



OPINION ARTICLE

Puzzles in modern biology. IV. Neurodegeneration, localized origin and widespread decay [version 1; referees: 2 approved]

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Abstract

The motor neuron disease amyotrophic lateral sclerosis (ALS) typically begins with localized muscle weakness. Progressive, widespread paralysis often follows over a few years. Does the disease begin with local changes in a small piece of neural tissue and then spread? Or does neural decay happen independently across diverse spatial locations? The distinction matters, because local initiation may arise by local changes in a tissue microenvironment, by somatic mutation, or by various epigenetic or regulatory fluctuations in a few cells. A local trigger must be coupled with a mechanism for spread. By contrast, independent decay across spatial locations cannot begin by a local change, but must depend on some global predisposition or spatially distributed change that leads to approximately synchronous decay. This article outlines the conceptual frame by which one contrasts local triggers and spread versus parallel spatially distributed decay. Various neurodegenerative diseases differ in their mechanistic details, but all can usefully be understood as falling along a continuum of interacting local and global processes. Cancer provides an example of disease progression by local triggers and spatial spread, setting a conceptual basis for clarifying puzzles in neurodegeneration. Heart disease also has crucial interactions between global processes, such as circulating lipid levels, and local processes in the development of atherosclerotic plaques. The distinction between local and global processes helps to understand these various age-related diseases.

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	1	2
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1 Christos Proukakis , University College London UK		
2 Anya Plutynski , Washington University St. Louis USA		
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Introduction

Initial symptoms of motor neuron disease present as localized muscle weakness. Motor loss often progresses to widespread paralysis over a few years¹.

The onset of this disease poses a puzzle. Does the disease arise in a localized focus of neural tissue and then spread from that focal lesion? Or does the decay arise independently in diverse spatial locations?

Suppose that disease begins from a localized origin²⁻⁶. Then onset may start by local changes in a tissue microenvironment, by somatic mutation, or by various epigenetic or regulatory fluctuations in a few cells. Those local processes may transform a small piece of tissue into a focal lesion that can spread disease to other cells. The widespread decay that ultimately follows happens by local transformation and then spread.

By contrast, suppose that widespread decay originates independently in each small site across the broad spatial domain of diseased tissue. Then localized genetic, epigenetic and regulatory changes in a single site cannot be the origin of the disease. Instead, spatially separated positions must progress independently.

Clues from sporadic versus inherited disease

Consider the pattern of onset and spread in the most common motor neuron disease, amyotrophic lateral sclerosis (ALS).

The majority of cases occur sporadically⁷. Sporadic means that there is no direct evidence of predisposing inherited mutations. These apparently random cases typically occur after age 40, with incidence increasing up to age 75 and then declining at later ages⁸.

Inherited mutations predispose individuals to ALS, causing familial occurrence¹. For example, individuals carrying an inherited mutation in *SOD1* or *C9orf72* often have greatly increased risk of disease.

The age of onset in genetically predisposed cases typically occurs several years earlier than sporadic disease^{9,10}. Genetically predisposed individuals also have much higher incidence than those without genetic predisposition.

The puzzle is whether disease begins with a local change that triggers global spread or with dispersed decay over a broad spatial range. The observed shift in age and incidence associated with inherited mutations provides clues.

Interpreting the clues from the age-incidence shift between familial and sporadic cases requires attention to two aspects. First, the puzzle concerns the dynamics of disease progression. To understand dynamics, we must consider the time-related aspects of the disease. Second, we must frame the clues in relation to the alternatives of localized versus dispersed origin.

Time from onset to full disease

Individuals with certain inherited mutations have a high probability of developing ALS. However, the age at which symptoms first appear varies widely, even for carriers of the same mutation⁹. In sporadic cases, the age of first onset also varies widely.

Once initial symptoms arise, most individuals progress to final widespread paralysis within a few years. What could explain variable age for the first appearance of localized symptoms and the subsequent relatively rapid development of widely dispersed disease?

Localized versus dispersed origin

I mentioned two possible solutions. First, disease may originate locally in a small piece of tissue and then spread from that origin. Second, degeneration may happen nearly simultaneously and independently across diverse spatial locations.

The first solution of local origin and spread fits nicely with the observed pattern of variable age of onset and rapid subsequent progression.

