process, intra-axonal protein degradation, including proteasome-regulated degradation, was recently highlighted as part of the mechanism involved in new growth-cone formation following axonal injury [5].

Taken together, it is becoming increasingly clear that the UPS is critical to learning and memory formation within the brain, regulating synaptic neurotransmission and downstream signalling by modulating local synaptic protein concentration. This function in plasticity may explain in part the subset of human neurodegenerative diseases that are caused by mutations affecting ubiquitin pathway genes, described later in this chapter.

**Ubiquitin and neurodegeneration**

*Lessons from immunohistochemistry*

Long before ubiquitin was implicated in the normal physiological processes described above, a tantalizing link between the UPS and pathological events in the nervous system had already been uncovered.

A consistent feature of the major human neurodegenerative disorders such as Alzheimer’s disease, which causes the majority of cases of dementia in the Western world, is the presence of abnormal protein aggregates in the diseased brain. In Alzheimer’s disease, these deposits include filamentous inclusions within neurons called neurofibrillary tangles, and extracellular-protein deposits termed amyloid plaques or senile plaques. Since these aggregates are thought to be involved in, or at the very least to be an indicator of, the patho-
logical process, identification of the specific proteins deposited provides a logical route towards advancing the understanding of disease. For example, the finding that the Aβ (amyloid β) peptide is the major constituent of amyloid plaques led to the discovery that rare familial cases of early-onset Alzheimer’s disease are caused by highly penetrant mutations in the gene encoding the amyloid precursor protein [6]. Likewise, the identification of hyper-phosphorylated filamentous forms of the microtubule-associated tau protein as a principal constituent of paired helical filaments, which make up neurofibrillary tangles, eventually led to the discovery that certain frontotemporal dementias (but not Alzheimer’s disease) are caused by mutations in the tau gene [7].

In the late 1980s, over 70 years after Alois Alzheimer made his first pathological description of the disorder, ubiquitin was identified as a new player in the neurodegenerative process. Using immunohistochemical techniques with antibodies raised against the ubiquitin protein, workers in several research groups almost simultaneously reported intense staining of neurofibrillary tangles as well as neurites (axons or dendrites) associated with amyloid plaques, in brain sections taken from patients with Alzheimer’s disease [8,9] (Figure 1). Other structures were also seen with ubiquitin antibodies, including persiomatic granules [10], dystrophic neurites, and dot-like bodies in white matter [11]. Soon after, it was realized that ubiquitin staining was not only a feature of the lesions in cases of Alzheimer’s disease, but could also be detected in inclusions in other disorders involving tau pathology (so-called tauopathies, such as Pick’s disease), as well as in disorders involving α-synuclein pathology.

Figure 1. Ubiquitin-immunoreactive structures in Alzheimer’s disease (A–D) and Huntington’s disease (E and F) brain sections
For comparison, some nuclei are indicated (n). (A) Neurofibrillary tangles. (B) Neuritic plaque (a prominent ‘bulbous’ dystrophic neurite is arrowed). (C) Persiomatic granules. (D) Dot-like ubiquitin immunoreactivity. (E) Huntington’s disease neuronal intranuclear inclusion. (F) Huntington’s disease dystrophic neurite.

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Ubiquitin immunohistochemistry soon facilitated worldwide diagnostic awareness of a ‘new’ neurological condition, dementia with Lewy bodies. Inclusion bodies, previously very hard to see by conventional staining, could now be easily detected by light microscopy in the cerebral cortex of affected patients. It became apparent that this was the second commonest neurodegenerative cause of dementia after Alzheimer’s disease, and the technique was adopted as the recommended method for detection of inclusions in a clinical setting [15,16]. The availability of ubiquitin-immunohistochemistry revolutionized the pathological diagnosis of MND by allowing identification of a novel inclusion in affected neurons [13,17]. A ‘new’ form of dementia was soon discovered, representing the commonest cause of frontotemporal dementia, in which inclusion bodies resemble those seen in the non-motor cortex in MND [18]. In addition to neurons, in some conditions (e.g. progressive supranuclear palsy) glial cells were found to involve ubiquitin inclusions, and ubiquitin-immunoreactivity of protein aggregates was also found to extend beyond the nervous system, with Mallory bodies in alcoholic liver disease as well as cytoplasmic bodies in muscle being stained by anti-ubiquitin [12]. In fact, it seemed that in almost every disorder in which protein aggregation was occurring, ubiquitin immunoreactivity could be detected.

