

a possible amplifier, which may, at least in part, be responsible for the exceptionally warm AW advection.

Instrumental air and AW temperatures in the Arctic during the 20th century and beyond display quasi-synchronous multidecadal oscillations that make isolation of the industrial warming trend difficult (3, 21). Basinwide observations since the 1980s detected multiyear events of AW spreading in the Arctic Ocean that featured both a strong warming and an increased inflow to the Arctic (7, 27, 28). Although we cannot quantify from our data the variability of previous AW inflow to the Arctic by volume, our temperature data series and the above observational link suggest that the modern warm AW inflow (averaged over two to three decades) is anomalous and unique in the past 2000 years and not just the latest in a series of natural multidecadal oscillations. Both effects—a temperature rise as well as a volume transport increase—introduce a larger heat input into the Arctic Ocean. Although there is no direct contact of the AAWL with the ocean surface in the Arctic, such an increased heat input has far-reaching consequences. The strong AW warming event in the Arctic Ocean in the 1990s caused a shoaling of the AW core and an enhanced heat flux to the surface (29), concurrent with decreasing sea ice (4). Recent oceanographic data from the Laptev Sea continental margin indicate the impact of warm AW-related water masses on the shallow (<50 m) shelf (30), a feature not observed before in a >80-year time series. The data also provide evidence for a significant heat flux to the overlying shelf waters (30). Even without any modification of the vertical heat transfer processes, the enhanced temperature contrast between the AW and the surface sea water freezing point (increased from

~5 to 7 K as identified here) leads to an increase in the vertical heat flux of ~40%. Any positive-feedback mechanism will magnify the effect of this flux increase on the ice cover. Complementing the strong feedback between ice and atmospheric temperatures (1), warming of the AW layer, unprecedented in the past 2000 years, is most likely another key element in the transition toward a future ice-free Arctic Ocean.

References and Notes

- J. A. Screen, I. Simmonds, *Nature* **464**, 1334 (2010).
- R. G. Graversen, T. Mauritzen, M. Tjernström, E. Källén, G. Svensson, *Nature* **451**, 53 (2008).
- P. Chylek, C. K. Folland, G. Lesins, M. K. Dubey, M. Muiyin Wang, *Geophys. Res. Lett.* **36**, L14801 (2009).
- J. C. Comiso, C. L. Parkinson, R. Gersten, L. Stock, *Geophys. Res. Lett.* **35**, L01703 (2008).
- D. V. Divine, C. Dick, *J. Geophys. Res.* **111**, C01001 (2006).
- D. S. Kaufman *et al.*, *Science* **325**, 1236 (2009).
- B. Rudels, E. P. Jones, L. G. Anderson, G. Kattner, in *The Polar Oceans and Their Role in Shaping the Global Environment*, O. M. Johannessen, R. D. Muench, J. E. Overland, Eds. (American Geophysical Union, Washington, DC, 1994), pp. 33–46.
- U. Schauer, E. Fahrbach, S. Osterhus, G. Rohardt, *J. Geophys. Res.* **109**, C06026 (2004).
- S. Bonnet, A. de Vernal, C. Hillaire-Marcel, T. Radi, K. Husum, *Mar. Micropaleontol.* **74**, 59 (2010).
- D. Hebbeln, T. Dokken, E. S. Andersen, M. Hald, A. Elverhøi, *Nature* **370**, 357 (1994).
- T. M. Dokken, M. Hald, *Geology* **24**, 599 (1996).
- R. F. Spielhagen *et al.*, *Quat. Sci. Rev.* **23**, 1455 (2004).
- M. Hald *et al.*, *Quat. Sci. Rev.* **26**, 3423 (2007).
- H. H. Lamb, *Climate: Present, Past and Future* (Methuen, London, 1977).
- U. Pflaumann, J. Duprat, C. Pujol, L. D. Labeyrie, *Paleoceanography* **11**, 15 (1996).
- R. Volkman, *J. Foraminiferal Res.* **30**, 157 (2000).
- T. Johannessen, E. Jansen, A. Flatøy, A. C. Ravelo, in *Carbon Cycling in the Glacial Ocean: Constraints on the Ocean's Role in Global Change*, R. Zahn, T. F. Pedersen, M. A. Kaminski, L. Labeyrie, Eds. (Springer-Verlag, Berlin, 1994), pp. 61–85.

