leave non-placental mammals (marsupials and monotremes) and other vertebrates which must also cope with their microbiomes? Is the relationship between the eutherian immune system and microbiome a uniquely privileged one, or are other forces at work here? Comparative studies between eutheria and their non-placental vertebrate relatives should provide answers.

Kinder et al. establish a mechanism of inheritance that operates differently from traditional Mendelian genetics and requires the participation of adaptive immunity. And although this clearly impacts reproductive fitness to female offspring, what of male offspring? Why does the maternal microchimerism not result in strong NIMA-specific pTreg responses in males? Is this due to the tissue-specific nature of the generation and/or maintenance of these NIMA responses? Or, is it a more universal phenomenon underscoring a difference between male and female physiology that could shed light on the sex differences observed in autoimmune disease? Either way, these findings add a potential evolutionary constraint to diversification of the major histocompatibility complex (MHC) in a population by enhancing reproductive fitness if non-inherited maternal MHC alleles are reintroduced back into its offsprings' gene pool. This flies in the face of conventional wisdom that argues for reproductive strategies that favor outbreeding as a means to increase MHC haplotype diversity and hybrid vigor that benefit the individual and the broader population. Might a little inbreeding also be a good thing? Maybe mother knows best.

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Barley: From Brittle to Stable Harvest

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Selection and domestication of plants with genes that prevent grains from shattering in cereals was essential for human civilization's transition to agriculture-based societies. In this issue, Pourkheirandish et al. show that domestication of barley required evolution of a molecular system distinct from other grains, such as rice and maize, and reveal that present-day cultivars derive from two ancient domestication centers.

The domestication and cultivation of wild plants was a hallmark in the development of human civilization and the catalyzer of the transition from ancient hunter and gatherer cultures to early farming communities. Around 10,000 BC, during the Neolithic Revolution, domestication of cereals like wheat, barley, rice, and maize occurred during a relatively short time span and at different geographical sites. The breeding selections were directed toward diverse traits, e.g., plant architecture, taste, or the number and size of seeds. An important breeding target was the modification of the seed dispersal system for which our ancestors selected in all cereal species very early during domestication. For effective reproduction, wild progenitors of our major cereal crops shed their seeds upon maturation. To enable efficient harvesting and to avoid yield losses caused by seed shattering, today's cereal cultivars are derived from progenitors in which this dispersal system is modified and grains are retained at the inflorescence rather than being dispersed. Grasses exhibit a remarkable biological variability in the location of the abscission zone and the diaspore, the dispersal unit, ranging from

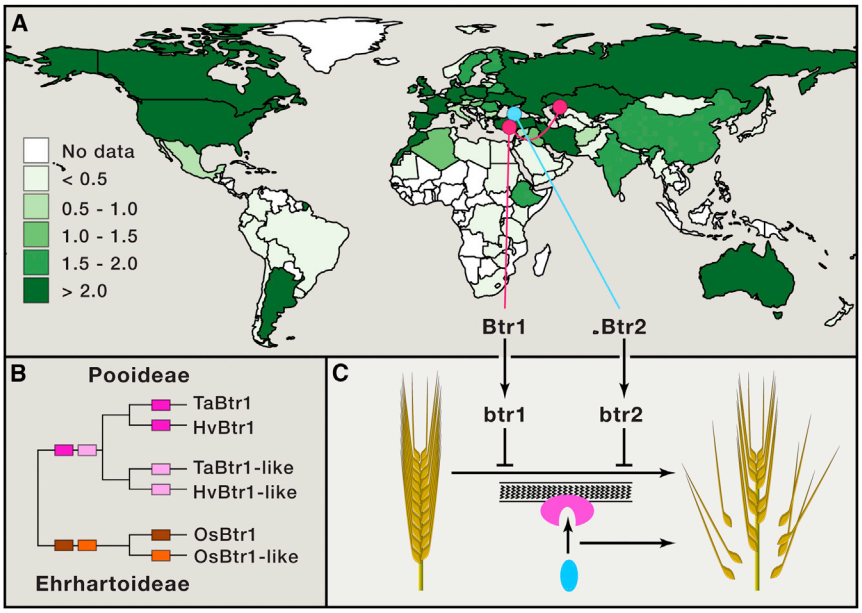

Figure 1. The Barley Domestication Genes Btr1 and Btr2

Barley ranks fourth among cereals in terms of worldwide production quantity.

