motor coordination. Thus, α-Syn pathology is sufficient to induce the cardinal behavioral and pathological features of sporadic PD.

References and Notes

1. J. M. Fearnley, A. J. Lees, *Brain* **114**, 2283 (1991).
2. J. Simón-Sánchez *et al.*, *Nat. Genet.* **41**, 1308 (2009).
3. A. B. Singleton *et al.*, *Science* **302**, 841 (2003).
4. M. Poulopoulos, O. A. Levy, R. N. Alcalay, *Mov. Disord.* **27**, 831 (2012).
5. M. G. Spillantini *et al.*, *Nature* **388**, 839 (1997).
6. M. Baba *et al.*, *Am. J. Pathol.* **152**, 879 (1998).
7. H. Braak, E. Braak, *J. Neurol.* **247** (suppl. 2), II3 (2000).
8. T. M. Dawson, H. S. Ko, V. L. Dawson, *Neuron* **66**, 646 (2010).
9. J. R. Cannon, J. T. Greenamyre, *Prog. Brain Res.* **184**, 17 (2010).
10. M. Meyer-Luehmann *et al.*, *Science* **313**, 1781 (2006).
11. F. Clavaguera *et al.*, *Nat. Cell Biol.* **11**, 909 (2009).
12. A. de Calignon *et al.*, *Neuron* **73**, 685 (2012).
13. C. Hansen *et al.*, *J. Clin. Invest.* **121**, 715 (2011).
14. P. Desplats *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **106**, 13010 (2009).
15. A. Aguzzi, L. Rajendran, *Neuron* **64**, 783 (2009).
16. E. Angot, J. A. Steiner, C. Hansen, J. Y. Li, P. Brundin, *Lancet Neurol.* **9**, 1128 (2010).
17. H. Braak *et al.*, *Neurobiol. Aging* **24**, 197 (2003).
18. J. H. Kordower, Y. Chu, R. A. Hauser, T. B. Freeman, C. W. Olanow, *Nat. Med.* **14**, 504 (2008).
19. J. H. Kordower, Y. Chu, R. A. Hauser, C. W. Olanow, T. B. Freeman, *Mov. Disord.* **23**, 2303 (2008).
20. K. C. Luk *et al.*, *J. Exp. Med.* **209**, 975 (2012).
21. L. A. Volpicelli-Daley *et al.*, *Neuron* **72**, 57 (2011).
22. H. Fujiwara *et al.*, *Nat. Cell Biol.* **4**, 160 (2002).
23. W. X. Pan, T. Mao, J. T. Dudman, *Front. Neuroanat.* **4**, 147 (2010).
24. S. Fahn, *Ann. N.Y. Acad. Sci.* **991**, 1 (2003).

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Supplementary Materials

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Materials and Methods
Figs. S1 to S6
Tables S1 to S2
References (*25*–*43*)

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Orbitofrontal Cortex Supports Behavior and Learning Using Inferred But Not Cached Values

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Computational and learning theory models propose that behavioral control reflects value that is both cached (computed and stored during previous experience) and inferred (estimated on the fly on the basis of knowledge of the causal structure of the environment). The latter is thought to depend on the orbitofrontal cortex. Yet some accounts propose that the orbitofrontal cortex contributes to behavior by signaling "economic" value, regardless of the associative basis of the information. We found that the orbitofrontal cortex is critical for both value-based behavior and learning when value must be inferred but not when a cached value is sufficient. The orbitofrontal cortex is thus fundamental for accessing model-based representations of the environment to compute value rather than for signaling value per se.

Computational and learning theory accounts have converged on the idea that reward-related behavioral control reflects two types of information (*1*–*3*). The first is derived from habits, policies, or cached values. These terms reflect underlying associative structures that incorporate a precomputed value stored during previous experience with the relevant cues. Behaviors based on this sort of information are fast and efficient but do not take into account changes in the value of the expected reward. This type of information contrasts with the second category, referred to as goal-directed or model-based, in which the value is inferred from knowledge of the associative structure of the environment, including how to obtain the expected reward, its unique form and features, and current value. The associative model is stored, but a precomputed value is not. Rather, the value is computed or inferred on the fly when it is needed. Whereas behavior based on inferred value is slower, it can be more adaptive and flexible.