However, the second solution of parallel distributed decay could be true. For example, each individual might be prone to a particular timing of decay across the broad neural landscape. Approximate synchrony may arise because of the common genetic background or environmental exposures shared by all locations.

For example, a global change in a widely circulating factor may initiate simultaneous decay across spatial locations. That global process shifts the locus of causality to the origin of the widely circulating trigger and to the susceptibility of the distributed sites across the neural landscape.

Trigger versus spread

Inherited cases have an earlier age of onset than sporadic cases. That fact refines the alternative solutions of local versus dispersed origin⁸⁻¹⁰.

In the local origin solution, a shared mutation across all locations may increase the rate at which the first localized origin arises. An origin may require several local changes before it can act as a trigger to initiate spatial spread. If all locations share a mutation that moves progression ahead, then the first trigger will happen at an earlier age.

Alternatively, the shared mutation across all locations may reduce the threshold for spread. A lower threshold may induce spread in response to a weaker local trigger.

Seed and soil

A reduced threshold for spread suggests a variant of the dispersed origin solution. A reduced global threshold expresses distributed decay, but one that still requires an additional local origin trigger.

The interaction between local origin and dispersed decay echoes an old idea from cancer research about seed and soil¹¹. In that theory, the metastatic spread of cancer requires both a transformed cell that can act as a seed and a transformed tissue that can act as a soil in which the seed may grow.

Candidate mechanisms

Alternative explanations focus attention on different mechanisms of disease.

Local triggers may arise from various processes: localized environmental insults, tissue microenvironment fluctuations such as infection or inflammation, local vascular changes, local hypoxia, and local changes in other kinds of environmental factors. Changes within one or few cells also initiate local changes: somatic mutation, epigenetic changes, fluctuations in regulatory state, phenotypic responses to altered environments, and so on.

Spread may follow from intercellular transfer of RNA or cytoplasmic components, transmissible misfolding of proteins, diffusible signals, attraction of inflammatory responses, and so on.

Dispersed origin may arise from wider environmental changes, including extrinsic insults, inflammation, broad vascular changes, and so on.

Dispersed origin seems less likely to follow from localized somatic mutation, random epigenetic changes in cells, or random fluctuations in cellular regulatory states. This limitation and the absence of important mechanisms of spread provide the clearest distinction between local versus dispersed origin.

Much research focuses on these kinds of alternative mechanisms. However, mechanistic studies often do not explicitly frame analysis of cause in terms of the variety of potential mechanisms for local triggers and spread versus the variety of potential mechanisms for dispersed origin. My only purpose here is to clarify the relation between different mechanisms and the broader framework in which we must understand the puzzles of disease onset and progression.

In the study of mechanism, one must also distinguish rate of onset versus physiological function¹². An inherited mutation may increase the rate at which disease-causing changes arise in physiological function, but the inherited mutation itself may have no direct physiological role in disease.

For example, inherited defects in modulators of protein folding or in clearance of misfolded proteins may raise the rate at which misfolded proteins act as local triggers of global spread. Similarly, an inherited increase in somatic mutation may raise the rate at which local triggers arise.

Alternatively, an inherited mutation may directly initiate a disease-causing change in a physiological function. For example, a mutation in a protein coding gene may increase the tendency for misfolding of that particular protein. The increased tendency for misfolding may act as a local trigger or may lower the global threshold in response to external triggers.

Neurodegenerative diseases

I have used ALS to illustrate the puzzle of local versus dispersed origin of disease. Similar puzzles arise in Parkinson's disease, Alzheimer's disease and other neurodegenerative diseases.

Within each disease, there will likely be different mechanisms of origin and timing of spread. Between diseases, there will also likely be different aspects of origin and spread. The similarities and differences help to understand broader aspects of disease.

Cancer

At first glance, cancer and neurodegenerative disease seem very different. Cancer arises at a localized site. One thinks about the origin of cancer in terms of the local changes in a few cells and the surrounding tissue microenvironment. Global factors such as immune system status or hormone levels may play a role, but they do so to the extent that they influence local changes at the site of cancer origin.

Progression of cancer depends on the factors that promote spread. The interactions between local triggers and global spread dominate all aspects of cancer research. The study of prevention, early detection, treatment, and basic understanding depends on the local-global interaction.