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**Table 1** Ubiquitin-positive inclusions which characterise human degenerative disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Pathology stained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s disease</td>
<td>Neurofibrillary tangles, neuritic plaques, perisomatic granules, neuropil threads, dot-like bodies</td>
</tr>
<tr>
<td>Dementia with Lewy bodies</td>
<td>Cortical Lewy bodies, Lewy neurites</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>Brainstem Lewy bodies, Lewy neurites</td>
</tr>
<tr>
<td>Pick’s disease</td>
<td>Pick bodies</td>
</tr>
<tr>
<td>ALS</td>
<td>MND inclusions</td>
</tr>
<tr>
<td>Frontotemporal dementia</td>
<td>Neuronal inclusions</td>
</tr>
<tr>
<td>Multiple system atrophy</td>
<td>Glial cytoplasmic inclusions</td>
</tr>
<tr>
<td>Huntington’s disease</td>
<td>Intranuclear inclusions, dystrophic neurites</td>
</tr>
<tr>
<td>Spinocerebellar ataxias</td>
<td>Intranuclear inclusions of polyglutamine-containing aggregates</td>
</tr>
<tr>
<td>*Alcoholic liver disease</td>
<td>Mallory bodies (liver)</td>
</tr>
<tr>
<td>*Cytoplasmic muscle myopathy</td>
<td>Cytoplasmic bodies (muscle)</td>
</tr>
</tbody>
</table>

*The disorders indicated affect tissues outside of the nervous system.*
In Alzheimer’s disease and Parkinson’s disease (and presumably the other protein conformation disorders) it is now clear that ubiquitin not only co-localizes with the filamentous protein aggregates that are composed of tau and α-synuclein (a presynaptic protein which may be involved in regulating synaptic transmission) respectively, but is covalently conjugated to modified (phosphorylated and truncated) forms of these proteins [19,20]. Ubiquitinated tau protein purified from brains of patients with Alzheimer’s disease includes forms with polyubiquitin chains which are Lys48-linked, suggesting attempted proteasomal degradation. In other cases, for example MND, the nature of the ubiquitinated proteins within the inclusions remains elusive, but once identified will no doubt be most informative in understanding the disease process.

Although suggestions had been made that the UPS was participating in a common biological response designed to eliminate abnormal proteins (the ubiquitin-intermediate filament response), the definition of the aggresomal response by Kopito and colleagues [20a] reinforced the important association between the UPS and protein aggregation in disease [21]. Regardless of whether the events that can be seen and characterized post mortem represent a normal cellular response to the accumulation of aggregated proteins, and/or a failed attempt by the UPS to degrade some form(s) of the aggregated protein, these combined observations gave some of the first indications of a possible link between protein aggregation events and UPS dysfunction. Whether protein aggregation leads to UPS dysfunction, or vice versa, and in fact whether ubiquitin inclusions are harmful or beneficial to cells, remain areas of intense debate.

**Lessons from genetics**

Genetic evidence clearly links disruption of ubiquitin-mediated processes and some neurodegenerative disorders. Studies of genetic forms of Parkinson’s disease and parkinsonism have been particularly fruitful in highlighting the importance of the UPS for neuronal health.