Although evidence suggests that different brain circuits mediate their respective influences (*1*–*3*), much of cognitive neuroscience—and particularly neuroeconomics—does not attend to these distinctions. For example, proposals for a common neural currency to allow the comparison of incommensurable stimuli (e.g., apples and oranges) typically do not clearly specify the associative structure underlying the value computation. And because economic value is typically measured through revealed preferences, with no explicit control for the source of the underlying value, it would, by default, include both cached and inferred value, at least as defined by computational and learning theory accounts (*1*–*3*).

The calculation of economic value is often assigned to the orbitofrontal cortex (OFC), a prefrontal area heavily implicated in value-guided behavior (*4*–*6*). Yet behavioral studies across species implicate this region broadly, not in value-guided decisions per se, but rather in behaviors that require a new value to be estimated after little or no direct experience (*7*–*14*). Further, the OFC is often involved in a behavior that depends on whether learning is required (*10*, *15*, *16*), even when that learning does not involve changes in value (*17*). These data seem to require the OFC to perform one function—anticipating outcomes, in some settings—whereas it performs another, calculating economic value, in others. However, an alternative hypothesis is that the OFC performs the same function in all settings and specifically contributes to value-guided behavior and learning when value must be inferred or derived from model-based representations. We tested this hypothesis in rats using sensory preconditioning and blocking.

In sensory preconditioning, a subject is taught a pairing between two cues (e.g., white noise and tone) and later learns that one of these cues predicts a biologically meaningful outcome (e.g., food) (*18*). Thereafter, the subject will exhibit a strong conditioned response to both the reward-paired cue and the preconditioned cue. The response to the preconditioned cue differs from the response to the reward-paired cue, in that it cannot be based on a cached value; rather, it must reflect the subject's ability to infer value by virtue of a knowledge of the associative structure of the task (see supplementary discussion for further details). If the OFC is required only for behavior that requires inferred value, then inactivating it at the time of this test should prevent behavior driven by this preconditioned cue, while leaving unimpaired behavior driven by the reward-paired cue.

Cannulae were implanted bilaterally in the OFC of rats [19 controls and 16 inactivated (OFCi)] at coordinates used previously (*12*, *19*) (Fig. 1, A and B). After recovery from surgery, these rats were deprived of food and then trained in a sensory preconditioning task (Fig. 1) (see materials and methods).

In preconditioning, rats were taught to associate two pairs of unrelated auditory cues (A→B and C→D; clicker, white noise, tone, siren; counterbalanced). Food cup responding was measured during presentation of each cue versus baseline

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as an index of conditioning; the rats responded at baseline levels to all cues (Fig. 1, A and B). A two-factor analysis of variance (ANOVA) (cue × treatment) comparing the percentage of time spent in the food cup during each cue found no effects (F values < 1.27; P values > 0.29).

In conditioning, rats were taught that one of the preconditioned cues (B) predicted reward. As a control, the other preconditioned cue (D) was presented without reward. Rats learned to discriminate between the rewarded (B) and nonrewarded (D) cue and to increase responding across sessions during the former more than the latter (Fig. 1, C and D). A three-factor AVOVA (cue × treatment × session) revealed significant main effects of cue ($F_{(1,33)}$ = 170.5, P < 0.0001) and session ($F_{(5,165)}$ = 54.75, P < 0.0001) and a significant cue × session interaction ($F_{(5,165)}$ = 64.6, P < 0.0001) but no significant main effect nor any interactions with treatment (F values <1.49, P values > 0.19).

