weight under normal or high-fat feeding. However, consistent with their previous studies, adult ghrelin-deficient animals are unable to prevent hypoglycemia developing in response to severe caloric restriction. Importantly these studies also highlight that replacement ghrelin dosing to physiological levels is without effect and that it is not until supraphysiological dosing that changes in food intake are observed. The complexity and extremity of the fasting protocol used may explain why it has not been supported in other animal models and from prior studies in humans.

These data highlight that not only are the peripheral ghrelin-producing cells responsive to glucose levels, but the GHSR cells, predominantly in CNS, are likely to be highly sensitive to glycemic levels to provide necessary feedback. This is also consistent with existing CNS glucose-sensing neural networks that respond to release hormones and contribute to maintaining energy requirements. Currently, NPY/AgRP neurons are generally considered to be inhibited when glucose levels rise (Chalmers et al., 2014) and activated by ghrelin, suggesting that NPY/AgRP neural function and glucose homeostasis are maintained by a balance between these two energy status signaling pathways. Whether function-specific NPY/AgRP subgroups and circuits or specific neurons with convergent signaling pathways are responsible for coordinating this behavior is currently unclear. In addition, other functions ascribed to ghrelin on the reproduction, stress, and immune system response have not been tested under these extreme environmental conditions. Given that under such extreme conditions behaviors geared toward seeking and consuming food to contribute to restoring glucose levels would be prioritized, understanding how ghrelin acts at the level of the motivation and reward pathways to control food intake also needs to be addressed.

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Rejuvenation: It's in Our Blood

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It has been known for some time that blood from young mice can positively impact aged animals, while blood from old mice has the opposite effect. Recent studies report that rejuvenating effects of young blood extend to multiple tissues and have identified GDF11 and CCL11 as factors mediating these effects.

Parabiosis is a surgical technique that involves joining the circulatory system of two animals such that they continuously exchange blood and other circulating factors. About a decade ago, this method was used to test whether the age of one animal has effects on the health of its partner through heterochronic parabiosis, where a young mouse shares its circulatory system with an old mouse. Strikingly, muscle stem cells and liver cells from the young mouse functioned less well, while the same cells from the old mouse showed molecular and functional evidence for rejuvenation (Conboy et al., 2005). Since then, similar effects have been demonstrated in other tissues including spinal cord (Ruckh et al., 2012), heart (Loffredo et al., 2013), and brain (Villeda et al., 2011). Recently, this work has been extended by the finding that injecting plasma from young mice is sufficient to enhance cognitive function and synaptic plasticity in aged mice (Villeda et al., 2014), and the identification of two molecules as key mediators of the beneficial and negative consequences from heterochronic parabiosis (Figure 1), growth differentiation factor 11 (GDF11) (Katsimpardi et al., 2014; Sinha et al., 2014), and C-C motif chemokine 11 (CCL11) (Villeda et al., 2011).

GDF11, a member of the TGF-β superfamily, declines in blood with age (Loffredo et al., 2013), and restoration of youthful levels of GDF11 are sufficient to

enhance stem cell and tissue function in heart (Loffredo et al., 2013). In contrast, blood levels of CCL11 increase with age, and this increase appears to contribute to the decline in neurogenesis and function of neural stem cells in the hippocampus (Villeda et al., 2011). Now, two new studies have found that GDF11 also has beneficial effects on skeletal muscle, the subventricular nuclei, and the hippocampus. Supplementation with GDF11 alone restored skeletal muscle strength, physical endurance, and regeneration following injury in aged mice (Sinha et al., 2014). Similarly, old mice treated with GDF11 had improved olfactory perception, brain vascularization, and neural stem cell function, which could translate into increased protection of the nervous system against age-related challenges (Katsimpardi et al., 2014). Conversely, injecting CCL11 impaired learning and memory in young mice, likely by reducing neurogenesis in the hippocampus (Villeda et al., 2011). A CCL11-neutralizing antibody abrogated the negative effects of CCL11 treatment in young mice, although it was not reported whether the CCL11-neutralizing antibody alone could improve function in aged mice.