The most common cause of heritable parkinsonism is mutations affecting the parkin gene. The parkin protein is an E2 (ubiquitin-conjugating enzyme)-dependent RING (really interesting new gene)-finger E3 (ubiquitin ligase) enzyme, and seven presumed substrates for parkin’s ligase activity have been identified to date. α-Synuclein is a key component of Lewy bodies in cases of Parkinson’s disease, and a glycosylated form of α-synuclein is ubiquitinated by parkin [22], with accumulation of non-glycosylated α-synuclein being evident in parkin-deficient brains. In addition, synphilin-1, an α-synuclein-interacting protein, is ubiquitinated by parkin [23] as are p38 and CDCrel-1 [24,25]. p38 functions within the aminoacyl-tRNA synthetase multiprotein complex involved in mammalian protein synthesis, and is present in dopaminergic neurons of the adult midbrain (a brain region affected in Parkinson’s disease) and also in Lewy bodies. CDCrel-1 is a member of the septin synaptic-vesicle-associated protein family.
Interaction and ubiquitination of synaptotagmin implicates parkin in the control of neurotransmitter trafficking at the presynaptic terminal [26]. Moreover, synaptotagmin XI immunoreactivity is evident in Lewy bodies in cases of idiopathic Parkinson’s disease. The misfolded Pael receptor [Pael-R (parkin-associated endothelin-receptor-like receptor)], a putative G-protein-coupled seven transmembrane protein, is ubiquitinated by parkin, which is necessary to protect the cell against Pael-R-induced endoplasmic reticulum stress [27]. Parkin may also function as part of an SCF (Skp1–Cdc53/Cul1–F-box protein)-like E3 macromolecule, interacting with hSel-10 and Cullin-1, together with the E2 UbcH7 [28]. Via hSel-10, a cyclin-E-interacting protein, the parkin E3 complex is implicated in the control of neuronal survival, ubiq-
uitinating and thereby regulating the levels of pro-apoptotic cyclin E. To sup-
port this role, mid-brain parkin-deficient neurons, for example, have increased cyclin E levels.

It is hypothesized that the ubiquitination of parkin substrates targets the proteins for proteasomal degradation. Disease-linked mutations impair the E3 function of parkin, and hence the underlying cause of neurodegeneration may be alterations in protein turnover by the UPS, leading to the accumulation of substrates of parkin and compromised cell survival. These proteins are often evident in, and are components of, Lewy bodies in the idiopathic Parkinson’s diseased brain, suggesting similarities in disease mechanisms. However, despite considerable emphasis being placed on the identification of potential substrates for parkin, a recent in vivo analysis demonstrated that the steady-state levels of at least three of these substrates, CDCrel-1, α-synuclein and synphilin-1, are unaltered in parkin-deficient mouse brains [29]. However, their synaptic activ-
ity may be modulated by parkin-mediated ubiquitination. The parkin−/− pheno-
type implicates additional factors in the mechanism of neurodegeneration.

Recent work has identified an interesting relationship between parkin and synphilin-1 that may be related to the formation of Lewy bodies [30]. Parkin appears to have the ability to ubiquitinate synphilin-1 with both Lys48- and Lys63-linked polyubiquitin chains, with the relative levels of either type of modification being dependent on the parkin to synphilin-1 expression ratio. Surprisingly, Lys63-linked ubiquitination of synphilin-1 by parkin seems to occur at ‘normal’ relative expression levels of these proteins. Furthermore, the proteasomal-independent ubiquitin Lys63 linkages appear to be predominant in Lewy-like inclusions formed by parkin, synphilin-1 and α-synuclein co-
expression. Together, this work suggests that Lewy body formation may require functional parkin, and supporting this, some cases of familial parkin-
sonism carrying parkin mutations do not present with Lewy bodies [31].

In addition to parkin mutations, a missense mutation (Ile93→Met) in the gene encoding UCH-L1 (ubiquitin C-terminal hydrolase L1, also known as PGP9.5), an abundant neuronal enzyme, was identified in a German family with a strong history of Parkinson’s disease [32]. Although the physiological function of this protein is not completely understood, it appears that decreased
protease function associated with the Ile\textsuperscript{93}→Met mutation leads to defects in protein turnover \textit{in vivo}. Investigations of the gracile axonal dystrophy (gad) mouse, which is characterized by an in-frame deletion in the \textit{UCH-L1} gene, including exons 7 and 8 that harbour a catalytic residue, strengthened the importance of \textit{UCH-L1} in neurodegeneration [33]. Work has also shown that \textit{UCH-L1} has dimerization-dependent E3 activity \textit{in vitro} [34]. This ligase function catalyses Lys\textsuperscript{63}-linked polyubiquitination of α-synuclein, similar to that described for parkin, and a decreased E3 activity was linked to a decreased susceptibility to Parkinson’s disease, which may explain the protective effects of a Ser\textsuperscript{139}Tyr polymorphism (a naturally occurring variant of the parkin sequence).