In the probe test, we assessed responding to the preconditioned cues (A and C) after infusions of either saline or a γ-aminobutyric acid agonist cocktail containing baclofen and muscimol. Rats received three presentations of B and D, reinforced as in prior training, followed by six unrewarded presentations of A and C, in a counterbalanced design. Both control and OFCi rats exhibited robust responding to the reward-paired cue (B) (Fig. 1, E and F) and not to the cue that was presented without reward (D). An analysis restricted to the first presentation of each cue, before any reward delivery, revealed a significant main effect of cue ($F_{(1,33)}$ = 53.21, P < 0.0001) and no significant effect or interaction with treatment (F values < 1.9, P values > 0.17). However, only controls showed elevated responding to the preconditioned cue (A) that had been paired with the reward-paired cue (B) (Fig. 1E). Controls responded significantly more to this cue than to the preconditioned cue (C), which signals the nonrewarded cue (D), whereas OFCi rats responded to both preconditioned cues similarly and at a level comparable to the responding shown to the cue signaling nonreward (D) (Fig. 1F). A two-factor ANOVA (cue × treatment) indicated a significant main effect of cue ($F_{(1,33)}$ = 14.7, P < 0.001) and a significant interaction between cue and treatment ($F_{(1,33)}$ = 7.33, P < 0.01). Both groups responded significantly more to B than D, and controls responded significantly more to A than to either C or D (Bonferroni post hoc correction; P values < 0.05), whereas OFCi rats responded similarly to these three cues (P values > 0.05).

These results show that the OFC is required when behavior must be based on inferred, but not cached, value. However, they do not address how OFC is involved in learning. To test this question, we used blocking (*20*). In blocking, a subject is taught that a cue predicts reward (e.g., tone predicts food); later, that same cue is presented together with a new cue (e.g., light-tone), still followed by reward. If this is done, the subject will subsequently show little conditioned responding to the new cue (e.g., the light in our example). The ability of the original cue to predict the reward is said to block learning. The OFC is not required for this type of blocking (*17*, *21*), which indicates that the OFC is not necessary for modulating learning based on cached value, but this does not address whether the OFC is necessary for blocking on the basis of inferred value. If the OFC performs the same function during learning, then inactivating the OFC during blocking with the preconditioned cue should result in unblocking.

To test this, we trained a subset of rats from the experiment described above in an inferred value blocking task (Fig. 2) (see supplementary materials). Rats underwent 2 days of training in which the preconditioned auditory cues (A and C) were presented with novel light cues (X and Y; house light, flashing cue light; counterbalanced). Both pairs of cues were reinforced with the same reward previously paired with B (AX→sucrose; CY→sucrose). Before each session, rats received infusions of saline or the baclofen-muscimol cocktail. Both groups showed a significant increase in responding, and there was no overall difference between the two groups (Fig. 2A). A three-factor ANOVA (treatment × cue × session) demonstrated a significant effect of session ($F_{(1,19)}$ = 16.53, P < 0.001), but there was no significant main effect nor any interactions with treatment (F values < 1.44, P values > 0.24).

One day after blocking, these rats were presented with several AX and CY reminder trials, followed by unreinforced trials in which cues X and Y were presented. Controls exhibited significantly higher conditioned responding to the control cue (Y) than to the blocked cue (X). Indeed, responding to the blocked cue was no greater than baseline (Fig. 2B) ($t_{(1,11)}$ = 0.67, P = 0.52). By contrast, OFCi rats showed increased responding to both cues, consistent with an inability to use inferred value to block learning (Fig. 2B). A two-factor ANOVA (treatment × cue) revealed a significant interaction between cue and treatment ($F_{(1,19)}$ = 7.70, P = 0.012), and controls responded significantly more

