Wolf + Starchy Food = Dog

Humans and dogs may have forged their best friendship over their shared ability to digest starchy foods, says a study recently published in *Nature* (published online 23 January 2013; doi10.1038/nature11837). It is widely agreed among canine-domestication experts that all dogs, regardless of breed, are the descendants of wolves, but when, where and how the two animals diverged along the evolutionary path is still unclear.

Fossilized dog remains dating from 33,000 years ago were recently discovered in a Siberian cave, and 12,000-year-old fossils of humans and dogs buried together have been found in Israel. Genetic analysis of modern dogs indicate that domestication started at least 10,000 years ago; however, distorting this timeline is the widely held belief that domestication arose from multiple source populations and that back-breeding with wild wolves commonly occurred.

Attempting to clear up the blurry origins of man's best friend, Uppsala University

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(Sweden) geneticist Kerstin Lindblad-Toh and her team designed a study to identify which genetic variants between wolves and dogs underlie the behavioral and morphological changes that led to domestication. They analyzed the genomes of 12 wolves and 60 individual domestic dogs (from 14 breeds), looking for differences in their genetic code and ultimately identified 36 regions that set dogs apart.

Nineteen of those regions contained genes central in brain function which could

explain why dogs are friendlier to humans than wolves are. But most interesting to Lindblad-Toh and her colleagues were the 10 genes they identified that play a key role in the dog's ability to break down starches and metabolize fat. The researchers think it is possible that these genetic variants may have been selected to aid adaptation from a primarily carnivorous diet to one more composed of starchy foods.

Furthermore, the Uppsala University team believes that the appearance of these genetic variations coincides with the dawn of the agricultural revolution, proposing that the driving force behind the domestication process was the scavenging from waste dumps of early human settlement. This suggested a case of parallel evolution, whereby the benefits of tolerating a diet increasingly rich in starch caused similar adaptive responses in humans and dogs.

Thomas Rowley

STIMULATING A NEW TREATMENT FOR SEPSIS

Sepsis is a complex, serious condition that affects more than 400,000 people in the US each year. It begins when a bacterial infection produces endotoxins called lipopolysaccharides that bind to endothelial cells lining the insides of blood vessels. This binding causes oxidative stress and an influx of calcium, activating the endothelial cells and increasing the expression of pro-inflammatory molecules. This activation, in turn, kicks off a chain of cellular events in which the normal immune reaction is overstimulated and the immune system attacks the body's own organs and tissues, culminating in unchecked inflammation. Lung inflammation, a common feature of sepsis, can lead to edema (fluid in the lungs) and possibly death. Sepsis is currently treated with antibiotic therapy, but its efficacy is limited.

"While antibiotics are improving, more than 25 percent of those who develop sepsis will die from it. This is partly because we don't fully understand the mechanisms behind the widespread inflammation it causes," says Muniswamy Madesh, a biochemist at Temple University (Philadelphia, PA). Madesh and his collaborators recently reported that blocking the activity of a protein called STIM1 in endothelial cells can halt the sepsis cascade and protect against lung damage. "We've provided evidence indicating that without STIM1 driving calcium signaling, the exacerbation of inflammation can't occur," Madesh explains. The study results provide new insight into the cellular processes underlying sepsis and may lead to new treatment strategies.

STIM1 is involved in calcium sensing and signaling, which is important in cellular communication, including the sequence of events that takes place in sepsis. To learn more about its role in sepsis, Madesh's group knocked out expression of STIM1 in endothelial cells of mice and compared them with wild-type mice after exposure to lipopolysaccharides. Calcium transport was disrupted in STIM1-deficient mice, interrupting the sepsis cascade and preventing lung injury (*J. Clin. Invest.* doi:10.1172/JCI65647; published online 25 January 2013). Blocking STIM1-driven calcium signaling using a small molecule called BTP2 also prevented lung damage. "Eliminating STIM1 or blocking the channel both reduced the permeability of the lungs' blood vessels and lessened lung edema. We can block this pathway using both genetic and pharmacological approaches, and both protected against endotoxin-induced lung inflammation," Madesh summarized.

His team's future work includes developing new molecules that target STIM1 activation as potential therapeutic strategies. In addition to sepsis, such treatments could be useful in other diseases and conditions that involve STIM-driven calcium signaling, such as stroke.

Monica Harrington