- J. Carstens, D. Hebbeln, G. Wefer, *Mar. Micropaleontol.* **29**, 257 (1997).
- A. Moberg, D. M. Sonechkin, K. Holmgren, N. M. Datsenko, W. Karlen, *Nature* **433**, 613 (2005).
- R. Kozdon, A. Eisenhauer, M. Weinelt, M. Y. Meland, D. Nürnberg, *Geochem. Geophys. Geosyst.* **10**, Q03005 (2009).
- I. V. Polyakov *et al.*, *J. Clim.* **17**, 4485 (2004).
- N. Koç, E. Jansen, in *Climate Development and History of the North Atlantic Realm*, G. Wefer, W. H. Berger, K.-E. Behre, E. Jansen, Eds. (Springer-Verlag, Berlin, 2002), pp. 165–173.
- D. Klitgaard Kristensen, H. P. Sejrup, H. Hafliðason, I. M. Berstad, G. Mikalsen, *Paleoceanography* **19**, PA2007 (2004).
- M. Serreze, J. A. Francis, *Clim. Change* **76**, 241 (2006).
- H. Goosse, M. M. Holland, *J. Clim.* **18**, 3552 (2005).
- V. A. Semenov, W. Park, M. Latif, *Geophys. Res. Lett.* **36**, L14709 (2009).
- M. J. Karcher, R. Gerdes, F. Kauker, C. Köberle, *J. Geophys. Res.* **108**, 3034 (2003).
- I. A. Dmitrenko *et al.*, *J. Geophys. Res.* **113**, C05023 (2008).
- M. Steele, T. Boyd, *J. Geophys. Res.* **103**, 10419 (1998).
- I. A. Dmitrenko *et al.*, *J. Geophys. Res.* **115**, C08010 (2010).
- R. R. Dickson *et al.*, *J. Clim.* **13**, 2671 (2000).
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Supporting Online Material

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Methods

Fig. S1

Table S1

References

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The Southern Route “Out of Africa”: Evidence for an Early Expansion of Modern Humans into Arabia

Simon J. Armitage,¹ Sabah A. Jasim,² Anthony E. Marks,³ Adrian G. Parker,⁴ Vitaly I. Usik,⁵ Hans-Peter Uerpmann^{6*}

The timing of the dispersal of anatomically modern humans (AMH) out of Africa is a fundamental question in human evolutionary studies. Existing data suggest a rapid coastal exodus via the Indian Ocean rim around 60,000 years ago. We present evidence from Jebel Faya, United Arab Emirates, demonstrating human presence in eastern Arabia during the last interglacial. The tool kit found at Jebel Faya has affinities to the late Middle Stone Age in northeast Africa, indicating that technological innovation was not necessary to facilitate migration into Arabia. Instead, we propose that low eustatic sea level and increased rainfall during the transition between marine isotope stages 6 and 5 allowed humans to populate Arabia. This evidence implies that AMH may have been present in South Asia before the Toba eruption (1).

The deserts of the Arabian Peninsula have been thought to represent a major obstacle for human dispersal out of Africa. AMH

were present in East Africa by about 200 thousand years ago (ka) (2). It is likely that the first migration of AMH out of Africa occurred im-

mediately before or during the last interglacial [marine isotope stage (MIS) 5e] (3). During MIS 6, the Afro-Asiatic arid belt was hyperarid, restricting movements of human populations out of Africa. Finds from Qafzeh and Skhul in the Near East, dated between 119 ± 18 and 81 ± 13 thousand years ago (ka) (4, 5), suggest that AMH first migrated along the “Nile Corridor” and into the Levant. A later pulse from <65 to 40 ka is thought to have led to further colonization into Europe

¹Department of Geography, Royal Holloway, University of London, Egham, Surrey TW20 0EX, UK. ²Directorate of Antiquities, Department of Culture and Information, Government of Sharjah, United Arab Emirates. ³Department of Anthropology, Southern Methodist University, 3225 Daniel Avenue, Heroy Building 408, Dallas, TX 75275, USA. ⁴Department of Anthropology and Geography, School of Social Sciences and Law, Oxford Brookes University, Headington, Oxford OX3 0BP, UK. ⁵Archaeological Museum, Institute of Archaeology, National Academy of Sciences, B. Khmelniitsky Street, 15, 01030 Kiev, Ukraine. ⁶Center for Scientific Archaeology, Eberhard-Karls-University Tübingen, Rümelinstraße 23, 72070 Tübingen, Germany.