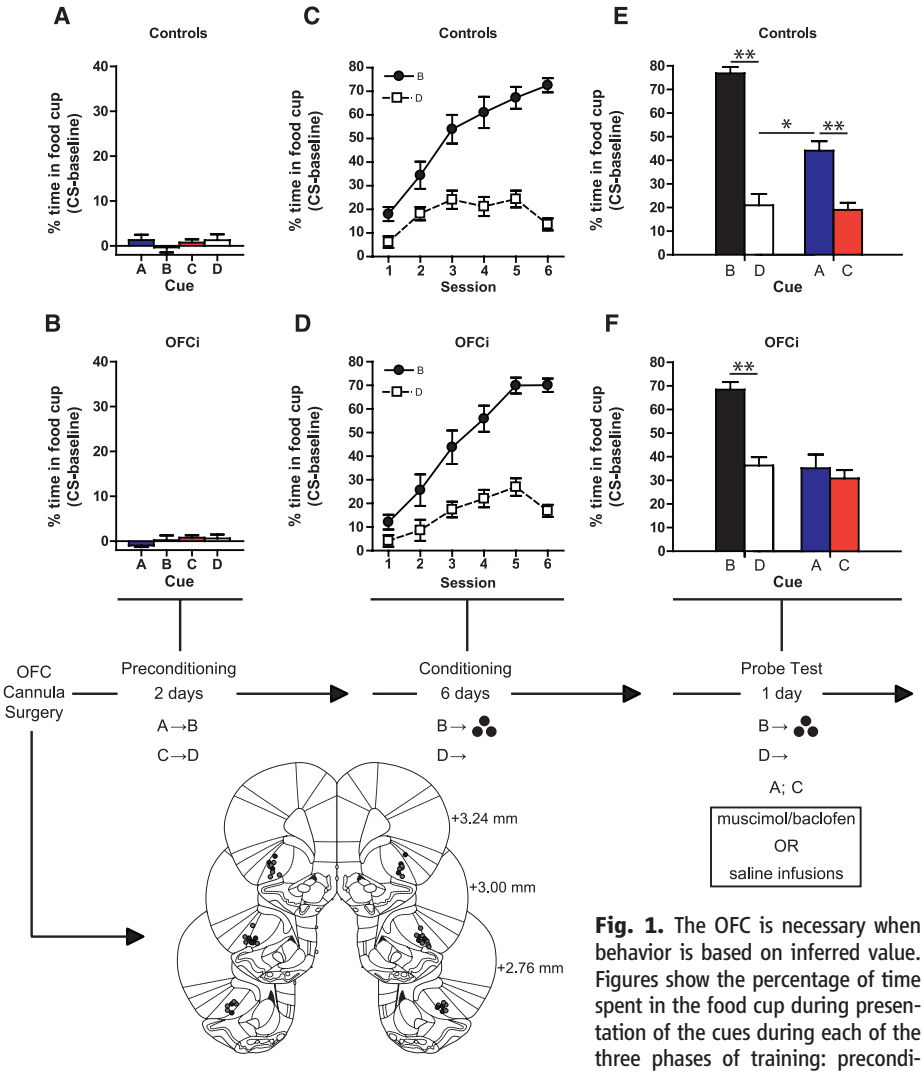

Fig. 1. The OFC is necessary when behavior is based on inferred value. Figures show the percentage of time spent in the food cup during presentation of the cues during each of the three phases of training: preconditioning (**A** and **B**), conditioning (**C** and **D**), and the probe test (**E** and **F**). OFC was inactivated only during the probe test. Cannulae positions are shown below; vehicle (black circles), OFCi (gray circles). *P < 0.05, **P < 0.01 or better. Error bars show SEM.

to Y than to X (Bonferroni post hoc correction; $P < 0.05$), whereas OFCi rats responded similarly to these two cues ($P > 0.05$).