Another recent study suggests that the fruit fly homolog of GDF11, myogliannin, is secreted by muscle to regulate aging in that organism (Demontis et al., 2014). Demontis and colleagues found that overexpression of the Mnt transcription factor specifically in muscle was sufficient to attenuate age-associated declines in climbing ability and extend lifespan. Interestingly, it also caused changes in nucleolar structure of both muscle and adipocyte cells, suggesting that muscle Mnt has both cell-autonomous and non-cell-autonomous effects. Myogliannin was identified as a secreted factor induced by Mnt that mediates these effects, and overexpression of myogliannin specifically in muscle extends lifespan. Although it remains unclear whether myogliannin functions similarly to GDF11 (myogliannin is also homologous to myostatin and appears to function in some ways similarly to myostatin), the observation that both myogliannin and GDF11 are secreted factors that modulate aging-related phenotypes in flies and mice is intriguing.

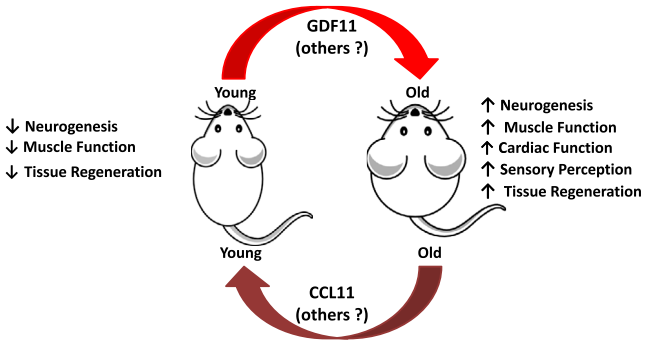

Figure 1. Opposing Effects of Heterochronic Parabiosis in Mice
Heterochronic parabiosis, in which a young mouse and an aged mouse share circulatory systems, improves the health of the aged mouse while having negative health consequences for the young mouse. GDF11 and CCL11 have recently been identified as two of the factors mediating these effects.

Recent advances in aging research have led to the identification of a small but growing number of interventions that enhance longevity and promote healthy aging. For example, dietary restriction and treatment with the mTOR inhibitor rapamycin have both been found to increase lifespan in yeast, nematodes, fruit flies, and mice. Such interventions, if they can be successfully translated to people, have the potential to dramatically impact human health by simultaneously delaying the onset and progression of multiple age-related disorders (Kaeberlein, 2013). As such, the discovery of systemic factors that appear to modulate aging, such as GDF11 and CCL11, has potentially profound therapeutic implications. If similar mechanisms occur in people, then providing elderly individuals with plasma from young individuals, or even more specifically with GDF11 or a CCL11-neutralizing antibody, may lead to improved function of multiple organ systems. Given that these approaches are essentially restoring levels of our bodies' own molecules toward a more youthful state, they may prove less prone to side effects compared to pharmacological interventions that slow aging, such as rapamycin.

On the other hand, altering the abundance of specific molecules in the context of an aged system may have unanticipated effects that are different from the young state. In this regard, it is rather surprising that it hasn't yet been reported whether longer-term heterochronic parabiosis, or more specific treatments in aged animals such as young plasma or GDF11, does in fact significantly improve healthspan or lifespan of mice. This is important both for evaluating the effects of such interventions in the context of aging animals and for understanding whether there are any substantial negative side effects associated with such treatments.

A related question is whether continuous treatment is required to fully rejuvenate tissues of aged mice, or perhaps a transient exposure to these factors might be sufficient. For example, injecting young plasma into aged mice eight times over a period of 24 days resulted in significant improvements in hippocampal-dependent learning and memory immediately following treatment (Villeda et al., 2014), but it is unclear whether these benefits persist or are rapidly lost once treatment is stopped. Finally, it remains to be ascertained whether these systemic factors act within well-known aging pathways, such as mTOR and growth hormone/insulin-IGF-1 signaling, or if they are effectors of novel aging pathways. Indeed, the factors regulating the expression of GDF11 and CCL11, the tissues involved in their production, their mechanism(s) of action, and why their expression changes during aging remain to be determined.