*To whom correspondence should be addressed. E-mail: hans-peter.uerpmann@uni-tuebingen.de

and Asia (6–8). An early southern dispersal from East Africa into south Arabia has been suggested as an alternative route out of Africa, drawing upon faunal and floral evidence (9), human genetics (10–12), and several Paleolithic surface occurrences (3), some of which were first described in the 1930s (13). Here, we describe evidence for the presence of AMH by about 125 ka at Jebel Faya (25.119°N 55.847°E, Fig. 1) (14). Jebel Faya is a 10-km-long, north-south-oriented limestone mountain outlier rising to ~350 m above sea level (m asl). It is located ~55 km from both the Gulf of Oman and the Persian Gulf and directly south of the Straits of Hormuz. At its closest, the present coast of Iran is 165 km away.

The archaeological site, named *FAY-NE1*, is a rock-shelter (180 m asl) at the northeastern end of Jebel Faya. Excavations at the site were undertaken between 2003 and 2010. A 24-m-long section, up to 5 m in depth, was cut from the back wall of the shelter outward (fig. S3). Several other trenches were opened within and in front of the shelter. An area exceeding 150 m² has been excavated. The site contains archaeological levels and artifacts that include the Iron and Bronze Ages, the Neolithic, and the Paleolithic. We used single-grain optically stimulated luminescence (OSL) dating (15) to determine the age of Paleolithic layers. The Holocene levels are separated from the Paleolithic layers by archaeologically sterile sediments. We deal here with the three Paleolithic assemblages designated as A, B, and C (16) because they do not conform to any known named Paleolithic industries. Assemblage A is the uppermost and is separated from the lower assemblages by sterile sediments. Assemblages B and C are not always well separated but are clearly superimposed upon one another.

Three OSL samples associated with assemblage C yielded ages of 127 ± 16 (1 SE uncertainties), 123 ± 10 , and 95 ± 13 ka (table S8). Lithics from assemblage C (Fig. 2) exhibit a number of different reduction strategies; blank production was by the Levallois, volumetric blade, and simple parallel methods. Typologically the tools include small hand axes, foliates, foliate preforms, end scrapers, sidescrapers, and denticulates (16).

Assemblage B blanks, mainly flakes and few blades, were largely produced from flat flaking surfaces with parallel, converging, and crossed removals. Tools include sidescrapers, end scrapers, denticulates, retouched pieces, burins, and perforators. Unlike assemblage C, there was no evidence for the Levallois technique, although there were some small volumetric blade cores. The number and range of tools suggests that the occupation was multipurpose.

Assemblage A contains mainly flakes struck from multiple platform cores with parallel removals on each face. Blades are rare. Tools include burins, retouched pieces, end scrapers, sidescrapers, and denticulates. Both assemblages A and B lack Levallois flaking and bifacial reduction, and, typologically, the use of backing was unknown. Assemblage A is overlain by ~40 cm of sterile

sand. Two OSL samples from within assemblage A yielded ages of 38.6 ± 3.1 and 40.2 ± 3.0 ka, and two samples from the overlying sterile layer yielded ages of 38.6 ± 3.2 and 34.1 ± 2.8 ka. Scattered early Holocene lithics, including Fasad points, were found immediately above the sterile sand layer. Two marine shells found in association with Fasad points yielded radiocarbon ages

of 10,405 to 9711 and 10,380 to 10,078 calendar years before the present (cal. yr B.P.), indicating early Holocene human occupation of the southeastern Arabian Peninsula (17).

