Jeff's View

The severed chains

What makes us humans special? I had always thought that our ancestors picked up some genes that let them say good bye to their ape-like relatives. Maybe so, but genome-gazers have not yet found these magic genes. Perhaps I have posed the question the wrong way around. Perhaps we became what we are because our ancestors got rid of genes that kept them from being human. Perhaps these ancestors were smart enough to know that sometimes one must lose genes to gain function.

Human behavior is complex and often unpredictable. At least mine is, if you believe my former students and postdocs. I never took their complaints personally. Why should I? It is my receptors and signal processing circuits that take care of the chemical communications within me, tell me what is going on outside, help me think about it, and then shape my moods and decisions.

Most of these receptors sit in the membranes around my cells, meandering back and forth across the membrane seven times. They are my *seven-transmembrane receptors*. How many different types do I have? I do not know the exact number, because their amino acid sequences are so diverse that there is no safe way to pinpoint all their genes in my genome. Some of them form subgroups with similar sequences, but overall they share only their seven transmembrane spans and their role as antennae for signals from the cells' outside. I have at least a thousand different "seven-transmembrane" receptors, but there could be hundreds more. Between 3% and 4% of my genes are set aside for them – by far the largest gene family in my genome. Three to 4% may seem extravagant, but most families spend about the same fraction of their budget on communication.

All my seven-transmembrane receptors work by the same basic mechanism. They bind the incoming signal in a pocket within their hydrophobic transmembrane spans and then attract an intracellular "G-protein" that has three different polypeptide chains and a molecule of GDP. Next, this G-protein exchanges GDP for GTP and activates an enzyme that converts AMP to cyclic AMP. Cyclic AMP can either open or close an ion gate in the cell membrane, changing the membrane's electric potential, or activate or inhibit other enzymes. Although there are many variations to this downstream signal transduction cascade, all of them amplify the original signal by as much as a million-fold or more. And amplification can continue in the target organs, such as the muscles – just think of a six-ton elephant scared into a run by a few photons hitting its retina.

My seven-transmembrane receptors are tuned to many different signals. Some are tuned to proteins, peptides or small organic molecules in my body fluids – they are hormone receptors. Four of them – the different rhodopsins of my retina – are tuned to light and color. But the vast majority of these receptors keep track of smells and tastes.

I have about 900 genes for different smell receptors, but more than 60% of these genes are defective in some way – they are pseudogenes. That leaves me with about 400 smell receptors – still not too bad. But a mouse has three times as many and a rat even more. Most of these receptors sit in the smell-sensitive nerve cells of my nose and register the hundreds of thousands, perhaps even millions of different chemicals in the air I breathe. Each smell-sensitive nerve cell harbors only a single type of smell receptor and feeds its signal to the *olfactory bulb*, which compares the signal with those from the other smell-sensitive nerve cells and then sends the processed information on to my forebrain. That's why I can detect subtle shadings of fragrances, such as the difference between a Bordeaux and a Burgundy. Most of the time, anyway. My sense of smell is important for me, but I could manage without it because I can also see and hear. This may explain why we humans accumulated defective smell genes much faster during evolution than all other known animals. Worms such as *Caenorhabditis elegans* badly need their sense of smell, because they are deaf and blind. *C. elegans* reserves about 5% of its genes for smell receptors. That is a heavy investment: the worm needs almost as many house-keeping genes as I do, yet has a genome 30 times smaller than mine.

I cannot only *smell* chemicals with my nose, but also *taste* them through my tongue and palate. I can distinguish five tastes: bitter, sweet, *umami* (the taste of monosodium glutamate), sour, and salty. I sense the first three of these tastes through *seven-transmembrane taste receptors*. I do not know how many of these I have; chemosensory heavyweights such as mice have about 40 of them, so I might have ten or twenty. Even though I cannot sense any shadings of sweet, bitter or *umami*, taste enhances my sensory repertoire, allowing me to detect some ten thousand different aromas. I can not categorize them all; even professional "noses" who test perfumes, wines or spirits can define at best a few thousand of them.

