is clearly a major driving force in the formation of the rare encounter complexes described by Tang and colleagues. Less studied, however, is the role of short-range desolvation effects — where the protein–protein interactions force solvent molecules away from the proteins — during and after collisions. It has been suggested that hydrophobicity is involved in reorientating the molecules to form the final, productive complex[5]. Computational simulations also show that desolvation energy plays a part in orientating the encounter complexes' interacting subunits around the final, specific complex state[9].

Tang *et al.*[2] describe structural features of the encounter complexes (assuming that they interact as rigid bodies), and their results are consistent with the general idea of a funnel-shaped binding-energy well that narrows as the two proteins approach one another. This implies that there are many possible routes for arriving at the final complex at the bottom of the energy well, and that these are determined by transient interactions between the partners in the encounter complexes, with the pathways converging as they get lower in energy and closer to the final complex. Indeed, rigid-body docking calculations based on optimization of the binding energy of the interacting molecules[9–11] already describe a pool of alternative encounter complexes on the way to forming the functional complex. Whether these ensembles of orientations reflect the true binding-energy landscape will depend on the accuracy of the energy description of these computer models and the efficiency of the sampling method, an area of current debate. Molecular-dynamics simulations show that some encounter complexes could be sufficiently long-lived for their side chains to acquire a variety of conformational states, some of which are similar to those in the final, functional complex[12]. But it remains to be seen how many of the minor species are true productive encounter complexes, and which are the preferred paths to the specific binding mode of the final complex.

It is now apparent that rare encounter complexes might control not only the kinetics of the assembly process, but also the way the complex is put together and hence its cooperativity. Furthermore, the population of non-specific complexes can be restricted by the order in which the different subunits are assembled. Greater understanding of the route to longer-term relationships between molecules will no doubt emerge from integrating a wide variety of experimental data with theoretically sound computer modelling[13,14] of their brief encounters. ■

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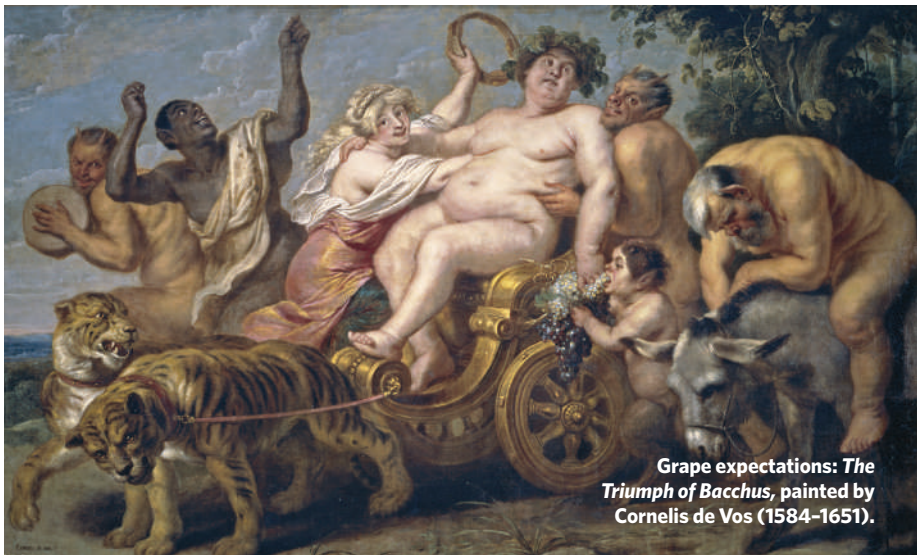
MEDICINE

Grapes versus gluttony

Matt Kaeberlein and Peter S. Rabinovitch

A compound found in red grapes called resveratrol improves the health and lifespan of mice on a high-calorie diet. This is potentially good news for overweight humans. Does it bode well for the rest of us too?



MUSEO DEL PRADO, MADRID

Grape expectations: *The Triumph of Bacchus*, painted by Cornelis de Vos (1584–1651).

Bacchus (Dionysus to the Greeks) has been long out of style, but may be granting new favours — particularly if you long to be one of those people who can seemingly eat whatever they want, whenever they want, without having to worry about the consequences. A paper by Baur *et al.*[1] on page 337 of this issue suggests that guilt-free gluttony might not be a fantasy*.

In this report, mice fed a diet akin to coconut cream pie for every meal showed a striking increase in survival and health when their chow was supplemented with resveratrol, a polyphenolic compound found in red grapes or wine. Compared with animals fed a more standard diet, mice fed the high-calorie (60% from fat) diet without resveratrol had a shorter lifespan. They also showed many of the problems that plague humans who overindulge at the dinner table, including obesity, insulin resistance and heart disease. Baur *et al.* found that although resveratrol did not prevent obesity, it did prevent obesity-associated disease, at least in one strain of mouse, and conferred a nearly normal lifespan on these mice.

With the present epidemic of obesity in some Western societies, this could be very good news. But might resveratrol improve health or lifespan beyond that achieved with a healthy diet? The link between diet and longevity has been known to gerontologists since the discovery in the 1930s that reduced caloric intake can increase the lifespan of rodents by up to 50%. Dietary restriction has since been observed to have a similar effect on longevity in many different organisms, including yeast, worms, flies, spiders and fish. Importantly, dietary restriction not only increases lifespan, but it also delays the onset of nearly all age-associated diseases. For this reason, most gerontologists believe that dietary restriction affects the intrinsic ageing process at a fundamental level. The genetic pathways influencing this phenomenon are currently

*This article and the paper concerned[1] were published online on 1 November 2006.

a hot topic of research and debate.