Assemblage C ages are consistent with those of the Levantine Middle Palaeolithic, but the assemblage is neither technologically nor typologically related to that of the Levant. Notably

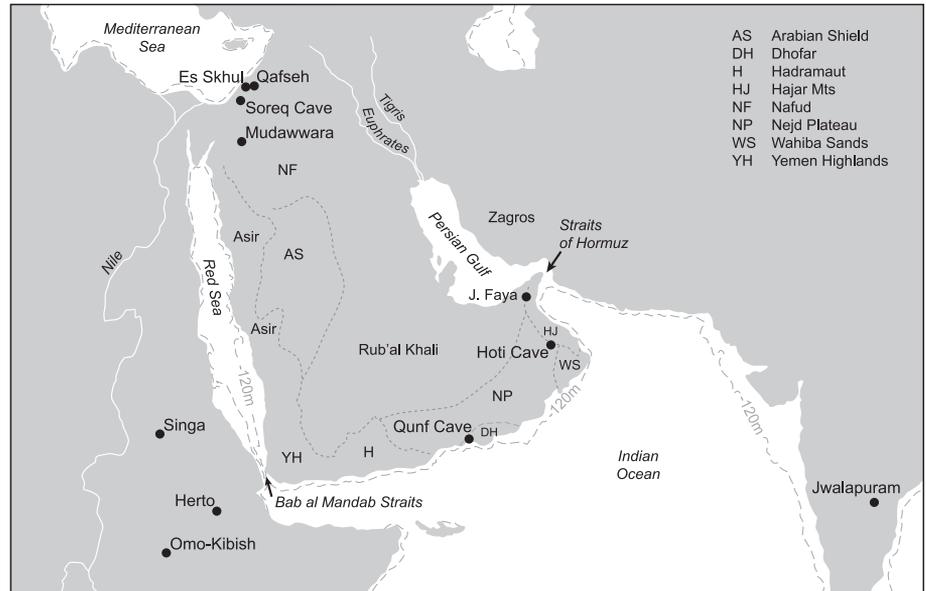


Fig. 1. The location of Jebel Faya, United Arab Emirates, along with key sites mentioned in the text. The dashed line represents the -120-m paleoshoreline, indicating the maximum exposure of land during marine lowstands.

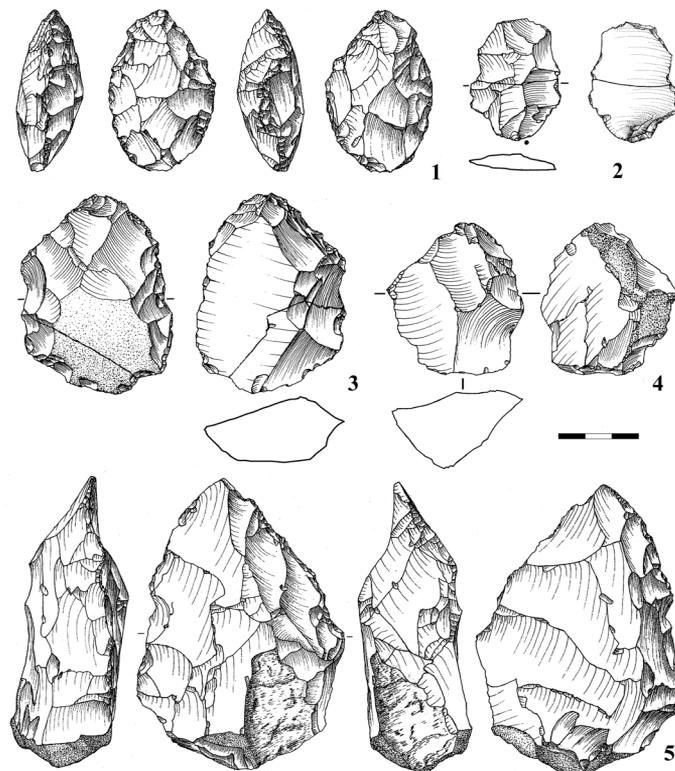


Fig. 2. Assemblage C: 1, bifacial foliate; 2, Levallois flake; 3, bifacial preform; 4, radial core; and 5, hand ax preform.

