biochemical processes that have been implicated in neurodegenerative diseases such as Ca^{2+} homeostasis, autophagy (the process of cellular organelle recycling), and mitochondrial dynamics (*15*). More importantly, it is known that ER-mitochondrial tethering is disturbed in Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis with associated frontotemporal dementia (*15*). However, the molecular mechanisms underlying ER-mitochondrial disruption are not fully understood. Although ER-mitochondrial contact sites represent a nexus for many signaling cascades and biochemical reactions, it is yet to be determined whether a disruption in tethering is causative in neurodegenerative disease initiation or represents a secondary alteration that occurs during disease progression. Clearly, this discovery will provide new tools to better understand the ER-mitochondrial axis with respect to physiology and disease across cell types.

Although several mammalian ER-mitochondrial tethering proteins have been proposed, most lack clear indisputable evidence, and the identification of bona fide ER-mitochondrial tethers has remained elusive. We now have the first description of a protein that appears to primarily function as a member of an ER-mitochondrial tethering complex that can be genetically manipulated without confounding alterations in ER or mitochondrial integrity. This exciting discovery will provide not only new molecular tools to begin to define the physiological functions of ER-mitochondrial connections but also stimulate the search for the mitochondrial interaction partner of PDZD8 and other potential yeast ERMES homologs in mammals. ■

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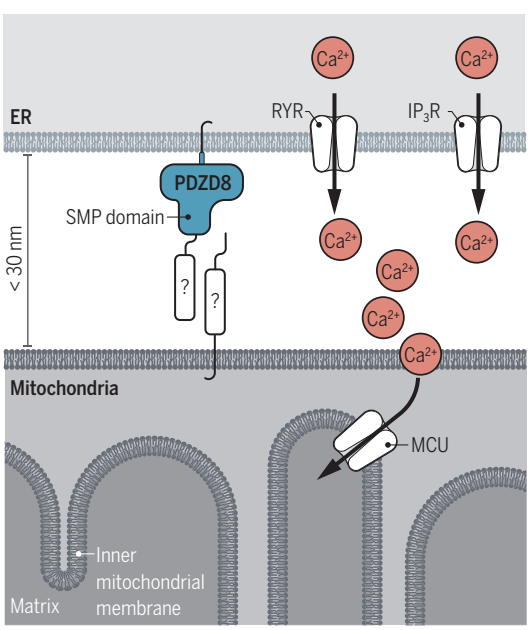
Coupling ER and mitochondrial membranes

The proteins that mediate the close coupling of ER and mitochondrial membranes (tethering) in mammalian cells have remained elusive. PDZD8 is an ER-bound protein that is critical for the tight association of ER and mitochondrial membranes. This will now allow the search for other possible binding partners and regulators that make up this newly identified tethering complex in mammalian cells. The close proximity of the ER and mitochondria is essential for several cellular processes. IP_3R, inositol-1,4,5-trisphosphate receptor; MCU, mitochondrial calcium uniporter; RYR, ryanodine receptor.



ER-mitochondrial tethering

- Calcium transport
- Subcellular signaling domains
- Lipid/membrane homeostasis
- Neurotransmitter release
- Cell death
- Autophagy
- Mitochondrial dynamics
- Inflammation

GRAPHIC: V. ALTOUNIAN/*SCIENCE*

ARCHAEOLOGY

Finding the first Americans

The first humans to reach the Americas are likely to have come via a coastal route

By **Todd J. Braje,[1] Tom D. Dillehay,[2] Jon M. Erlandson,[3] Richard G. Klein,[4] Torben C. Rick[5]**

For much of the 20th century, most archaeologists believed humans first colonized the Americas ~13,500 years ago via an overland route that crossed Beringia and followed a long and narrow, mostly ice-free corridor to the vast plains of central North America. There, Clovis people and their descendants hunted large game and spread rapidly through the New World. Twentieth-century discoveries of distinctive Clovis artifacts throughout North America, some associated with mammoth or mastodon kill sites, supported this "Clovis-first" model. North America's coastlines and their rich marine, estuarine, riverine, and terrestrial ecosystems were peripheral to the story of how and when the Americas were first settled by humans. Recent work along the Pacific coastlines of North and South America has revealed that these environments were settled early and continuously provided a rich diversity of subsistence options and technological resources for New World hunter-gatherers.