(A) Color-coded production of barley in million metric tons per country in the year 2013 (source FAOSTAT). A key event in barley domestication was the selection of the seed dispersal system to prevent yield losses. In this issue of *Cell*, Pourkheirandish et al. confine two ancestral domestication centers: for the *btr1* genotype in the Southern Levant and Central Asia (pink circle) and the second in the Northern Levant (light blue circle), corresponding to the *btr2* genotype.

(B) Phylogenetic analysis revealed two independent duplications of the Btr1 (and Btr2, not shown) gene in the *Ehrhartoideae* and *Pooideae* lineages, indicating a specific function of the Btr genes in the *Pooideae*, including barley and wheat. (Ta, Triticum aestivum, wheat; Hv, Hordeum vulgare, barley; Os, Oryza sativa, rice.)

(C) In wild barley, the Btr1 and Btr2 genes control the disarticulation of mature spikelets. They are hypothesized to act as receptor and ligand, respectively. All modern barley cultivars are derived from recessive mutations in either btr1 or btr2 that reduce seed shattering.

the entire inflorescence to a single spikelet or grain (Doust et al., 2014). Hence, an open question in the study of this key domestication trait is whether there is a common seed shattering pathway shared by all grasses or whether novel, species-specific genes and mechanisms have evolved and selected. In this issue, Pourkheirandish et al. report that evolution of the barley dispersal system followed a different molecular path from other grains and provide insight on when and where acquisition of this molecular mechanism may have taken place in human history.

Numerous quantitative trait locus (QTL) studies revealed a number of major domestication loci in various grass clades that associate with the control of seed disarticulation. These include the economically highly important tribes *Andropogoneae* (maize, sorghum), *Ehrhartoideae* (Asian and African rice), and the *Triticeae* (wheat, barley) (Doust et al., 2014; Li et al., 2006; Lin et al., 2012; Sakuma et al., 2011; Simons et al., 2006). Notably, several QTLs in sorghum, maize, and rice overlapped in their syntenic regions, suggesting that the same orthologous genes have been selected by early farmers and control the seed dispersal in these species by a common pathway (Doust et al., 2014; Lin et al., 2012). However, detailed mapping studies also revealed pronounced differences between, for example, the *Pooideae* and other cereals, indicating the involvement of specific loci. Two rice genes affecting panicle shattering, qSH1 and sh4, have been domesticated for their non-shattering phenotype both in African and Asian rice independently by ancient farmers but seem to have no orthologs in the *Triticeae* (Doust et al., 2014; Wang et al., 2014). Conversely, two loci conferring a brittle rachis, Btr1/2 and Br1/2 in barley and emmer wheat, respectively, have no mapping counterpart in other cereals (Doust et al., 2014; Sakuma et al., 2011).

Now, in this issue of *Cell*, Pourkheirandish et al. report the molecular cloning and characterization of two genes—non-brittle rachis 1 and 2 (Btr1 and Btr2, respectively)—that cause identical phenotypes and affect grain dispersal in barley (Pourkheirandish et al., 2015). In *Hordeum vulgare ssp. spontaneum*, the wild barley ancestor, mature spikelets are released by disruption at specific abscission zones located at the individual nodes of the rachis. Histological analysis shows an expansion of five to six cell layers in wild-type barley, resulting in thin primary and secondary cell walls. Two recessive alleles, *btr1* and *btr2*, do not develop such expanded cells at the rachis nodes and convert the brittle rachis into a non-brittle rachis, thereby preventing the early disarticulation of mature grains. The tightly linked loci were fine-mapped and cloned. They encode novel proteins with close homologs in grass tribes, including the *Ehrhartoideae* (rice) and *Andropogoneae* (sorghum, maize). Genome-wide searches identified intra-genomic local duplications of both Btr1 and Btr2 in wheat, barley, and rice. Interestingly, this duplication has occurred independently in the *Ehrhartoideae* and *Pooideae* lineages, suggesting that rice Btr1/2 are not orthologs but, rather, homologs to their wheat and barley counterparts and hence may have a different function (Figure 1B). In addition, the paralogous copies Btr1-like and Btr2-like failed to complement the mutant *btr1* and *btr2* phenotypes, respectively, and thus have distinct roles. Based on predicted localization and molecular signatures found for Btr1 and Btr2 and the identical mutant phenotypes, the authors hypothesize that Btr1 may act as a receptor for the ligand Btr2 (Figure 1C).

