The hippocratic finger points the blame at PGE_2

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Digital clubbing has been recognized since the time of the ancient Greeks as a sign of systemic disease. Now, a new study identifies a role for prostaglandin E2 in the pathogenesis of digital clubbing observed in familial hypertrophic osteoarthropathy.

Digital clubbing, the most prominent feature of hypertrophic osteoarthropathy (HO), is characterized by a bulbous deformity at the tips of the digits. Individuals with fully developed HO also show excessive dermal proliferation and joint disease secondary to osteoblast proliferation in distal tubular bones, with new bone formation below the periostium (periostosis) and softening and destruction of bone involving the distal phalanges of the fingers and toes (acroosteolysis). The first report of clubbing is attributed to Hippocrates; therefore, this finding is also referred to as 'Hippocratic fingers' (**Fig. 1**). Through the years, a finding of digital clubbing has been used by clinicians as a sign of serious systemic disease. However, the precise pathogenesis of HO has remained obscure.

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Figure 1 Hippocrates examining an individual with digital clubbing.

Primary hypertrophic osteoarthropathy

Rare cases of HO, clustered in families, have been documented in the absence of systemic disease, and it is in such families that Uppal *et al.*[1] identified mutations in *HPGD*, which encodes 15-hydroxyprostaglandin dehydrogenase (15-PGDH), a prostaglandin E_2 (PGE_2) catabolizing enzyme. PGE_2 is a ubiquitous lipid mediator generated from membrane stores of arachidonic acid by the sequential actions of a number of enzymes, including cycooxgenase (COX)-1 and COX-2. The COX enzymes are the pharmacological targets of nonsteroidal anti-inflammatory (NSAID) drugs such as ibuprofen and aspirin. PGE_2 has been implicated as a mediator in a plethora of physiological systems, and PGE_2 production is often elevated in regions of inflammation. Therefore, not surprisingly, circulating levels are very low in healthy individuals. A major pathway of PGE_2 metabolism is mediated by 15-PGDH, which is highly expressed in the lung, where it catabolizes PGE_2 in blood collected from various vascular beds. In the three families with primary HO (PHO) examined by Uppal *et al.*, the *HPGD* gene of affected individuals contained mutations likely to result in loss of enzymatic function. Elevated urine PGE_2 was observed in all individuals with HO and in some heterozygous carriers. Although this provides a compelling case for abnormal PGE_2 metabolism in the pathogenesis in HO, 15-PGDH can metabolize other substrates, raising the possibility that altered metabolism of another molecule(s) may explain the phenotype in affected family members[2]. However, the observation that individuals chronically treated with PGE_2 develop typical signs of HO, and that these symptoms resolve when the therapy is discontinued, supports the idea that impaired metabolism of PGE_2 is critical in HO pathogenesis[3]. A key question raised by the Uppal study is whether progression of HO can be attenuated in individuals with PHO by treatment with NSAIDs, which block PGE_2 synthesis. Along with its clinical utility, such an outcome could help to close the loop of causality for PGE_2 in PHO.

$Hpgd^{-/-}$ mice die in the perinatal period with patent ductus arteriosus (PDA), a condition in which the ductus arteriosus, a large artery that connects the pulmonary trunk with the aorta allowing fetal blood to bypass the lung *in utero*, fails to close[4]. These findings demonstrated that metabolism of PGE_2 by 15-PGDH after establishment of the adult pattern of blood flow is required for remodeling of the ductus arteriosus. The sensitivity of the human ductus arteriosus to PGE_2 has also been documented both by the ability of PGE_2 to maintain the patency of the vessel after birth, and by the ability of NSAIDs to close the vessel in neonates with PDA[5]. Although alterations consistent with HO have not been reported in the $Hpgd^{-/-}$ mice, an increased risk for PDA is observed in individuals with HO. PDA is observed in about 0.05% of full-term births; PDA was observed in 25% of individuals with PHO[6].

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Secondary hypertrophic osteoarthropathy

An exciting question raised by the study of Uppal *et al.* is whether dysregulated levels of PGE_2 can provide a unifying mechanism for the range of clinical conditions in which secondary HO (SHO) is observed[7]. Dickinson and Martin have proposed a mechanism for HO that centers on abnormal platelet production[8]. Fragmentation of megakaryocytes into platelets takes place, at least in part, in the pulmonary circulation. When congenital malformations of the heart, or changes in blood flow in the lung itself, allow blood to bypass the capillary beds of the lung, megakaryocytes, or fragments of the platelet-producing cells, could reach the periphery, lodging in the digital capillary beds. Interaction of these megakaryocyte fragments with endothelial cells could result in local release of inflammatory and growth-promoting factors, including PDGF and VEGF, leading to the edema and disorganized vascular beds observed in the clubbed digits. A role for abnormal platelet activation is supported by histological examination of clubbed digits showing focal loss of endothelial cells and platelet microthrombi[9,10]. Immunohistochemical studies of the stroma of clubbed digits have also shown increased levels of VEGF and PDGF[11]. Can the evidence placing activated platelets at the 'scene of the crime' be reconciled with the altered PGE_2 metabolism? Perhaps. As PGE_2 is metabolized in the lung, diseases allowing venous blood to bypass pulmonary capillary beds could also result in exposure of platelets to high levels of this lipid mediator. Studies have shown that even modest increases in PGE_2 can increase platelet activation through the EP3 receptor[12]. It is therefore conceivable that normal homeostatic mechanisms preventing activation of the platelets as they pass through particular systemic capillary beds might be challenged or inadequate in the presence of elevated PGE_2.

Explaining the pathogenesis of SHO, including a role for PGE_2, is more difficult in diseases that do not primarily affect the lung or pulmonary blood flow, such as Graves' disease and inflammatory bowel disease[13,14]. However, based on the identification of mutations in *HPGD* as the cause of PHO, careful examination of PGE_2 and other catabolites of 15-PGDH in individuals with SHO is clearly warranted.

Missed opportunity?

Hippocrates was aware of the potent medicinal properties of willow leaves, now known to be a rich source of NSAIDs. If Hippocrates had prescribed willow leaves to individuals with SHO, would we have been spared many centuries of speculation on the pathogenesis of this disorder? On the other hand, perhaps he did prescribe this remedy but, like so many scientists since, did not trouble himself to report negative results and lack of efficacy.

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