These findings demonstrate that the OFC is involved in value-based behavior when the value must be inferred from an associative model of the task but not when the same behavior can be based on a value cached or stored in cues during past experience. This is consistent with previous results implicating the OFC in changes in conditioned responding after reinforcer devaluation (*7*, *8*, *10*, *13*, *22*, *23*). Our results confirm that OFC is required for knowledge of the associative structure at the time of the decision, rather than the results owing to some idiosyncratic involvement in taste perception, reward learning per se, or devaluation. This is because, in our task, we did not alter the reward in any way. By inactivating only at the time of the probe test, we show clearly that the OFC is required for using the previously acquired associative structure. Thus, the structure may be stored elsewhere, but it cannot be applied to guide behavior effectively without the OFC. By including an explicit control for cached value, we show that this deficit is specific for inferred value at the time of decision-making. These data are also consistent with several functional magnetic resonance imaging studies showing that neural activity in OFC may be particularly well-tuned to reflect model-based information at the time of decision-making (*13*, *24*). In this regard, it is notable that this same function was also required for modulating learning, because the preconditioned cue also failed to function as a blocker after OFC inactivation. This suggests that the OFC plays a general role in signaling inferred value, which might be used by other brain regions for a variety of purposes, rather than having a special role in the service of decision-making.

It is remarkable that the inferred value signal evoked by this cue resulted in blocking. Blocking normally uses a cue that has been paired directly with reward. Theoretical accounts focus on the fact that the value of the expected reward is already fully predicted, and therefore, there is no prediction error to drive learning (*25*–*27*). However, these accounts do not specify the source of this value, and generally, it is assumed to be a sort of cached or general value. In fact, temporal-difference reinforcement learning is specific on this point (*3*). Our experiment shows that inferred value can also modulate learning by serving as a blocking cue, which allows learning to be modulated, not only by experienced information, but also by inferred knowledge.

These results also contradict the argument that the OFC is specifically tasked with calculating value in a common currency, devoid of identifying information about identity and source, because the OFC was necessary for value-based behavior only when calculation of that value required a model-based representation of the task. Indeed, the OFC is necessary for behavior and learning when only the identity of the reward is at issue (*17*, *28*), which suggests that the OFC functions as part of a circuit that maintains and uses the states and transition functions that make up model-based control systems, rather than as an area that simply calculates general or common value. Indeed, none of these results require that value be calculated within OFC at all. Although radical, such speculation is in line with evidence that other prefrontal regions do as well, or better, than OFC in representing general outcome value (*29*). Moreover, whereas activity in some OFC neurons correlates with economic value, representations are usually much more specific to elements of task structure (*29*, *30*). The OFC may only be necessary for economic decision-making insofar as the value required reflects inferences or judgments analogous to what we have tested here. Data implicating the OFC in the expression of transitive inference (*11*) or willingness to pay (*14*) may reflect such a function, because, in each setting, the revealed preferences are expressed after little or no experience with the imagined outcomes. Limited experience, a defining feature of economic decision-making (*5*), would minimize the contribution of cached values and so bias subjects to rely on model-based information for the values underlying their choices.