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different is the reduction by *façonnage* for the production of small hand axes and foliate tool forms. Technological patterns at FAY-NE1 show greater similarities with East and northeast Africa (18) than with other sites known in Arabia. On the basis of these affinities and the contemporaneous presence of AMH in East and northeast Africa, we suggest that assemblage C occupation is attributed to AMH expanding out of Africa during early MIS 5. An autochthonous development for assemblages A and B is suggested be-

cause they bear no affinities with Middle Stone Age/Late Stone Age assemblages known from East Africa, the Upper Palaeolithic from the Levant, or the Zagros. Assemblage A occupation may have been terminated by the onset of hyperarid conditions, as indicated by the sterile sand layer. Certainly, there is no evidence for human presence at Jebel Faya between 38 and 10 ka. This hiatus coincides with a period of hyperaridity and the emplacement of major aeolian dune networks across the Arabian Peninsula (19).

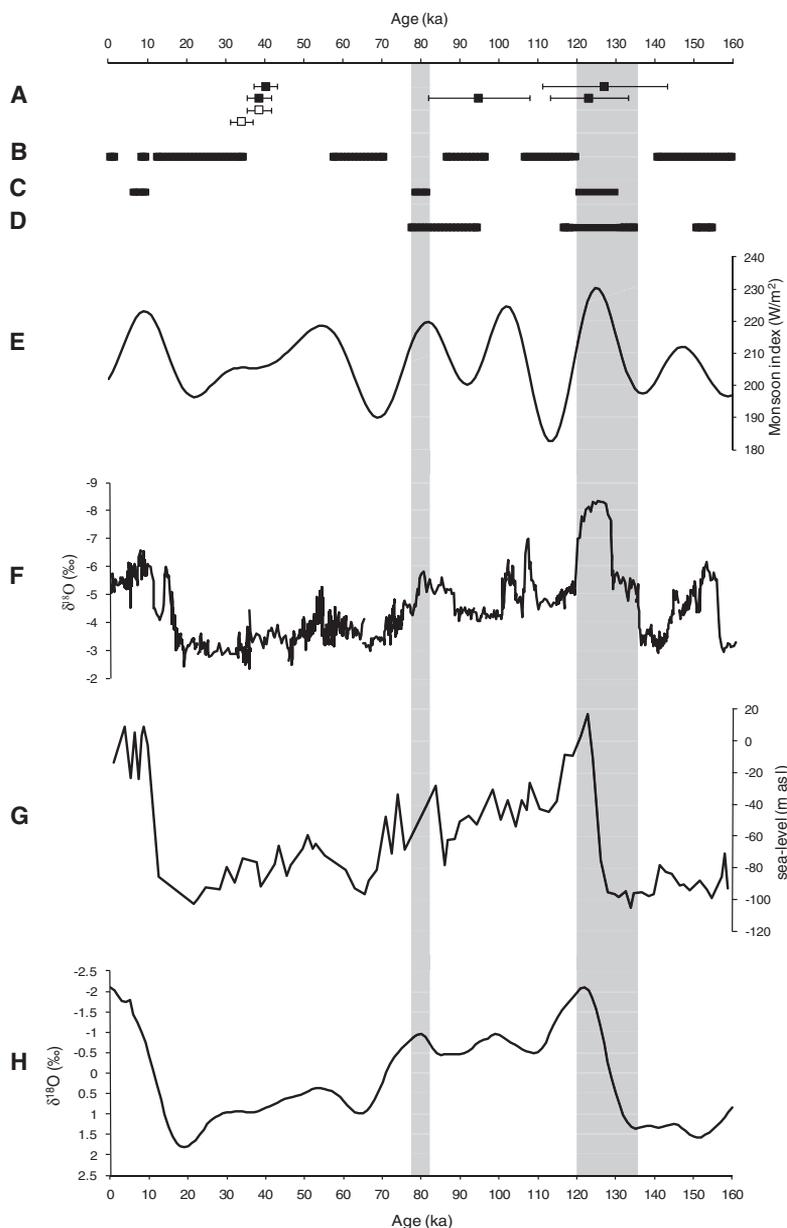


Fig. 3. Compilation of the Jebel Faya chronology with regional and global proxy records. Vertical gray bars represent periods of humidity (19). (A) OSL ages from Jebel Faya. Solid squares represent ages from within occupation phases C and A, whereas open squares represent ages from the sterile sand layer superimposed on top of assemblage A (this study). Error bars indicate 1 SE. (B) Phases of aeolian dune accumulation in the Wahiba Sands, Oman (28). (C) Timing of wet phases in Oman from Hoti and Qunf Cave speleothem records (29, 30). (D) Phases of lacustrine development, Mudawwara, Jordan (31). (E) Indian Ocean Monsoon Index (32). (F) Oxygen isotope ($\delta^{18}\text{O}$) record from Soreq Cave (33). ‰ indicates per mil. (G) Red Sea eustatic changes (20). (H) SPECMAP stacked oxygen isotope record (34).