But there is more. Many animals release chemicals that induce an involuntary stereotyped response in other members of the same species. These *pheromones* can travel over large distances through air or water and control social status, mate selection, aggressiveness and hormonal status. They are irresistible chemical commands that higher animals may not even consciously perceive as smells. Queen bees release a pheromone that prevents worker bees from rearing another queen. Worker bees use alarm pheromones to persuade their nest mates to sting an intruder. Female mice choose Pheromone Speak to inform interested males of their menstrual status. And the pheromone emitted by a newly hatched female moth can attract dozens or hundreds of eager males who will travel for a mile or more to pay their respect. With insects, pheromones are often the only means by which individuals of one species can find one another. Pheromones come in a huge variety of chemical structures, but many of them are aliphatic or aromatic alcohols or their esters, aldehydes, or terpenes. Most pheromones function as chemical mixtures, the exact composition of which is crucial. If one component of the mixture is missing or present in the wrong proportion, pheromone function may be lost, elicit the opposite effect, or affect the wrong species. In higher animals, pheromones may also be steroids or proteins, and trigger discrete sensory nerve cells in a sub-region of the nose, the *vomeronasal organ*. These *vomeronasal receptor cells* work with a separate family of

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seven-transmembrane receptors and distinct downstream signal transduction cascades that feed into a special processing center, the *accessory olfactory bulb*. This bulb sends the processed signals not to the brain cortex, the site of voluntary decisions, but directly to the limbic system that controls involuntary hormone secretion and behavior. A mouse has about 300 different vomeronasal receptors, most of them probably responding to pheromones.

Even we humans with our complex and malleable brains may be unwitting slaves to pheromones. Women living together for extended time periods in college dormitories or Bedouin tents generally menstruate in synchrony, because they release substances that regulate the menstrual cycle of others. These substances can be collected from the armpits and are not perceived as odors, suggesting that they are pheromones. There are also hints that glycoproteins in our sweat and urine contribute to our very personal body odor and influence our sexual attractiveness. These glycoproteins are encoded by the *MHC1* locus which, by recombining its hundred or so genes during sexual reproduction, can specify as many as 3600 million different proteins. Controlled human experiments on sexual attractiveness are difficult and touchy. They also fascinate perfume makers who flood the world-wide-web with wacko reports on pheromone-based ''irresistible perfumes''. So it is no surprise that the effects of secreted *MHC1* proteins on human behavior are still poorly documented and highly controversial. It is also open whether these proteins are typical pheromones and whether they work directly or through indirect mechanisms. But in mice they clearly determine the selection of mating partners and aggression towards other mice. Female mice prefer males whose *MHC1* proteins differ from their own, and the sketchy experiments with humans point in the same direction. Obviously, such a mechanism could help mice to maintain genetic diversity. That is fine, but how adamant is this chemical directive for me? Why had I asked that particular girl to be my dance partner for our high school's senior prom? I hate to think that it was only her *MHC1* proteins. There may well have been other chemical signals that shaped my decision at that time. Indeed, I consider it very likely that we shall uncover additional human pheromones, and that not all of them will be about attraction. There must be a deeper reason why the French and Germans, among others, refer to an unpleasant type as someone ''they cannot smell''. Does our liberal use of deodorants throw a monkey wrench into this delicately balanced communication system? There is a molecular biology of hate and love even for us humans. But there *are* moments when I would prefer to ignore it.

Human pheromones frighten me, because they are a potential threat to my humanity. If I want to find out who I am, there is no way around the question of how much I am tyrannized by pheromones. To my relief, the probable answer is ''not very much''. I lack an accessory olfactory bulb and a typical vomeronasal organ, even though I may have had vestiges of it at birth. Also, more than 95% of my putative pheromone receptor genes are non-functional pseudogenes and the few intact ones may be useless because I lack key parts of the downstream signal transduction machinery. I cannot exclude that some pheromones work through my smell receptors, but overall my pheromone–related genes are a colossal genetic junk yard littered with evolutionary debris. That is very, very good news. Here are the pieces of the chains that had kept our ancestors in chemical bondage. To become humans, we had to invent genetic wings that let us soar. But then we had to sever the chains that tied us to the ground.

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