Confidence in the Clovis-first theory started to crumble in the late 1980s and 1990s, when archaeological evidence for late Pleistocene seafaring and maritime colonization of multiple islands off eastern Asia (such as the Ryukyu Islands and the Bismarck Archipelago) accumulated. By the early 2000s, the Clovis-first theory collapsed after widespread scholarly accep-

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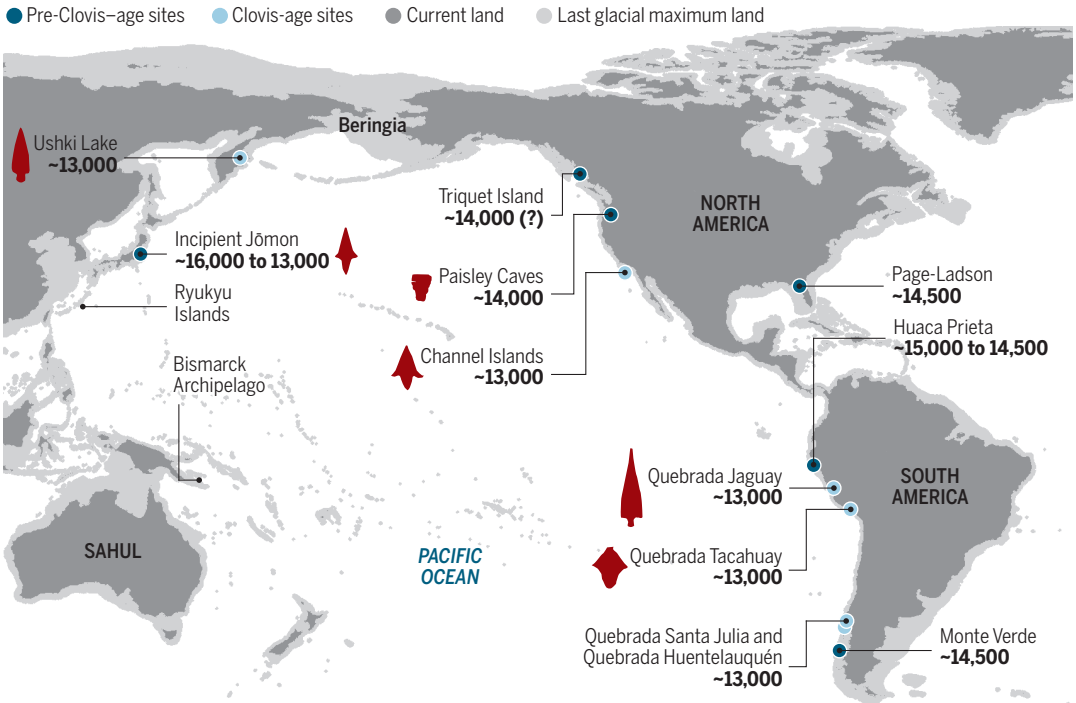
A coastal route for the first Americans

Recent archaeological finds show that pre-Clovis people arrived in the Americas before 13,500 years ago, likely via a coastal route along the Pacific Coast. Higher sea levels make finding direct evidence difficult.



GRAPHIC: J. YOU AND N. CARY/SCIENCE

tance that the Monte Verde locality near central Chile's Pacific Coast was occupied at least ~14,500 years ago (and possibly 16,000 to 18,000 years ago), a millennium or more older than Clovis and the opening of a viable ice-free corridor no earlier than ~13,500 years ago (*1*, *2*). Several more pre-Clovis sites in North America's interior dated between ~14,000 and 16,000 years ago have gained broad scholarly acceptance (*3*–*6*), along with possible evidence for human presence in eastern Beringia ~24,000 years ago (*7*).