Within the Arabian section of the southern route, the Nejd Plateau, along with the Straits of Bab al-Mandab and Hormuz, are the three major obstacles to human expansions. The Nejd Plateau is flat and today has poor vegetation cover and lacks surface water. Contrasting climatic conditions are required to allow human migration through these bottlenecks. The straits were easiest to cross during periods of low sea level, associated with glacial epochs, during which the interior of Arabia and the Nejd Plateau was hyperarid. Conversely, during interglacials, when sea level was high, the Nejd Plateau had increased vegetation density and water was more available. Consequently, the phasing of changes in eustatic sea level and terrestrial moisture availability is the key to understanding the timing of human expansion along the southern route.

We suggest that the initial expansion of AMH from East Africa to southern Arabia occurred at the transition from MIS 6 to MIS 5e, when the width of the Bab al-Mandab was at a minimum (20, 21). Once humans had crossed into southern Arabia, this migrant population would have experienced decreased predation and competition for resources. Southern Arabia may have become a secondary center for human population growth. During pluvial episodes, southern Arabia would thus have facilitated further hunter-gatherer range expansions onto the peninsula. There is evidence for wetter phases in southern Arabia at 135 to 120 ka (MIS 6-5e) and 82 to 78 ka (MIS 5a) (19) (Fig. 3). It is likely that populations expanded and moved through the interior of Arabia, as well as via the coastline, and used adaptive strategies incorporating terrestrial resources. The presence of humans at Jebel Faya early in MIS 5 indicates that a significant range expansion occurred during MIS 5e (22). The African affinity of assemblage C implies that a wetter southern Arabian climate rather than technological innovation was responsible for this range expansion (9). With more arid conditions during MIS 5d and 5b, this population probably became disconnected from that in south Arabia, as the corridor across the Nejd Plateau was lost. The continued deposition of Paleolithic artifacts at FAY-NE1, which have no known affinities to other lithic industries in the surrounding areas (16), suggests that AMH presence continued in southeast Arabia throughout MIS 5.

Because the Persian Gulf averages just 40 m in depth (23), lowered eustatic sea levels during MIS 5d and 5b, and between 75 ka and 14 ka, would have provided a land connection between southeastern Arabia and Iran (24). The former Tigris-Euphrates river system flowed through the exposed Persian Gulf and into the Indian Ocean. This landscape periodically formed a corridor for animals including Mesopotamian fallow deer, aurox, and water buffalo (25), as well as Indian elephants, which existed in northwestern Mesopotamia until early historic times (26).

Consequently, the extended Persian Gulf region is likely to have formed another population center from which early modern humans could

radiate during favorable times (22). This probably includes the reoccupation of FAY-NE1 during MIS 3 by the population that produced assemblage A. Access from southeast Arabia to the Persian Gulf and vice versa is likely to have been via the numerous wadi channels that extend from the Hajar Mountains and into the Persian Gulf basin, passing Jebel Faya to the north and the south. These channels would also have facilitated human migration by providing access to fresh water along the shores of the proto-Gulf (22, 27).

