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Review

The overview of channels, transporters, and calcium signaling molecules during amelogenesis

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ABSTRACT

Enamel is a highly calcified tissue. Its formation requires a progressive and dynamic system for the regulation of electrolyte concentration by enamel epithelia. A critical function of enamel epithelial cells, ameloblasts, is the secretion and movement of electrolytes via various channels and transporters to develop the enamel tissue. Enamel formation generates protons, which need to be neutralised. Thus, ameloblasts possess a buffering system to sustain mineral accretion. Normal tooth formation involves stage-dependent net fluctuations in pH during amelogenesis. To date, all of our information about ion transporters in dental enamel tissue is based solely on immunostaining-expression techniques. This review critically evaluates the current understanding and recent discoveries and physiological role of ion channels and transporters, Mg^{2+} transporters, and Ca^{2+} regulatory proteins during amelogenesis in enamel formation. The ways in which ameloblasts modulate ions are discussed in the context of current research for developing a novel morphologic-functional model of enamel maturation.

1. Introduction

Tooth formation is a dynamic system involving the regulation of electrolyte concentrations by enamel epithelia. A cardinal function of enamel epithelial cells is electrolyte secretion facilitated by various channels and transporters. The enamel organ requires fidelity of ionic regulation for its tissue to physically harden. For example, the abnormal tooth formation and development in patients with cystic fibrosis (CF) provides strong evidence that electrolyte regulation via ion channels and transporters is involved in normal tooth formation (Duan, Mao, Wen, Yang, & Xue, 2011). While the secretion of electrolytes such as HCO_3^- and Cl^- by non-mineral tissues including pancreatic and salivary acinar and ductal cells has been studied and reviewed extensively (Lee, Ohana, Park, Yang, & Muallem, 2012), the molecular mechanisms of ion channels and transporters in ameloblasts is only partially understood, despite much progress in our overall understanding of enamel formation.

2. Overview of tooth development

Odontogenesis takes place in a continuous process. Initiation of odontogenesis leads to identifiable stages in tooth development, including the bud stage, the cap stage, and the bell stage, while systematic differentiation of the tooth germ continues. Odontogenesis then progresses to the stage of secretory with formation of the hard dental tissues, such as enamel, dentin, and cementum, and then finally to the stage of maturation for these structures. Especially, amelogenesis is the process of enamel matrix formation and maturation that occurs in two stages of tooth development, the stages of secretory and maturation. During the secretory stage of amelogenesis, enamel matrix which is produced by ameloblast initially is partially mineralized because it is protein-rich matrix which is composed of only a small amount of hydroxyapatite crystals (Simmer et al., 2010). However, during the maturation stage, enamel matrix completes its mineralization process after the secretory of enamel matrix. Ameloblasts modulate their morphology between ruffle-ended ameloblast (RA) and smooth-ended ameloblast (SA) forms. Ruffle-ended ameloblasts add mineral to the enamel; smooth-ended ameloblasts allow removal of water and degraded matrix proteins (Hand & Frank, 2014).

3. Major ions for pH regulation

A unique phenomenon during the maturation stage is that ameloblasts modulate. They are involved in several cellular activities including pH regulation and ion transport (Smith, 1998). The enamel is formed by ameloblasts containing many ion transporters and channels,

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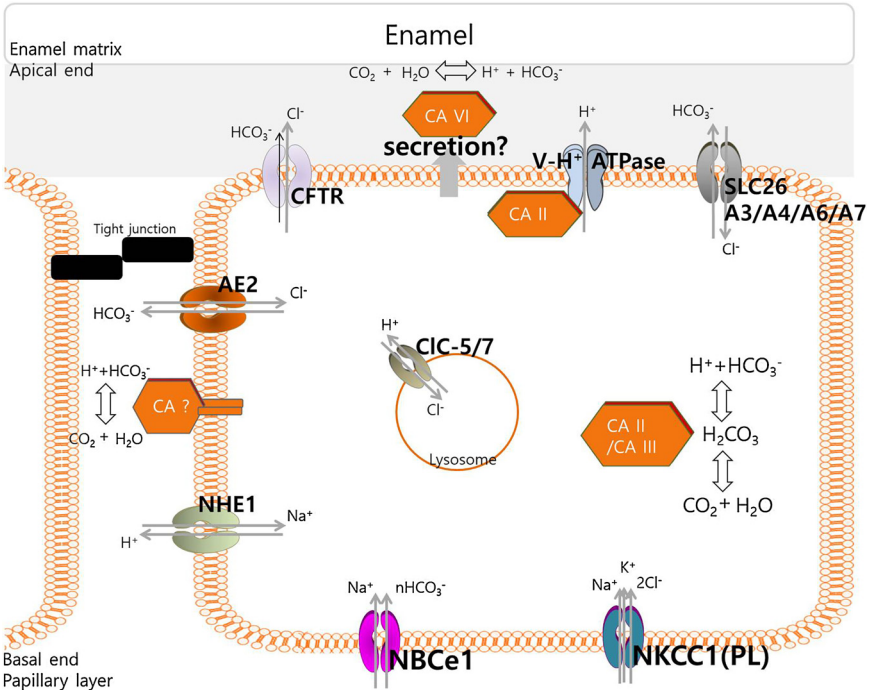