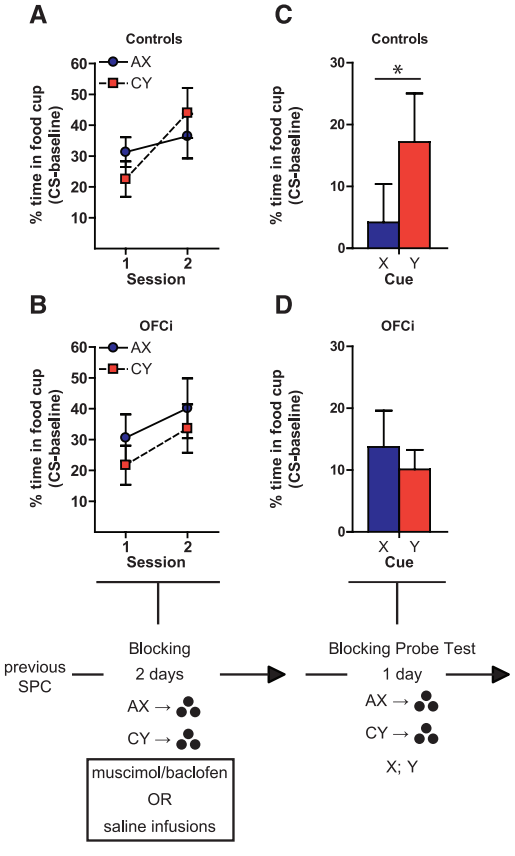

Fig. 2. The OFC is necessary when learning is based on inferred value. Figures show the percentage of time spent in the food cup during presentation of the cues during blocking (**A** and **B**) and the subsequent probe test (**C** and **D**). OFC was inactivated during blocking. *$P < 0.05$, **$P < 0.01$ or better. Error bars show SEM.

References and Notes

1. N. D. Daw, Y. Niv, P. Dayan, *Nat. Neurosci.* **8**, 1704 (2005).
2. R. N. Cardinal, J. A. Parkinson, J. Hall, B. J. Everitt, *Neurosci. Biobehav. Rev.* **26**, 321 (2002).
3. B. W. Balleine, N. D. Daw, J. P. O'Doherty, in *Neuroeconomics: Decision Making and the Brain*, P. W. Glimcher, C. F. Camerer, E. Fehr, R. A. Poldrack, Eds. (Elsevier, Amsterdam, 2008), pp. 367–388.
4. P. R. Montague, G. S. Berns, *Neuron* **36**, 265 (2002).
5. C. Padoa-Schioppa, *Annu. Rev. Neurosci.* **34**, 333 (2011).
6. H. Kim, S. Shimojo, J. P. O'Doherty, *Cereb. Cortex* **21**, 769 (2011).
7. M. Gallagher, R. W. McMahan, G. Schoenbaum, *J. Neurosci.* **19**, 6610 (1999).
8. E. A. West, J. T. DesJardin, K. Gale, L. Malkova, *J. Neurosci.* **31**, 15128 (2011).
9. C. J. Machado, J. Bachevalier, *Eur. J. Neurosci.* **25**, 2885 (2007).
10. A. D. Izquierdo, R. K. Suda, E. A. Murray, *J. Neurosci.* **24**, 7540 (2004).
11. N. Camille, C. A. Griffiths, K. Vo, L. K. Fellows, J. W. Kable, *J. Neurosci.* **31**, 7527 (2011).
12. Y. K. Takahashi *et al.*, *Neuron* **62**, 269 (2009).
13. J. A. Gottfried, J. O'Doherty, R. J. Dolan, *Science* **301**, 1104 (2003).
14. H. Plassmann, J. O'Doherty, A. Rangel, *J. Neurosci.* **27**, 9984 (2007).
15. B. Jones, M. Mishkin, *Exp. Neurol.* **36**, 362 (1972).
16. J. Hornak *et al.*, *J. Cogn. Neurosci.* **16**, 463 (2004).
17. M. A. McDannald, F. Lucantonio, K. A. Burke, Y. Niv, G. Schoenbaum, *J. Neurosci.* **31**, 2700 (2011).
18. W. J. Brogden, *J. Exp. Psychol.* **25**, 323 (1939).
19. K. A. Burke, Y. K. Takahashi, J. Correll, P. L. Brown, G. Schoenbaum, *Eur. J. Neurosci.* **30**, 1941 (2009).
20. L. J. Kamin, in *Punishment and Aversive Behavior*, B. A. Campbell, R. M. Church, Eds. (Appleton-Century-Crofts, New York, 1969), pp. 242–259.
21. K. A. Burke, T. M. Franz, D. N. Miller, G. Schoenbaum, *Nature* **454**, 340 (2008).
22. C. L. Pickens, M. P. Saddoris, M. Gallagher, P. C. Holland, *Behav. Neurosci.* **119**, 317 (2005).
23. H. D. Critchley, E. T. Rolls, *J. Neurophysiol.* **75**, 1673 (1996).
24. A. N. Hampton, P. Bossaerts, J. P. O'Doherty, *J. Neurosci.* **26**, 8360 (2006).