These discoveries set the stage for interesting times, as many remaining questions begin to be answered and the translational potential is explored. It seems likely that GDF11 and CCL11 are only the first two in a series of circulating molecules that will be found to influence aging of different tissues. Whether these are the most important or most potent molecules remains to be seen. Future studies in this area will likely bring forth new and exciting knowledge about the dynamics of aging and novel approaches to regenerative medicine.

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Too Little mTORC1 Activity Injures the Liver

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Obesity promotes chronic activation of mTORC1 and is a known risk factor for hepatic injury, inflammation, and carcinogenesis. In this issue, Umemura et al. (2014) demonstrate that a persistent reduction in hepatic mTORC1 activity also promotes cell damage and inflammation and sensitizes the liver to cancer development.

> Perhaps too much of everything is as bad as too little.—Edna Ferber

This quotation from the 20th century American novelist applies to so many facets of human life, that most would consider the statement more aphoristic than enlightening. From a health perspective, there is no better supportive example of this axiom than the human diet, which, in different parts of the world, aptly illustrates the devastating consequences of undernutrition (too little) or excessive food intake (too much). In developed countries, too much caloric intake coupled with too little physical activity have fueled an epidemic of obesity that threatens to overburden the healthcare system with sundry, life-threatening maladies. One of the many unfortunate sequelae of the obesity epidemic is an increasing incidence of hepatocellular carcinoma (HCC), an aggressive disease with limited treatment options (Caldwell et al., 2004). Environmental factors, such as persistent hepatitis B or C infection, are etiologically linked to the majority of cases of HCC; however, chronic overnutrition is a rapidly emerging etiologic factor for this disease (Sanyal et al., 2010). Preclinical and clinical studies indicate that the nutrient-stimulated, rapamycin-sensitive mammalian target of rapamycin complex 1 (mTORC1) is both activated and functionally important for HCC development and progression (Bhat et al., 2013). Strong evidence that HCC is characterized by "too much" mTORC1 activity prompted clinical trials with rapamycin analogs (rapalogs), which unfortunately yielded disappointing results. An ironic twist to this negative outcome is that the clinical use of rapalogs to reduce mTORC1 activity in HCC is associated with increased liver injury, which could, in principle, promote disease progression (Yamanaka et al., 2013).

A article in this issue of *Cell Metabolism* explores the impact of reduced hepatic mTORC1 activity on diet- and carcinogen-induced inflammation and HCC development in mice (Umemura et al., 2014). In the initial studies, mice were fed a high-fat diet (HFD), and mTORC1 activity was systemically reduced by treatment of the animals with rapamycin. Consistent with expectations, rapamycin treatment markedly suppressed the accumulation of free fatty acids in the livers of these mice; however, chronic drug treatment elicited additional alterations in liver physiology that were consistent with an enhanced inflammatory response and hepatocellular damage. A noteworthy effect of this drug was a dramatic increase in serum interleukin-6 (IL-6), the source of which was presumably, but not definitively, proven to be the liver. Rapamycin is a well-established inducer of autophagy, and Umemura et al. (2014) noted that the livers of drug-treated mice displayed changes in autophagy biomarkers indicative of increased autophagic flux in liver cells. Interestingly, previous studies showed that autophagy is required for the production of IL-6 during oncogene-induced stress (Narita et al., 2011). Future studies should examine whether autophagy supports IL-6 production and the consequent activation of STAT3 in the rapamycin-treated liver. Nonetheless, the contributions of autophagy to HCC development seem very complex, with tumor promotion or suppression as outcomes, depending on the evolutionary stage of the HCC (Cui et al., 2013).

In subsequent studies, Umemura et al. (2014) employed an elegant genetic approach to examine whether the effects of reduced mTORC1 activity on hepatocyte physiology were truly cell autonomous. The authors generated mice bearing a hepatocyte-specific knockout of the *Raptor* gene, which is specifically associated with and required for mTORC1 function. The $Raptor^{\Delta hep}$ mice were