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Applied Darwinian medicine: Artificial selection for less-harmful parasites

The short generation time of many pathogens causes serious medical problems, such as the evolution of resistance. However, this causal force can be used against pathogens, potentially inhibiting or preventing the spread of some diseases in humans.

More or less virulent strains of infectious diseases can be produced *in vitro* (e.g. [2]) and infectious agents can be engineered to depend on a cofactor such as an enzyme in order to survive. (Providing a population of pathogens large amounts of a cofactor leads to selection for strains that do not have the burden of retaining the cellular machinery for the production of that cofactor. Selection can therefore do the work that might otherwise be difficult or impossible with current alternative technology.) A virulent, cofactor-dependent strain can then be released, along with the cofactor, into natural populations, such that it outcompetes the natural strain, driving down the frequency of the natural strain, at which point the cofactor can be removed and we are left with much lower rates of any strain than prior to the intervention. In principle, such a strain could even be introduced into individual hosts along with continuous doses of the cofactor; after the cofactor-dependent strain spread at the expense of the original pathogen, the cofactor could cease to be administered, leading to the death of the cofactor-dependent strains.

Ito et al. [1] produced a genetically-altered mosquito that is incapable of passing malaria to people. However, absent a selective advantage, such mosquitoes, if released into the wild, would not necessarily become the dominant strain. But, again in principle, such a mosquito could also be selected through careful artificial selection to be able to feed on a substance wild-type mosquitoes cannot, and that substance could be provided by people in regions with high prevalence of malaria. Mosquitoes reproduce sexually: by releasing malaria-safe males and providing them with a selective advantage (e.g. keeping them especially well-fed), the anti-malarial gene could rapidly spread through the population. (To speed the process of replacing harmful mosquitos with harmless mosquitos, the provisioning substance could include a poison that especially affects non-engineered mosquitos.)

We might produce and provision new strains of mosquitoes and cockroaches that fear people and would spread at the expense of current strains, leaving us with less harmful and more controllable parasites and pests. We could then decide to live with or exterminate these relatively harmless populations. Artificial selection turned wolves into poodles. Now, combining what we know about the evolution of virulence, sexual selection, and genetic engineering, we might do the same for a wide variety of human pathogens.

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Alteration of the critical cell cycle genes might contribute to carcinogenesis by disrupting the asymmetric division of somatic stem cells

Presently it is regarded that uncontrolled proliferation is the hallmark of cancer cells. The notion generally leads some novices to take it for granted that cancer cells divide faster, or the length of the cell cycle is shorter, than normal cells. Molecular genetics shows that cell cycle progression requires the co-ordinated activation of several cyclin-dependent kinases and inactivation of cyclin-dependent kinase inhibitors [1]. Thus it was presumed that the frequently alterations of cell cycle regulators contribute to carcinogenesis by altering the length of cell cycle. However, previous substantial evidences indicated that the length of cancer cell cycle is not shorter, sometimes even longer, than that of normal cells. One example is that Dormer et al. compared cycle times of mouse epidermis and chemically induced skin carcinomas and found cycle times, respectively, of 32 and 150 h [2]. Although it may be possible that in many instances tumor cells proliferate faster than their normal counterparts, the conclusion is that the growth of a tumor is not due exclusively to an acceleration of the proliferative process but to the much more fraction of cells participating in the proliferative pool [2,3]. So Prehn argued that the essence of the cancer problem is the disturbance of ''growth ratio'', an imbalanced ratio of cell birth to cell death, not the rate or frequency of cell division [4]. This argument infers a conclusion that the nature of cancer might be the deregulation of asymmetric division rather cell cycle of somatic stem cells [4,5]. In fact, there is increasing results confirmed this suggestion [6]. However, there were many evidences indicated that the alteration of cell cycle regulators participated in carcinogenesis. For example, animals with mutated Cdk4 develop a wide spectrum of spontaneous tumors and are highly susceptible to specific carcinogenic treatments [7]. In order to reconcile this paradox, we propose that cell cycle regulators might play a critical role in regulating the asymmetric division of somatic stem cells. Indeed, recent data show that cell cycle regulator cdc2 is required for asymmetric localization of cell fate determinants and for cell fate determination [8]. Given these considerations, we propose the abnormal expression or activation of positive regulators and functional suppression of negative regulators of cell cycle might contribute to carcinogenesis by disrupting the asymmetric division of somatic stem cells.

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