All modern barley cultivars are either homozygous for the *btr1* or the *btr2* allele, and no double homozygous line is found: most European/West Asian varieties are of genotype btr1Btr2, while most East Asian barleys have the Btr1btr2 genotypes. To unveil the domestication history of barley, the authors re-sequenced and analyzed geographical distributions along with genotype and phenotype relations in F1 hybdrids that have been generated by

crosses of a worldwide collection of barley cultivars and landraces with a *btr1* or *btr2* tester (Pourkheirandish et al., 2015). In both cases, the 1bp and 11bp deletions of the *btr1* and *btr2* alleles, respectively, were demonstrated to be monophyletic. In their survey for shared haplotypes, the immediate wild ancestors of *btr1* were confined to varieties of Jordan, Israel, and Turkmenistan, Uzbekistan, and Afghanistan, suggesting the Southern Levant and Central Asia as domestication centers. The analysis reveals a second independent domestication center for *btr2*-type cultivars in the Northern Levant comprising North Syria and the southeast of Turkey. From these two confined areas, barley cultivation spread and rendered the grain that is the world's fourth most important crop today, globally grown as mainly animal feed and brewing malt (Figure 1A).

The cloning and physiological characterization of the barley Btr genes provide novel insights into the evolution and domestication of different clade- and species-specific mechanisms of seed dispersal systems in grasses. Different genes and molecular mechanisms for seed shattering in rice and barley, as well as the absence of rice seed shattering QTLs in regions syntenic to the barley Btr genes, are apparent. This suggests a novel—or at least modified—pathway in the *Pooideae*. However, additional functional analysis of these loci in rice and other cereals is required to test this hypothesis. This will help to understand the fascinating evolution and parallel domestication of the seed dispersal system and will be instructive about the molecular basis that laid the foundation for the cultural development of modern societies.

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You Down With ETC? Yeah, You Know D!

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Although the mitochondrial electron transport chain (ETC) is best known for its role in ATP synthesis, two studies, Sullivan et al. and Birsoy et al., conclude that its only essential function in proliferating cells is making aspartate (D).

Within the inner mitochondrial membrane, 73 individual subunits translated from two distinct genomes are assembled into the four multimeric protein complexes that comprise the electron transport chain (ETC). This machine of unrivaled complexity and elegance plays a critical role in enabling the mitochondria to synthesize ~34 molecules of ATP from the oxidization of one molecule of glucose. Therefore, it may be surprising that two papers published in this issue of *Cell* (Sullivan et al., 2015; Birsoy et al., 2015) provide compelling evidence that in proliferating cells the only essential function of these massive complexes is the biosynthesis of a single, seemingly insignificant, amino acid—aspartate, known to most scientists only as Asp or D.

The story starts with an observation made some 25 years ago by King and Attardi (1989), who demonstrated that cells lacking mtDNA failed to proliferate as a result of ETC dysfunction, but that this could be rescued by adding supraphysiological concentrations of pyruvate to the media. While many of us have encountered this fact when culturing mammalian cells, the etiology of this phenomenon is not at all obvious. Why would pyruvate rescue the growth of cells lacking functional mtDNA, which are highly glycolytic and generate large amounts of pyruvate inherently (which is typically converted to lactate and excreted)? Sullivan et al. and Birsoy et al. clearly show that ETC dysfunction impairs the redox balance of the cell and that the operative role of pyruvate is to restore redox homeostasis by serving as an electron acceptor.

The ETC enables the passage of an electron from NADH (leaving NAD^+) to O_2 (resulting in H_2O). As a result, loss of ETC function not only blocks mitochondrial ATP synthesis, it also causes a decrease in the NAD^+ pool and NAD^+/NADH ratio. Based on this rationale, Sullivan et al. hypothesize that the pro-proliferative capability of pyruvate may be to accept electrons and regenerate NAD^+