In a dramatic intellectual turnabout, most archaeologists and other scholars now believe that the earliest Americans followed Pacific Rim shorelines from northeast Asia to Beringia and the Americas (*8*). According to the kelp highway hypothesis, deglaciation of the outer coast of North America's Pacific Northwest ~17,000 years ago created a possible dispersal corridor rich in aquatic and terrestrial resources along the Pacific Coast, with productive kelp forest and estuarine ecosystems at sea level and no major geographic barriers (*9*, *10*). Kelp resources extended as far south as Baja California, and then—after a gap in Central America, where productive mangrove and other aquatic habitats were available—picked up again in northern Peru, where the cold, nutrient-rich waters from the Humboldt Current supported kelp forests as far south as Tierra del Fuego.

But finding proof for this dispersal route has remained elusive (*8*). Archaeological evidence for early maritime activity has been growing in several areas along the Pacific Coast of North America, including the ~13,000-year-old Arlington Man skeletal remains from California's Santa Rosa Island. But no definitively pre-Clovis coastal sites in North America have been well documented or widely accepted.

"...most archaeologists and other scholars now believe that the earliest Americans followed Pacific Rim shorelines..."

Testing the kelp highway hypothesis is challenging because much of the archaeological evidence would have been submerged by rising seas since the last glacial maximum (LGM) ~26,500 years ago. The earlier such a dispersal took place, the further offshore (and at greater depth) the evidence may lie, enlarging already vast potential search areas on the submerged continental shelf. Although direct evidence of a maritime pre-Clovis dispersal has yet to emerge, recent discoveries confirm that late Pleistocene archaeological sites can be found underwater. Recent discoveries at the Page-Ladson site, for example, produced ~14,500-year-old butchered mastodon bones and chipped stone tools in the bottom of Florida's Aucilla River (*3*). Several multidisciplinary studies are currently mapping and exploring the submerged landscapes of North America's Pacific and Gulf of Mexico coasts, searching for submerged pre-Clovis sites (*8*).

With Clovis-first's demise, debate has shifted to whether colonization occurred well before the last deglaciation (before 25,000 years ago) or after it. Currently, most archaeological and genomic data suggest that the Americas were colonized between ~25,000 and 15,000 years ago (*11*), probably in the latter half of that range, by anatomically modern humans (*Homo sapiens*) who followed a Pacific Rim coastal corridor from northeast Asia into the New World.

The uncertainty left by the collapse of the Clovis-first paradigm, however, has opened a Pandora's box of alternative scenarios for the peopling of the Americas, with some scholars and members of the general public quick to accept implausible claims based on limited and equivocal evidence. For example, a recent report on the Cerutti Mastodon Locality (CML) in California would dramatically extend initial occupation of the Americas to ~130,000 years ago, possibly by a hominin other than *Homo sapiens* (*12*). The CML claim hinges on ambiguous artifacts associated with broken mastodon bones and provides minimal evidence for their geological and stratigraphic context (*13*). The CML claim—similar to a handful of previous assertions for human occupation of North and South America before the LGM—is at odds with most archaeological, paleoecological, and genomic evidence. And despite considerable effort, scientists have found no clear evidence that humans were even in far northeast Asia before ~50,000 years ago.

Answers to the questions of how, when, and where humans first reached the Americas remain tentative. The small sample of pre-Clovis sites has yet to produce a coherent technological signature with the broad geographic patterning that characterizes Clovis. Distinctive fluted Clovis, other fluted

Paleoindian, and fishtail points previously provided a roadmap that archaeologists used to trace the spread of Paleoindians throughout the Americas. Such a roadmap is lacking for pre-Clovis sites. Assemblages with distinctive stemmed ("tanged") chipped-stone projectile points, crescents (lunate-shaped), and leaf-shaped bifaces found in Japan, northeast Asia, western North America, and South America (see the figure) have been proposed as potential markers of a pre-Clovis coastal dispersal (*14*) that seems generally consistent with genomic data, which suggest a northeast Asian origin for Native American ancestors some time in the past 20,000 years. But more data are needed to close substantial spatial and temporal gaps between these far-flung finds and trace a dispersal route from Asia to the Americas. Work on early coastal localities along the Pacific Coast from Alaska to Baja California (*8*), Peru (*10*), and Chile (*1*) is helping to fill these gaps.