By contrast, most studies of neurodegeneration are vague about the origin and spread of disease. If a neurodegenerative disease does arise locally and then spread, then such a disease shares with cancer its general causal structure and dynamics.

Recently, several studies of neurodegeneration have focused on the spread of misfolded proteins in a prion-like manner^{5,6}. However, those studies remain vague about the variety of mechanisms that influence local triggers and about the broader conceptual framing of interactions between local and global processes.

Certainly, different neurodegenerative syndromes vary in their causal structure, and various aspects of cancer and neurodegeneration differ in significant ways. It would be useful to understand explicitly the broad conceptual similarities and differences between the diseases. It would also be useful to understand the broader ways in which we can analyze the dynamics of interactions between local and global processes.

Heart disease

Heart disease typically arises from an interaction of local and global processes. Initially, global factors such as lipid levels set the preconditions for localized plaque formation in the inner lining of artery walls.

Although widespread conditions for plaque formation may occur, severe disease often requires a series of local changes at individual plaque sites¹³. For example, the early stages of local site progression typically include recruitment of leukocytes that mature into macrophages, which take up lipid.

Changes in the local tissue microenvironment associate with proliferation of nearby muscle cells and tumor-like expansion and

physiological transformation. An advanced plaque may rupture, attracting platelets and wound healing processes that make a clot. The clot may block local blood flow or break off to block flow at a distant site.

Once again, a strong interaction between local and global processes drives disease progression. The particular timing of the local and global factors differs between heart disease, cancer and neurodegeneration. However, these age-related diseases share a common frame of interacting local and global processes that cause disease onset^{14,15}.

Conclusions

Why does emphasis on interacting local and global processes matter? Consider the basic understanding of disease onset in neurodegeneration.

If a local trigger starts the process, then a localized microenvironmental change or a local somatic mutation can be the event that initiates disease²⁻⁴. By contrast, if a global change initiates disease, then we must look for a factor that can circulate or diffuse widely and that can alter conditions over dispersed spatial sites.

With either initial local or global changes to start disease, progression typically depends on further interactions between subsequent local and global processes. For example, a high global level of certain lipids may be an important trigger of heart disease. Subsequent progression depends on local changes at plaque sites.

Much biological research hunts for the causes of disease. With better basic understanding of cause, one may improve prevention, detection and treatment. However, the notion of cause is always slippery and requires careful thought to frame properly.

Competing interests

No competing interests were disclosed.

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Anya Plutynski

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I had only few minor comments and a suggested reference:

- First, there was some redundancy in the paper: local v. spatially distributed origins as possibilities was mentioned at least twice.
- Second, I really liked the following point, and wondered if this might be developed further, “mechanistic studies often do not explicitly frame analysis of cause in terms of the variety of potential mechanisms for local triggers and spread versus the variety of potential mechanisms for dispersed origin. My only purpose here is to clarify the relation between different mechanisms and the broader framework in which we must understand the puzzles of disease onset and progression.” The idea here seems to be that mechanistic approaches must always be supplemented or contextualized in specific ways, if our aim is to differentiate between alternative hypotheses about origins of disease? Perhaps a firmer and more general statement to this effect might be worth making. As a general point, this is worth emphasizing!
- Last: are local v. spatially distributed initiations of the disease mutually exclusive options for a given disease, or could one be in play in some cases, and another be in play in other cases? To explain, perhaps in some cases a local lesion may advance so quickly that it clearly is a single origin story. In other cases (perhaps for other cancer types or subtypes), typically, many independent populations of proto-cancer cells may be arising simultaneously. For cancers of epithelial origin, the latter seems likely; Martincorena *et al.*, (2015) provide independent evidence in favor of the notion that mutations are always accumulating in healthy tissue, most epithelial cells slough off and do not become cancers, but some acquire sufficient mutations to advance to disease.

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I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

Author Response (F1000Research Advisory Board Member) 02 Dec 2016

Steven Frank, Department of Ecology & Evolutionary Biology, University of California, Irvine, USA

I appreciate Anya Plutynski's thoughtful and encouraging comments. On F1000Research, the referee reports and author comments are part of the final publication, so I will respond here.