25. J. M. Pearce, H. Kaye, G. Hall, in *Quantitative Analyses of Behavior,* M. L. Commons, R. J. Herrnstein, A. R. Wagner, Eds. (Ballinger, Cambridge, MA, 1982), vol. 3, pp. 241–255.
26. R. S. Sutton, A. G. Barto, *Reinforcement Learning: An introduction*. (MIT Press, Cambridge, MA, 1998).
27. R. A. Rescorla, A. R. Wagner, in *Classical Conditioning II: Current Research and Theory,* A. H. Black, W. F. Prokasy, Eds. (Appleton-Century-Crofts, New York, 1972), pp. 64–99.
28. S. B. Ostlund, B. W. Balleine, *J. Neurosci.* **27**, 4819 (2007).
29. S. W. Kennerley, T. E. Behrens, J. D. Wallis, *Nat. Neurosci.* **14**, 1581 (2011).
30. C. Padoa-Schioppa, J. A. Assad, *Nature* **441**, 223 (2006).

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Figs. S1 and S2
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Akt-Mediated Regulation of Autophagy and Tumorigenesis Through Beclin 1 Phosphorylation

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Aberrant signaling through the class I phosphatidylinositol 3-kinase (PI3K)–Akt axis is frequent in human cancer. Here, we show that Beclin 1, an essential autophagy and tumor suppressor protein, is a target of the protein kinase Akt. Expression of a Beclin 1 mutant resistant to Akt-mediated phosphorylation increased autophagy, reduced anchorage-independent growth, and inhibited Akt-driven tumorigenesis. Akt-mediated phosphorylation of Beclin 1 enhanced its interactions with 14-3-3 and vimentin intermediate filament proteins, and vimentin depletion increased autophagy and inhibited Akt-driven transformation. Thus, Akt-mediated phosphorylation of Beclin 1 functions in autophagy inhibition, oncogenesis, and the formation of an autophagy-inhibitory Beclin 1/14-3-3/vimentin intermediate filament complex. These findings have broad implications for understanding the role of Akt signaling and intermediate filament proteins in autophagy and cancer.

Mutations leading to activation of the serine/threonine kinase Akt are frequent in human cancer (*1*). Akt has many downstream targets involved in tumorigenesis, including mTOR (mammalian target of rapamycin) (*2*). Akt also inhibits autophagy (*3*), a lysosomal degradation pathway that removes unwanted or damaged cellular constituents and functions in tumor suppression (*4*). Akt suppression of autophagy can be mediated by activation of mTOR, which inhibits the autophagy-initiating Unc-51–like kinase 1 (ULK1) kinase complex (*4*).

We investigated whether Akt inhibits autophagy by directly regulating the core autophagy machinery independently of mTOR. Expression of constitutively active myristoylated (*5*) and tagged Akt1 (Flag-tagged myr-Akt) in HeLa cells inhibited autophagy during growth in normal medium; in response to serum and amino acid starvation (a physiological inducer of autophagy); in response to treatment with an adenosine 5′-triphosphate (ATP)–competitive inhibitor of mTOR, Torin1 (*6*); and in response to both starvation and Torin1 treatment (Fig. 1, A and B). In all conditions, cells expressing myr-Akt1 had decreased numbers of puncta upon transfection with a fusion protein of green fluorescent protein with LC3 (GFP-LC3), a fluorescent marker of autophagosomes; increased amounts of p62 (a substrate that is degraded by autophagy); and increased amounts of the cytosolic nonlipidated form of LC3 (LC3-I) and of total LC3 (*7*). Amounts of phospho-4E-BP1, a phosphorylation target of mTOR, were decreased in Torin1-treated cells, including those expressing myr-Akt1. Thus, myr-Akt1 suppresses basal autophagy, starvation-induced autophagy, and Torin1-induced autophagy, indicating that active Akt can inhibit autophagy through mTOR-independent mechanisms.

