Changes in commensal oral flora and fauna and a breach in the junctional epithelium can lead to periodontitis (deep pockets of localized infection adjacent to teeth), the chronic destruction of the periodontal ligaments and alveolar bone supporting each tooth, and eventual exfoliation of teeth.

The perils of periodontitis

Although periodontitis has long been considered a localized infection, it is now clear that periodontal diseases are linked to conditions with systemic implications and affect more than 30% of the population. Oral microbial infections are associated with cerebrovascular disease; pregnant women with periodontitis are at greater risk of delivering preterm babies; and people with periodontitis are more likely to develop heart disease (for review, see ref. 2). The impact of this chronic battle against oral microbes increases with age (see figure; refs 3,4), leading to loss of teeth, compromised nutrition, psychosocial effect and challenges to general health.

Susceptibility to periodontal disease and the severity of the disease results from the interactions of genetic mutations and polymorphisms with numerous environmental agents. Diseases associated with early-onset (before puberty) periodontitis include Papillon-Lefèvre syndrome (PLS; ref. 5), leukocyte adhesion deficiency, Down syndrome, leukaemia and early-onset type I diabetes, among others[6]. In elucidating the genetic aetiology of PLS, Toomes *et al*. provide insight into how periodontal disease may arise. The syndrome is a rare autosomal recessive disorder characterized by severe, early-onset periodontitis and palmoplantar hyperkeratosis (thickening and scaling of the skin of the palms and soles). People with PLS lose their primary teeth by the age of four years; by age fourteen, most lose all permanent teeth[7].

By analysing samples from eight consanguineous families with PLS, Toomes *et al.* identified loss-of-function mutations in the gene (*CTSC*) encoding the papain-like, lysosomal cysteine protease cathepsin C (also known as dipeptidyl peptidase I), which is expressed in a wide range of cell types. The enzyme processes and activates a number of granule serine proteases critical to immune and inflammatory responses of myeloid and lymphoid cells[8]. Assays of cathepsin C activity in family members with PLS revealed near complete loss in affected individuals, and partial loss of activity in heterozygous carriers.

Cathepsin C function

The PLS phenotype suggests that cathepsin C is essential for establishing or maintaining the structural organization of the epidermis of the extremities and the integrity or immunologic properties of the tissues surrounding the teeth. Several other syndromes involving palmoplantar hyperkeratosis (but not periodontal disease) are caused by mutations in the keratin genes. This suggests that cathepsin C may indirectly contribute to the processing of proteins such as keratins, that maintain the structural integrity of epithelia in a way that is unique to the tissues that are affected in these patients.

The processing and activation of granzymes A and B by cathepsin C has been well characterized[9–11]. Granzymes are serine proteases secreted by cytotoxic T lymphocytes (CTL) and natural killer cells in attempt to destroy their targets—other lymphocytes or cells compromised by infection or disease. Granzymes enter the target cell and trigger apoptosis. In addition to eliminating tumour cells or infected cells, this mechanism of cell-mediated cytotoxicity can act to dampen the immune response by eliminating activated lymphocytes—an action potentially critical to the protection of periodontal tissues from damage due to inflammation.

Mice deficient in cathepsin C develop normally and seem healthy, but their CTLs and lymphokine-activated killer cells lack cytotoxic activity, owing to the lack of processing of both granzymes A and B (ref. 12). One wonders whether these mice might develop periodontal disease or hyperkeratosis and, if so, under what conditions. Notably, human keratinocytes in culture secrete granzyme B, which has antimicrobial activity[13]. It is tempting to speculate that the periodonti-

Skeletal development in the zebrafish

A variety of growth and differentiation factors regulate the formation of the vertebrate skeleton by activating or repressing different transcription factors. Among the differentiation factors, members of the transforming growth factor-β (TGF-β) superfamily are implicated in both cartilage and bone-cell differentiation and in mediating the complex patterning of the skeleton. The bone morphogenetic proteins (BMPs), a small family of TGF-β–related proteins, stimulate mesenchymal cells to differentiate into chondrocytes and osteoblasts, which deposit the bone matrix and regulate the pattern of skeletal formation. Accordingly, inactivation or mutation of BMP genes causes skeletal malformations in mice, and some skeletal diseases in humans may also result from mutations or alterations in the levels or activities of BMPs.

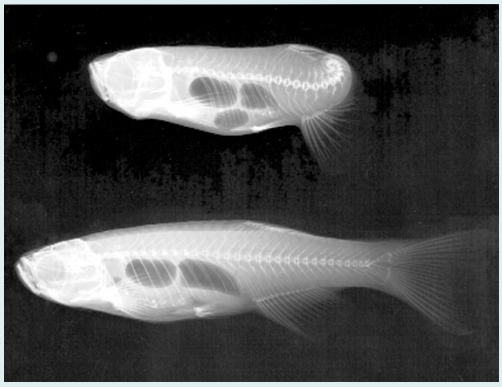

Image kindly provided by Shannon Fisher.

Achording to the zebrafish . . . a deficiency of chordin results in aberrant tail development (upper image).

Several secreted polypeptides, of which noggin and chordin are best characterized, regulate the extracellular activities of the BMPs. Their ability to associate with BMPs prevents them from binding to cell-surface receptors and thereby inhibits their effect on the cell. Last year, noggin was shown to inhibit BMP activity[1] in skeletal morphogenesis. So, mice deficient in noggin have skeletal defects due to excessive cartilage formation and increased bone formation. Shannon Fisher and Marnie Halpern now provide evidence[2] (see page 442) that skeletal development is regulated by chordin through its ability to block BMP activity. They show that zebrafish lacking chordin expression have aberrant levels of BMP proteins and abnormalities in fin and caudal skeletal patterning—which can be rescued by injections of chordin mRNA. In so doing, they underscore the advantages of using genetic screens of zebrafish to identify regulators of skeletal formation in vertebrates.

—Rik Derynck

1. Brunet, L. *et al*. *Science* **280**, 1455–1457 (1998).
2. Fisher, S. & Halpern, M. *Nature Genet.* **23**, 442–446 (1999).

Rik Derynck is a professor in the Departments of Growth and Development, and Anatomy, and the Programs in Cell biology and Developmental Biology at the University of California in San Francisco.