References and Notes

- M. D. Petraglia *et al.*, *Science* **317**, 114 (2007).
- I. McDougall, F. H. Brown, J. G. Fleagle, *Nature* **433**, 733 (2005).
- M. D. Petraglia, J. I. Rose, Eds. *Evolution of Human Populations in Arabia: Paleoenvironments, Prehistory and Genetics* (Springer, Dordrecht, Netherlands, 2009), pp. 1–14.
- R. Derricourt, *J. World Prehist.* **19**, 119 (2005).
- J. J. Shea, *Quat. Sci. Rev.* **27**, 2253 (2008).
- R. Klein, *Evol. Anthropol.* **9**, 17 (2000).
- P. Mellars, *Proc. Natl. Acad. Sci. U.S.A.* **103**, 9381 (2006).
- C. B. Stringer, *Nature* **405**, 24 (2000).
- D. E. Wildman *et al.*, *Mol. Phylogenet. Evol.* **32**, 287 (2004).
- L. O. Quintana-Murci *et al.*, *Nat. Genet.* **23**, 437 (1999).
- T. Kivisild *et al.*, *Am. J. Hum. Genet.* **75**, 752 (2004).
- P. Forster, S. Matsumura, *Science* **308**, 965 (2005).
- H. Field, *Am. J. Archaeol.* **36**, 426 (1932).
- Materials and methods are available as supporting material on *Science* Online.
- Z. Jacobs, R. R. Roberts, *Evol. Anthropol.* **16**, 210 (2007).
- A. Marks, in *Evolution of Human Populations in Arabia: Paleoenvironments, Prehistory and Genetics*, M. D. Petraglia, J. I. Rose, Eds. (Springer, Dordrecht, Netherlands, 2009), pp. 295–308.
- H.-P. Uerpmann, D. T. Potts, M. Uerpmann, in *Evolution of Human Populations in Arabia: Paleoenvironments, Prehistory and Genetics*, M. D. Petraglia, J. I. Rose, Eds. (Springer, Dordrecht, Netherlands, 2009), pp. 205–214.
- S. McBrearty, *World Archaeol.* **19**, 388 (1988).
- A. G. Parker, in *Evolution of Human Populations in Arabia: Paleoenvironments, Prehistory and Genetics*, M. D. Petraglia, J. I. Rose, Eds. (Springer, Dordrecht, Netherlands, 2009), pp. 38–49.
- G. N. Bailey *et al.*, *Coast. Arch.* **2**, 127 (2007).
- M. Siddall *et al.*, *Nature* **423**, 853 (2003).
- J. I. Rose, *Proc. Semin. Arabian Stud.* **37**, 219 (2007).
- M. Sarnthein, *Mar. Geol.* **12**, 245 (1972).
- K. Lambeck, *Earth Planet. Sci. Lett.* **142**, 43 (1996).
- H.-P. Uerpmann, *The Ancient Distribution of Ungulate Mammals in the Middle East - Fauna and Archaeological Sites in Southwest Asia and Northeast Africa*, Beihefte zum Tübinger Atlas des Vorderen Orients, Reihe A (Naturwissenschaften), Band 27 (Ludwig Reichert Verlag, Wiesbaden, Germany, 1987).
- C. Becker, *Munibe* **57**, 445 (2005).
- H. Faure *et al.*, *Global Planet. Change* **33**, 47 (2002).
- F. Preusser, *C. R. Geosci.* **341**, 621 (2009).
- S. J. Burns, D. Fleitmann, A. Matter, U. Neff, A. Mangini, *Geology* **29**, 623 (2001).
- D. Fleitmann, A. Matter, *C. R. Geosci.* **341**, 633 (2009).
- N. Petit-Maire *et al.*, *Global Planet. Change* **72**, 368 (2010).
- D. C. Leuschner, F. Sirocko, *Palaeogeogr. Palaeoclimatol. Palaeoecol.* **197**, 83 (2003).
- M. Bar-Matthews, A. Ayalon, M. Gilmour, A. Matthews, C. J. Hawkesworth, *Geochim. Cosmochim. Acta* **67**, 3181 (2003).
- D. G. Martinson *et al.*, *Quat. Res.* **27**, 1 (1987).
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Supporting Online Material

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Materials and Methods

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References and Notes

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Phosphorylation of ULK1 (hATG1) by AMP-Activated Protein Kinase Connects Energy Sensing to Mitophagy