Like dietary restriction, resveratrol has long been known to have interesting properties. During the 1990s it was extensively studied as a potential link between improvements in a variety of health indicators and moderate consumption of red wine[2]. The antioxidant properties of resveratrol, in particular, have been suggested to account for many of its beneficial properties, including putative cardioprotective and anticancer activities, as well as providing protection against liver failure. Here it is noteworthy that Baur *et al.*[1] show that resveratrol has a profound ability to prevent liver damage associated with the high-fat diet.

Resveratrol became of particular interest to gerontologists with the report[3] that it can increase lifespan in yeast by activating particular enzymes (protein deacetylases) of the Sir2 family of proteins (sirtuins). Sirtuins are evolutionarily conserved mediators of longevity that might also play a role in lifespan extension through dietary restriction[4]. Although the results from the initial study of resveratrol in yeast remain controversial[5], subsequent work has suggested that resveratrol has modest effects on lifespan in both worms and flies[6], and a more substantial effect on lifespan in a short-lived fish[7]. Based on these findings, it has been proposed that resveratrol increases lifespan in several different organisms by a mechanism similar to dietary restriction[8].

Baur *et al.*[1] favour the view that many (perhaps all) of the beneficial properties of resveratrol are the result of increased sirtuin activity, and various studies have supported the idea that sirtuins underlie the effects attributed to resveratrol *in vivo*[8]. However, there is a surprising lack of biochemical evidence that resveratrol directly increases sirtuin-mediated deacetylation of biologically relevant substrates, and some evidence that it may not[5,9]. Resveratrol is also known to interact with numerous proteins and pathways, including mitochondrial ATP synthase and complex III, fatty-acid synthase, protein kinase C, p53, MEK1, TNF-α and NF-κB, all of which are candidates for mediating its *in vivo* effects. In particular, activation of AMP kinase by resveratrol protects against atherosclerosis and liver damage in diabetic mice[10], suggesting a likely mechanism for the observations reported by Baur and colleagues.

Given the available data, it is difficult to predict the answers to a few key questions. Will resveratrol have an effect on health and longevity in mice fed a standard diet, rather than a high-calorie diet? Will it be effective in mice with genetic backgrounds other than the inbred strain used in the current report? Will it be effective in humans? Studies addressing these questions are under way: the answers will go some way towards determining whether or not resveratrol is a bona fide dietary-restriction mimetic.

Many people will wonder whether they should start supplementing their diets with resveratrol. After all, it is generally regarded as safe, and can be purchased over the Internet with promises of improved health and longevity. Our advice is to exercise caution. The safety of resveratrol at the high doses in humans comparable to those used by Baur *et al.*[1] is unknown, especially over the course of years or even decades, when relatively modest side effects could have dramatic consequences. A logical next step would be to initiate controlled studies to find out whether resveratrol can safely reduce the ill-effects associated with diabetes or obesity in humans.

In the most optimistic assessment, a true mimetic of dietary restriction could be effective against many age-associated human diseases, including heart disease, diabetes, cancer and neurological disorders such as Alzheimer's disease. Even if resveratrol doesn't make the grade, it is not the last hope of gerontologists, or necessarily even the best. Studies of several other compounds are under way in multicentre studies of mouse ageing sponsored by the National Institute on Aging[11]. These include potent antioxidants and compounds targeting other pathways thought to influence lifespan extension through dietary restriction.

For now, we counsel patience. Just sit back and relax with a glass of red wine — which, alas, has only 0.3% of the relative resveratrol dose given to the gluttonous mice (note also that increasing the dose via wine will not be healthy). But if you must have a Big Mac, fries and apple pie, we may soon know if you should supersize that resveratrol shake. ■

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FLUID DYNAMICS

Spinning discs in the lab

Steven A. Balbus

What causes gas to be drawn in towards black holes, rather than remain in a stable orbit as planets do around the Sun? A laboratory result indicates that something more than just hydrodynamics must be at work.

On page 343 of this issue, Ji *et al.*[1] describe a meticulous experiment in which they confined water between two independently turning cylinders. Through artful experimental design, the authors were able to reduce viscous effects in the resulting 'Couette' flow to a level of one part in two million. They chose the velocities of the cylinders so that they would mimic — and so compel the confined fluid to mimic — so-called keplerian rotation, which is typical of astrophysical disks around black holes. Here, velocity is inversely proportional to the square-root of the distance from the centre of the rotation.

The result was that nothing happened at all: the fluid continued to rotate stably. But why exactly do astrophysicists and fluid dynamicists find this apparently harmless result so surprising?

In the early 1970s, astrophysicists were struggling with the exciting and controversial question of whether black holes — objects whose gravity is so great that nothing, not even light, can escape once captured — were real[2]. Only slightly earlier, a series of compact sources of X-ray radiation had been discovered. One model held that this radiation originated from gas disks surrounding black holes in binary systems of close stars[3] and galactic nuclei[4]. This gas would dissipate its energy as heat, and ultimately X-ray radiation. Its angular momentum would be transported outward, and the gas would spiral inward towards the hole. By understanding these 'accretion disks', astronomers hoped that they would, in one fell swoop, both explain the mysterious X-ray sources and prove that black holes exist.

The existence of black holes and their accretion disks is now widely accepted by both theorists and observers. But understanding the dynamics of accretion disks, in black holes and in other types of system, has turned out to be an extremely knotty problem. Why do disks accrete at all? Why does gas in motion around a massive centre not remain in a stable, planet-like orbit?

The problem is that energy dissipation and angular-momentum transport are properties of a viscous fluid, and the viscosity of the disk gas is far too small to account for the angular-momentum loss that leads to accretion. This problem might be solved if a keplerian gas