Overall, perturbations in the UPS, whether they involve ubiquitination, deubiquitination, or both, are clearly linked to neurodegeneration. Although attention has focused on Parkinson’s disease and related disorders owing to the comparative wealth of information gleaned from heritable forms of these conditions, it seems quite likely that in the future rarer human neurodegenerative disorders will also be found to be caused by mutations in ubiquitin-pathway enzymes.

**Molecular misreading: a novel type of mutation affecting the UPS?**

Although genetic mutations affecting ubiquitin-pathway enzymes have not, at least to date, been found in cases of Alzheimer’s disease, detailed molecular studies of this disorder have led to the identification of a novel mechanism which might account for the ubiquitin pathology that is a feature of Alzheimer’s disease, as well as some other neurodegenerative disorders.

In 1998, a mutant frameshifted form of ubiquitin, termed UBB\textsubscript{+1}, was found to be a component of some of the pathological hallmarks of the Alzheimer’s disease brain, including the neurofibrillary tangles [35]. Rather than resulting from germline mutations, the UBB\textsubscript{+1} protein appears to arise by a mechanism known as ‘molecular misreading’, where correct genetic information gives rise to aberrant gene products owing to mistakes during protein synthesis. UBB\textsubscript{+1} immunoreactivity is also a feature of elderly (but not young) control brains, indicating that molecular misreading may represent an age-dependent event marking the early stages of neurodegeneration. As with ubiquitin-immunostaining, immunoreactivity to UBB\textsubscript{+1} has also been found in a range of other human degenerative conditions, including Huntington’s disease, and in particular disorders characterized by tau pathology such as frontotemporal dementias and Pick’s disease [36], although interestingly not in synucleinopathies (despite the fact that the misreading event still occurs in these conditions).

So how might UBB\textsubscript{+1} expression contribute to neurodegeneration? The UBB\textsubscript{+1} protein has an identical sequence to wild-type ubiquitin for the first 75 amino acid residues, with the C-terminal glycine residue (Gly\textsuperscript{76}) of the wild-type sequence replaced by 20 residues of ‘nonsense’ sequence in the mutant gene product. This defective C-terminus of UBB\textsubscript{+1} means that the
mutant protein cannot, like wild-type ubiquitin, be conjugated to target proteins. However, since the rest of the ubiquitin sequence is intact, UBB\textasciitilde can itself be ubiquitinated by wild-type ubiquitin [37] (Figure 2). The resulting polyubiquitinated UBB\textasciitilde can act as a potent competitive inhibitor of ubiquitin-dependent protein degradation, or may itself be a substrate of the 26 S proteasome. In the simplest model, polyubiquitinated UBB\textasciitilde could accumulate upon aging, impairing the 26 S proteasome with catastrophic consequences for the UPS. Of particular interest is the finding that the E2-25K E2, which is capable of generating polyubiquitinated UBB\textasciitilde, is one of the targets found to be up-regulated in neurons exposed to A\textbeta peptide [38]. This intriguing observation, coupled with the findings that E2-25K is in fact required for A\textbeta-induced neurotoxicity, as well as for neurotoxicity mediated by UBB\textasciitilde, is suggestive of a possible direct molecular link between A\textbeta and UPS dysfunction in Alzheimer’s-related disorders. A recent unique in vitro model of nuclear-inclusion formation in Huntington’s disease further implicated UBB\textasciitilde as an aggravating factor in protein aggregation and neurodegeneration, also confirming a central role for the UPS in polyglutamine diseases [39].
A possible explanation as to why UBB+1 accumulation is only a feature of tauopathies and polyglutamine diseases (but not synucleinopathies) has also been suggested; the UBB+1 protein itself appears to be a UPS substrate, and in this regard, UBB+1 accumulation may be a sensor or ‘reporter’ of UPS dysfunction [36]. So UBB+1 accumulation in neurons in certain neurodegenerative disorders may in fact reflect impairment of the UPS by a mechanism which does not necessarily involve UBB+1.