We examined whether autophagy execution proteins could be targets of Akt. We focused on Beclin 1 because of its role in autophagy and tumor suppression (*4*). Endogenous Akt coimmunoprecipitated with endogenous Beclin 1 in HeLa cells, and this interaction was weakened by starvation (Fig. 1C). In contrast, the interaction of myr-Akt1 with a Flag epitope-tagged construct of Beclin 1 was not affected by starvation (fig. S1). Kinase prediction algorithms (*8*, *9*) showed Beclin 1 to contain a motif (R-X-X-R-X-X-S295) that resembles the consensus Akt phosphoryation motif (R-X-R-X-X-S/T) (*10*) and another sequence (R-X-X-S234) that corresponds to a 14-3-3 protein binding motif (which may be generated by Akt phosphorylation) (fig. S2A) (*11*). Phospho-specific antibodies against these two candidate phosphorylation sites in Beclin 1 (S234 and S295) recognized wild-type Flag-Beclin 1 expressed in HeLa cells, and immunoreactivity was decreased with the corresponding Flag-Beclin 1 alanine substitution mutant (fig. S2B). Glutathione *S*-transferase (GST)–Akt1 phosphorylated Beclin 1 S295 but not Beclin 1 S234 in vitro (fig. S2C), and this was partially blocked by treatment with two Akt inhibitors, MK-2206 and Akt inhibitor X (Fig. 1D). Expression of active Akt1 (myr-Akt1) increased and expression of a catalytically inactive, non-phosphorylatable Akt1 mutant (K179M/T308A/S473A; DN-Akt1) decreased, respectively, phosphorylation of Flag-Beclin 1 S295 and Flag-Beclin 1 S234 in HeLa cells (fig. S2D). Expression of myr-Akt1 also led to phosphorylation of endogenous Beclin 1 S295 and endogenous Beclin 1 S234, which was not reversed by mTOR inactivation with Torin1 (Fig. 1E). Endogenous Beclin 1 S295 phosphorylation increased when starved HeLa cells were fed with normal medium (fig. S2E). Together, these studies demonstrate that Beclin 1 is phosphorylated by Akt on residue 295 (and possibly 234) in an mTOR-independent manner.

We compared the phosphorylation of Beclin 1 S295 in three paired sets of tumor cell lines with and without Akt activation (Fig. 1F). Melanoma cells with mutant phosphatase and tensin (PTEN) (WM793) had more phosphorylation of Beclin 1 S295 than did those with wild-type PTEN (451Lu) (*12*). U87-MG glioblastoma cells with high Akt activity due to inactivating mutations in PTEN showed more phosphorylation of Beclin 1 S295 than did U87-MG cells in which wild-type PTEN was reintroduced (*13*). In breast carcinoma cells, S295 phosphorylation was detected in MCF10A-DCIS cells with an activating H1047R mutation in *PIK3CA* but not in MDA-MB231 cells lacking constitutive Akt activation (*14*). Thus, in three different tumor types activation of Akt is associated with phosphorylation of Beclin 1 S295, indicating that phosphorylation of Beclin 1 S295 may be common in human tumors with activated Akt.

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Science

Orbitofrontal Cortex Supports Behavior and Learning Using Inferred But Not Cached Values

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Experience Versus Models

There is an ongoing debate over what the orbitofrontal cortex contributes to behavior, learning, and decision-making. **Jones *et al.*** (p. 953) found that the orbitofrontal cortex was important for value-based computations when value must be inferred from an associative model of the task but not when value estimates based on previous experience are sufficient. This result calls into question the assumption that this region simply signals economic value. However, it would be consistent with a concept of the orbitofrontal cortex as being important for constructing model-based representations of the world that are orthogonal to value.

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