Plutynski's second point mentions: *The idea here seems to be that mechanistic approaches must always be supplemented or contextualized in specific ways, if our aim is to differentiate between alternative hypotheses about origins of disease? Perhaps a firmer and more general statement to this effect might be worth making. As a general point, this is worth emphasizing!*

I think this is likely to be true. However, to address the "always" or even to say "usually," I would first have to give a lot of thought to other diseases and, for each, the variety of potential mechanisms. Perhaps this would be a good long-term project to develop, leading to a variety of insights about how to study the possible alternative causes of disease. For now, I will only say "thank you."

Plutynski's third point mentions: *Last: are local v. spatially distributed initiations of the disease mutually exclusive options for a given disease, or could one be in play in some cases, and another be in play in other cases?*

I agree. Once one is thinking along these lines, my main point has been made successfully. As emphasized by the referee, what appears to the "same" disease endpoint can arise from a variety of mechanistic pathways. Although the pathways may vary, it seems likely that distinguishing local and spatial aspects along particular trajectories will help to parse how the variety of causes interact, and the ways in which distinct pathways differ.

Competing Interests: None

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Christos Proukakis

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In this topical and well argued paper, Steve Frank proposes the framework within which one should consider causes of disparate disease processes as either primarily local, or primarily generalized. The focus is mainly on neurodegeneration, and specifically ALS. This condition does appear to start in one location, at least clinically, and spread in an apparently contiguous manner in most cases. A helpful contrast is drawn between the possibilities of a local event which may include a somatic mutation (on which he has eloquently written in the past) [1], and spread, which is an idea that has certainly spread over recent years. Importantly, the agents of spread may not be proteins in all cases, and this is stated here, as RNA and others are also mentioned.

One point that deserves some discussion is the assertion that somatic mutations would generally be

limited to causing local onset. This is true if one accepts that a single cell, or handful of neighbouring cells, could be the trigger. A more widespread onset, but still due to somatic mutations, could be caused by widespread dispersion of early somatic mutations. There is now clear evidence of extensive mixing of cells in early development, with work particularly from the Chris Walsh lab showing how a somatic mutation in brain could also be present throughout a broad region, and perhaps even further afield at a lower level.[2] Apparently synchronous or near-synchronous onset in disparate locations could be due to such a phenomenon, with multifocal onset reported in Parkinson's disease.[3] This would lead to spatially separated positions progressing independently as stated, but the origin could still be a somatic mutation, which happened early enough in development to allow its progeny to be spatially separated.

It is implicit that neurodegenerative diseases affect specific brain cell types, which differ in each one, with selective vulnerability being a key determinant of pathology, along with initiation / spread process. Most readers will be aware of this, but this could be explicitly clarified e.g. to page 2 "the broad neural landscape".

"Trigger versus spread". I note the suggestion that an inherited mutation, present therefore in all cells, may lead to earlier onset by allowing spread to start earlier. This is in line with a staging pathology scheme proposed in a genetic subset of ALS, which claims to describe the sequence of spread.[4] I do not conceptually understand why one has to invoke spread in situations where every cell carries a mutation which can act in a direct or indirect pathogenic way locally. If the mutation has a pathogenic effect, then surely no spread is required when it is present in all cells? I accept that this does not exclude spread, which could still underlie a temporal sequence of events, but differential vulnerability could also determine the sequence of events, particularly if it is stereotyped.

The author finally proceeds to compare this potential dichotomy with cancer and cardiovascular diseases, as situations where, after local initiation, pathology can spread through relevant factors. While it may seem obvious, it should be stated that in the case of cancer the agent of spread is the cell, which clearly is not the case in neurodegenerative disorders. Intriguingly perhaps one could actually invoke the cell as the agent of spread of somatic mutations through migration at the early neurodevelopmental stage, resulting in the spatially disparate somatic mutation situation I outlined above. Furthermore, the medium through which distant spread occurs in these disease categories, circulating blood, does not appear relevant to neurodegeneration, which (if spread is involved) would have to spread through physically connected neurons. Whether this occurs through trans-synaptic spread, secretion (which may or may not involve exosomes), or tunneling nanotubes, is an ongoing debate, albeit beyond the scope of this valuable opinion piece.

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I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

Author Response (F1000Research Advisory Board Member) 02 Dec 2016

Steven Frank, Department of Ecology & Evolutionary Biology, University of California, Irvine, USA

Christos Proukakis has provided an excellent commentary on the origins and spread of neurodegenerative disease, placing my article in that broader context. F1000Research includes referee reports as part of the final publication, and I am very pleased to have this report included. I add a few replies here, which will also be included as part of the final publication.