Daniel F. Egan,¹ David B. Shackelford,¹ Maria M. Mihaylova,^{1,2} Sara Gelino,⁴ Rebecca A. Kohnz,¹ William Mair,¹ Debbie S. Vasquez,¹ Aashish Joshi,⁵ Dana M. Gwinn,¹ Rebecca Taylor,¹ John M. Asara,⁶ James Fitzpatrick,³ Andrew Dillin,^{1,2} Benoit Viollet,⁷ Mondira Kundu,⁵ Malene Hansen,⁴ Reuben J. Shaw^{1,2,*}

Adenosine monophosphate-activated protein kinase (AMPK) is a conserved sensor of intracellular energy activated in response to low nutrient availability and environmental stress. In a screen for conserved substrates of AMPK, we identified ULK1 and ULK2, mammalian orthologs of the yeast protein kinase Atg1, which is required for autophagy. Genetic analysis of AMPK or ULK1 in mammalian liver and *Caenorhabditis elegans* revealed a requirement for these kinases in autophagy. In mammals, loss of AMPK or ULK1 resulted in aberrant accumulation of the autophagy adaptor p62 and defective mitophagy. Reconstitution of ULK1-deficient cells with a mutant ULK1 that cannot be phosphorylated by AMPK revealed that such phosphorylation is required for mitochondrial homeostasis and cell survival during starvation. These findings uncover a conserved biochemical mechanism coupling nutrient status with autophagy and cell survival.

A highly conserved sensor of cellular nutrient status found in all eukaryotes is the adenosine monophosphate (AMP)-activated protein kinase (AMPK). In response to decreases in intracellular ATP, AMPK is activated and serves as a metabolic checkpoint, restoring ATP levels through acute regulation of metabolic enzymes and inhibition of pro-growth anabolic pathways (1). Inactivation of LKB1, the upstream kinase necessary for activation of AMPK under low-energy conditions, is a frequent event in sev-

eral forms of human cancer (2). In addition, LKB1 signaling is required in the liver for the therapeutic effect of metformin, the most prevalent type 2 diabetes drug worldwide, and LKB1 inactivation in mouse liver results in a type 2 diabetes-like metabolic disease (3). Thus the LKB1-AMPK pathway provides a direct link between tumor suppression and control of cellular and organismal metabolism.

Similar to AMPK activation, the cellular process of autophagy is initiated under nutrient-poor

and low-energy conditions as a survival mechanism to ensure availability of critical metabolic intermediates and to eliminate damaged organelles, including mitochondria (4). Autophagy is thought to be initiated under nutrient-limited conditions by a conserved kinase complex containing the serine-threonine kinase Atg1 and its associated subunits, Atg13 and Atg17 (5). In mammals, this complex is encoded by two Atg1 homologs, ULK1 and ULK2, and the subunits Atg13 and FIP200, which signal to downstream autophagy regulators through still poorly understood mechanisms. In yeast and mammalian cells, Atg1 or ULK1 activity is suppressed under nutrient-rich conditions by the TOR (target of rapamycin) complex 1 (TORC1) (6). However, biochemical events that activate Atg1 or ULK1 have not yet been identified.

We used a two-part screen to identify substrates of AMPK that mediate its effects on cell

¹Molecular and Cell Biology Laboratory, Dulbecco Center for Cancer Research, Salk Institute for Biological Studies, La Jolla, CA 92037, USA. ²Howard Hughes Medical Institute, Salk Institute for Biological Studies, La Jolla, CA 92037, USA. ³Waitt Advanced Biophotonics Center, Salk Institute for Biological Studies, La Jolla, CA 92037, USA. ⁴Graduate School of Biomedical Sciences, Del E. Webb Neuroscience, Aging and Stem Cell Research Center, Sanford-Burnham Medical Research Institute, La Jolla, CA 92037, USA. ⁵Department of Pathology, St. Jude Children's Research Hospital, Memphis, TN 38105, USA. ⁶Division of Signal Transduction, Beth Israel Deaconess Medical Center, and Department of Medicine, Harvard Medical School, Boston, MA 02115, USA. ⁷Inserm, U1016, Institut Cochin, Université Paris Descartes, CNRS (UMR 8104), Paris, France.

*To whom correspondence should be addressed. E-mail: shaw@salk.edu

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Simon J. Armitage, Sabah A. Jasim, Anthony E. Marks, Adrian G. Parker, Vitaly I. Usik, and Hans-Peter Uerpmann

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