In this Issue: Natural Selection in the Skin

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Selection of cells and expansion of those selected cells is a theme cutting across reports from three continents in this issue. Selection can be beneficial or deleterious to the individual organism.

Almost 150 years ago Charles Darwin, before the details of molecular genetics were known, considered natural selection, the driving mechanism for the process of evolution. Darwin considered the process at the level of individuals and species; the authors in this issue describe selection at the cellular and tissue level with an ultimate impact on the survival of the individual. These articles are considered for their basic themes, assumptions and implications.

Darwin stated that 'All Nature, as the elder Decandolle has declared with respect to plants is at War' and that 'The struggle very often falls on the egg & seed, or on the seedling, larva & young' (Stauffer, 1975, p.175). The weapons in the struggle are transmittable phenotypic variations. 'An individual therefore, which from having some slight profitable variation, was preserved or naturally selected, would in many cases, tend to transmit the new, though slight modification to its offspring' (Stauffer, 1975, p. 214). A century and a half later these ideas are so imbedded in our thinking that they are often not explicitly discussed. This discussion may be useful for heuristic purposes, including considering new therapeutic modalities.

Gao and coworkers (p. 998) produced a transgenic mouse that lacked an X-chromosome gene, *Pig-a*, which codes for a gene catalyzing the initial step of adding the GPI (glycerol phosphatidylinositol)-anchor to a large number of epidermal proteins. Many proteins require this anchor and deficiency of the protein is lethal to the mouse embryo. An epidermal specific *Pig-a* epidermal specific knockout mouse was produced using cre-lox selection methodology, and the Keratin 5 promoter was used for tissue localization in epidermal basal cells. Males should lack *Pig-a* in all of their epidermal cells.

Male mice with this mutant were wrinkled, more scaly than normal and had a tightly packed and thickened stratum corneum (*PNAS* 1997;94:7400). Two-thirds of the affected mice died within 3 d. It was thought that the surviving mice did not have enough selective pressure through the Cre/lox system itself so that in some animals there was not complete disruption of the *Pig-a* gene.

In the current JID paper, female mice with the *Pig-a* mutation were studied. Based on the Lyon hypothesis of random X chromosome inactivation one might expect some expression of the mutant allele in female epidermis. Affected female mouse skin was slightly wrinkled and drier compared with litter mates and scales began by 4–5 d, were maximum at 7–10 d and completely disappeared by 4 wk. To determine the fate of GPI deficient keratinocytes, GPI anchored enhanced green fluorescence protein (EGFP) was used as a probe in the triple transgenic animals. Columns of fluorescent and nonfluorescent keratinocytes were seen shortly after birth and this mosaic pattern was associated with increased transepidermal water loss. The upper epidermis was replaced by EGFP positive cells beginning at 36 h. Thus, potentially related to the selective pressure of increased water loss occurring after birth, this mosaic epidermis was able to respond by increasing the mutant cells in the uppermost epidermis, although cells in the spinous and basal layers were not replaced. With this mutant, rather than a wholesale replacement of the epidermis by cells with the normal allele, a more subtle correction of the functional defect occurred. The work also suggests that *in utero* the functional defect in GPI did not exert selective pressure on the keratinocytes. Using the intrinsic heterogeneity with the epidermis may lead to novel forms of therapy. This situation is reminiscent of the work from Dennis Roop's laboratory in mice with a knockout mutation, but without selective pressure, there was mosacism within epidermal stem cells (*JCB* 152:645–650, 2001).

Malignant cells utilize phenotypic alterations to escape from intrinsic control mechanisms or from drugs. Helmbach and associates (p. 923) detail the mechanisms by which human melanoma cell lines can become resistant to the chemotherapeutic agents, etoposide and *cis*-platin. Melanomas do not use drug-resisting mechanisms such as altering transport mechanisms for drugs or increasing glutathione S-transferase. These studies in one human melanoma cell line showed the presence of reduced activity of several enzymes associated with the apoptotic pathway.

In another study of apoptosis, six of 44 (13%) patients with early mycosis fungoides had point mutations in Fas, one of the major regulators of apoptosis (Dereure *et al*, p. 949). In two cases, the mutation would lead to the absence of the Fas death domain and might allow those cells and their progeny a competitive advantage expanding that cell population.

In another form of cutaneous lymphoma, B cell lymphoma, another mechanism was detailed which may have given those cells a competitive growth advantage (Child *et al*, p. 941). Child and coworkers studied the tumor suppresser genes p15 and p16 that encode cyclin-dependent kinase inhibitors and are thus negative cell cycle inhibitors by binding to CDK4 and CDK6 and inhibit the kinase activity of cyclin-kinase complexes, functionally inactivating the retinoblastoma protein. These genes normally produce a block in the G1 phase of the cell cycle. Mutations affecting p15 or p16 control mechanisms would contribute to the enhanced growth of malignant clones. In 35 cases of cutaneous B cell lymphoma there was no instance of point mutations in p15 or p16 and two instances of loss of heterozygosity at 9p21, their chromosomal location. In 23% of the cases there was hypermethylation of the p15 promotor and 43% had hypermethylation of the p16 promotor. P15 and p16 protein levels were decreased in many, but not all instances, when there was promotor hypermethylation. This is especially intriguing and demonstrates the importance of generically altering gene function and ultimately of cell cycle control by ways other than mutation or DNA deletion.

Darwin would no doubt be pleased to see how his seminal ideas on selection are still contributing to modern biology.

REFERENCE

Stauffer RC: *Charles Darwin's Natural Selection*. New York: Cambridge University Press, 1975

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