If the first Americans followed a coastal route from Asia to the Americas, finding evidence for their earliest settlements will require careful consideration of the effects of sea level rise and coastal landscape evolution on local and regional archaeological records (*15*). Around the globe, evidence for coastal occupations between ~50,000 and 15,000 years ago are rare because of postglacial sea level rise, marine erosion, and shorelines that have migrated tens or even hundreds of kilometers from their locations at the LGM. Overcoming these obstacles requires interdisciplinary research focused on coastal areas with relatively steep offshore bathymetry, formerly glaciated areas where ancient shorelines have not shifted so dramatically, or the submerged landscapes that are one of the last frontiers for archaeology in the Americas. Methodological and analytical advances are moving us closer than ever toward understanding when, how, and why people first colonized the Americas. Coastal regions are central to this debate. ■

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CELL BIOLOGY

Competing chromosomes explain junk DNA

Asymmetric modification of microtubules explains preferential inheritance of chromosomes

By **Francis J. McNally**

The vast majority of eukaryotes have two copies of each chromosome and reproduce sexually. Meiosis is a vital process that produces gametes (eggs and sperm) by reducing the number of chromosome copies to one; fertilization between egg and sperm restores the chromosome copy number to two. During female meiosis, one set of chromosomes is expelled into a tiny cell called a polar body, whereas the other is segregated into the egg. It is a fundamental tenet of genetics that there is a random, 50% chance for any particular chromosome to be segregated into the egg versus the polar body. However, cases in which one copy of a chromosome is inherited with greater than 50% frequency have been reported in many species (*1*), but the molecular mechanism of this preferential inheritance has remained obscure. Recent work has indicated that centromeres, the chromosomal regions that form attachments to microtubules that mediate chromosome segregation during meiosis, compete with each other for inheritance during female meiosis (*2*). Thus, the essential DNA sequences that mediate accurate chromosome segregation are actually "selfish" (or parasitic) genetic elements that have invaded our genome. On page 668 of this issue, Akera *et al.* (*3*) provide the most detailed molecular mechanism to date that explains how a parasitic DNA sequence has used the asymmetry of oocyte meiosis to ensure its own inheritance and therefore its spread through populations.

"...the essential DNA sequences that mediate accurate chromosome segregation are actually 'selfish' (or parasitic) genetic elements..."

Centromeric DNA is composed of more than 1000 copies of a very short (100 to 300 base pairs) sequence that evolves rapidly in both copy number and sequence (*4*). This has led to two very different ideas. There could be something about extremely repetitive short DNA sequences that is essential for function, or these short DNA sequences might be selfish and promote their own inheritance without any functional benefit for the host organism (*2*). This is remarkable because centromeric repeats are the most abundant class of noncoding DNA in our genome, and we do not know what they are for, if anything. Recent work has lent strong support to the idea of centromeres as selfish fragments of DNA.

Standard laboratory mouse strains have 20 different chromosomes, each with its centromere at one end (telocentric). In contrast, certain isolated populations of wild mice have 10 chromosomes, each formed by fusion of two telocentric chromosomes into one chromosome, with its centromere in the middle (metacentric). The female offspring of a cross between a telocentric strain and a metacentric strain exhibit a property called meiotic drive. Instead of transmitting a pair of telocentric chromosomes to 50% of their offspring and the homologous metacentric chromosome to 50% of their offspring, they preferentially transmit either telocentric or metacentric chromosomes (*5*). These findings have remained somewhat obscure because the phenomenon only explains why wild populations of mice tend to have all metacentric or all telocentric chromosomes, and the mechanism has been largely unknown. Recent work has shown that chromosomes that are preferentially transmitted to offspring have up to sixfold more copies of the centromeric repeat sequence (*6*) and load more kinetochore proteins (*5*, *6*) than do chromosomes that are less frequently inherited. The preferentially inherited centromeres with more copies of centromeric repeats and more kinetochore proteins have been called "strong" centromeres and are preferentially oriented toward the egg side of the meiotic spindle. "Weak" centromeres, with fewer copies of centromeric repeats, are preferentially oriented toward the plasma

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Finding the first Americans

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