I list referee comments in italics.

One point that deserves some discussion is the assertion that somatic mutations would generally be limited to causing local onset. This is true if one accepts that a single cell, or handful of neighbouring cells, could be the trigger. A more widespread onset, but still due to somatic mutations, could be caused by widespread dispersion of early somatic mutations...

I agree. However, a key issue concerns the more or less synchronous decay across spatial locations. Dispersed mutations by themselves might lead to parallel independent decay in different locations, but the near synchrony of the decay remains a puzzle. For example, in cancers associated with an inherited mutation carried by all cells, aggressive tumors typically do not appear simultaneously in diverse spatial locations. Instead, different locations progress at different rates, leading to different foci that typically progress to aggressive disease at different times. Of course, there may be cases of approximate synchrony, but I had in mind the likely situation in which particular mutations predispose to disease but are not by themselves sufficient. I did discuss how dispersed mutations may play a key role as spatially distributed altered "soil" that would enhance the spread of a local trigger.

It is implicit that neurodegenerative diseases affect specific brain cell types, which differ in each one, with selective vulnerability being a key determinant of pathology, along with initiation / spread process. Most readers will be aware of this, but this could be explicitly clarified e.g. to page 2 "the broad neural landscape".

The role of different cell types is likely to be important. I suspect that following up on this point by careful reading of the current literature and further thought would lead to useful hypotheses and perhaps some insight. However, I do not have a properly detailed response at present, and so I will simply agree that this is a topic worth pursuing.

"Trigger versus spread". I note the suggestion that an inherited mutation, present therefore in all cells, may lead to earlier onset by allowing spread to start earlier. This is in line with a staging pathology scheme proposed in a genetic subset of ALS, which claims to describe the sequence of

spread.[4] I do not conceptually understand why one has to invoke spread in situations where every cell carries a mutation which can act in a direct or indirect pathogenic way locally. If the mutation has a pathogenic effect, then surely no spread is required when it is present in all cells? I accept that this does not exclude spread, which could still underlie a temporal sequence of events, but differential vulnerability could also determine the sequence of events, particularly if it is stereotyped.

This comment includes the answer that I favor and also emphasized in my article. With regard to triggers, the answer is given by the referee as **I accept that this does not exclude spread, which could still underlie a temporal sequence of events,** emphasizing the point I made above that a mutation likely predisposes but by itself does not change a cell to the diseased state. With regard to spread, **differential vulnerability could also determine the sequence of events,** that is the point of my emphasis in the text on the seed and soil hypothesis, in which differential vulnerability relates to an altered, receptive soil.

The author finally proceeds to compare this potential dichotomy with cancer and cardiovascular diseases, as situations where, after local initiation, pathology can spread through relevant factors. While it may seem obvious, it should be stated that in the case of cancer the agent of spread is the cell, which clearly is not the case in neurodegenerative disorders.

The agent of spread in cancer is perhaps a bit more complex than stated here. Many mechanistic aspects of cancer transcend single cells. For example, secretion of digestive factors that help to penetrate tissue barriers may often be crucial. Similarly, tumors may often secrete a variety of immunomodulatory factors that act both locally and globally, and the various mechanisms that stimulate angiogenesis can be crucial. In cancer, cells may be the key factor for triggering distant metastatic spread, but a variety of extracellular processes may be important in all phases of carcinogenesis.

Furthermore, the medium through which distant spread occurs in these disease categories, circulating blood, does not appear relevant to neurodegeneration, which (if spread is involved) would have to spread through physically connected neurons. Whether this occurs through trans-synaptic spread, secretion (which may or may not involve exosomes), or tunneling nanotubes, is an ongoing debate, albeit beyond the scope of this valuable opinion piece.

With regard to neurodegeneration, I think the issue may again be a bit more subtle. Diet, overall health, immune status, and many other global factors will influence the variety of potential ways in which circulating blood may carry the agents that change spatially distributed aspects of neural tissue. Those changes may act in two ways. First, such changes may interact with a local somatic mutation to transform one or a few cells, which can then act as a trigger. Second, such changes may alter many spatially distributed sites in parallel, fertilizing the soil to be more receptive to triggering seeds when they arise.

Competing Interests: None