**Mechanisms of ubiquitin inclusion formation**

The human neurodegenerative disorders that are characterized by ubiquitin-immunoreactive inclusions can essentially be viewed as protein aggregation disorders, in which the accumulation of the protein aggregates is likely to be related to the disease process. Although in rarer familial disorders, protein accumulation leading to aggregation events can in some cases be directly linked to dysfunctional protein turnover (be that of the mutant proteins themselves, or because of defective UPS components), clearly a major, but unresolved, question remains, related to the significance of ubiquitin inclusions in the more common idiopathic human neurodegenerative disorders (i.e. in the absence of obvious genetic mutations). There are several possibilities that might account for the presence of ubiquitinated protein aggregates in these cases (Figure 3), which include the following:

1. That a generalized failure of the UPS, upon, for example, aging occurs. Although age-dependent changes in the activity of a number of components of the UPS have been reported, and various mechanisms have been proposed that might account for such changes (such as proteasome inhibition by mutant UBB+1), the observation that the inclusions generally contain a single ubiquitinated protein (for example ubiquitinated tau protein in the case of Alzheimer’s disease), rather than accumulations of mixtures of ubiquitinated proteins, would argue against any primary general failure of the UPS.

2. That ubiquitination is a stabilizing signal that has served to aggregate toxic oligomers of abnormal protein into an inert form, as an inclusion body [40]. The evidence for this potential role is supported by experiments in which reduction of inclusion-body formation in certain models of protein aggregation disease leads to increased cell death [41]. In this regard, in some instances ubiquitin inclusions may have a clearly neuroprotective function, i.e. may be beneficial to cells [42]. Further experimental data suggest that the purpose of inclusion-body formation may be to eliminate material via the autophagic pathway [43].

3. That ubiquitin inclusions are indicative of a normal UPS degradative response to the accumulation of aggregated proteins. It may be significant that certain E3s appear to have a specificity for disease-related forms of cellular proteins, for example the CHIP (C-terminus of the heat-shock-protein-70-interacting protein) E3 targets Alzheimer’s disease-like phosphorylated forms of tau pro-
tein [44]. The localization of proteasome subunits within protein aggregates \textit{in vivo} is further supportive of such a model [45].

(4) A combination of 1 and 3 above, that is to say ubiquitin inclusions represent the failure (or perhaps remnants) of a normal UPS response to the presence of protein aggregates. Within this model, different mechanisms could account for impairment of proteasome function in the pathological state, for example protein-aggregation events [46] which are initiated for reasons that are currently unclear, and/or direct inhibition of proteasome function by (at least in the case of Alzheimer’s disease) Aβ peptide [47] or tau fibrils [48].

\textbf{Conclusion}

In conclusion, normal functioning of the nervous system relies upon the UPS, and disruption of ubiquitin-mediated processes, including proteasomal degradation, can in some cases directly cause neurodegeneration. Immunohistochemical evidence also indicates an involvement of ubiquitin in the disease process of the more common cases of idiopathic neurodegenerative disease [48].
disorders, and a significant future challenge will be to understand more fully the relationship between dysfunction of the UPS and protein aggregation events in the nervous system.

Summary

- The UPS is essential for normal functioning of the nervous system.
- The accumulation of ubiquitinated protein aggregates within neurons in tauopathies, synucleinopathies, as well as polyglutamine diseases, is a hallmark of the major human neurodegenerative disorders.
- These inclusions usually contain a single major ubiquitinated protein.
- Studies of rare familial cases of neurodegenerative disorders, in particular Parkinson’s disease-related conditions, show that disruption of ubiquitin-mediated processes resulting from loss-of-function mutations affecting ubiquitin pathway enzymes can directly cause neurodegeneration.
- A frameshifted mutant form of ubiquitin, UBB+1, which arises through a novel mechanism termed molecular misreading, may be related to the pathogenesis of a range of human disorders.
- The significance of the presence of ubiquitinated inclusions in cases of idiopathic neurodegenerative disorders is still unclear; whether UPS dysfunction is causally related to disease pathogenesis in these cases, or arises as a result of the disease process, is a key question.

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References


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