Fig. 1. Schematic representation of ion transporters related to the modulation of the physiological microenvironment of matured ameloblasts.
This model depicts our current knowledge of the ion channels associated with the main activities of ameloblasts during maturation. AE2: anion exchanger2; CFTR: cystic fibrosis transmembrane conductance regulator; SLC26 A: solute carrier 26 family A; ClC: Cl^- channel; V-H^+ ATPase: V (vacuole) type-H^+ ATPase; NHE1: Na^+-H^+ exchanger 1; NBCe1: Electrogenic $Na^+ - HCO_3^-$ co-transporter 1; NKCC: Na^+-K^+-$2Cl^-$ cotransporter 1; CA: carbonic anhydrase. PL: papillary layer.

which are well known from studies of related diseases conducted in the past two decades (Duan, 2014). HCO_3^-, the biological pH buffer responsible for maintaining intracellular and extracellular pH fluctuations, is present in the enamel fluid. Depending on the cell morphology found during maturation stage, the pH is mildly acidic in RAs and nearly neutral in SAs. Since ion transporters have been addressed in ameloblasts, we have begun to uncover the exact details of the molecular mechanism of enamel-crystal growth. The ion transporters that secrete HCO_3^- to the enamel matrix involve two kinds of HCO_3^--carrier proteins, the electrogenic $Na^+ - HCO_3^-$ cotransporter 1 (NBCe1) and anion exchanger 2 (AE2) (Lacruz, Nanci, White et al., 2010; Paine et al., 2008). Studies of NBCe1-knockout animals, in which the enamel is extremely hypo-mineralised and architecturally weak, showed that NBCe1 is strongly involved in the development of normal enamel (Lacruz, Nanci, White et al., 2010). NBCe1 protein levels are significantly increased in ameloblasts of *Cftr*-null and *Ae2*-null mice to import HCO_3^- to compensate for dysregulated Cl^--dependent buffering effect (Jalali et al., 2014). Such studies support the concept that the regulation of HCO_3^- secretion into the enamel space is important for understanding the molecular mechanisms of the enamel organ.

4. Ca^{2+} and Mg^{2+} for enamel growth

Ca^{2+} signalling is finely integrated for the performance of various cell functions including muscle contraction, transcription, and exocytosis. Excessive activation of the Ca^{2+}-release pathway is extremely toxic and is the nodal point of diseases associated with cell stress or death. Although enamel is the most highly calcified tissue in mammals, it is unclear how cells avoid the cytotoxic effects of excess Ca^{2+} while supplying sufficient bulk Ca^{2+} for enamel growth. Recently, understanding of Ca^{2+} transcytosis, a new concept for Ca^{2+} transport in the mineral-formation process, has been strengthened (Lacruz et al., 2011; Lacruz, Smith, Kurtz, Hubbard, & Paine, 2013); however, further investigation of the precise mechanism is needed. In terms of Ca^{2+} signalling in tooth biology, the down regulation of Ca^{2+} transport could contribute to multiple developmental defects in the enamel. The fundamental cellular mechanism of Ca^{2+} transport is a potential target for drugs to improve enamel quality (Hubbard, 2000). In addition to Ca^{2+} transport, it is also noteworthy that Mg^{2+} also involved in amelogenesis (Nakano et al., 2016; Ogata et al., 2017; Simmer et al., 2014; Yamazaki et al., 2013). Briefly we discuss below. Ameloblasts coordinate the transport of ions and molecules to mature the enamel, allow crystal growth, and resist excess acidity by biological pH buffer such as HCO_3^- (Simmer et al., 2010). It is therefore critical to understand how ameloblasts neutralise the acidity during the maturation stage, which is a typical by-product of hydroxyapatite formation. The goal of this article is physiologically to evaluate the current understanding of how the ion channels and transporters in ameloblasts handle fundamental electrolytes.

5. Amelogenesis and the polarity of ameloblasts

Various epithelial and enamel cells require a specialised structure with directionality from the basal pole to the apical pole. The ameloblast is one of prototypical example of polarized cells. The polarised cells compartmentalise the expression of proteins such as Ca^{2+}-signalling proteins and ion transporters. The polarised expression at the apical and basolateral membranes causes the unidirectional secretion of enzymes and fluid into the lumen (Kasai & Augustine, 1990). Ca^{2+}-signalling proteins and ion transporters are involved in the polarised signalling pattern and directional electrolyte secretion during enamel formation. In the basolateral membrane, proteins such as NBCe1, NHE1, AE2, and Na^+-K^+-ATPase that transport HCO_3^- and Na^+ are important for Na^+ influx, HCO_3^- secretion, and pH regulation. On the other side, in the apical membrane, proteins such as V-H^+ ATPase, NHE1, NKCC1, CFTR, SLC26 A, NCX, and NCKX that transport H^+, HCO_3^-, Cl^-, and Ca^{2+} adjust the pH and the ion concentration in a maturation-dependent manner. The channels and transporters mainly involved in enamel formation during maturation stage and these are illustrated in Fig. 1.

The polarised expression of Ca^{2+}-related proteins and receptors, which evoke polarised Ca^{2+} signals, is well established in non-enamel soft tissues such as those of the pancreas and salivary glands. Of the many proteins associated with Ca^{2+} signalling in various tissues, plasma membrane Ca^{2+} ATPase (PMCA) pumps (Borke, Zaki, Eisenmann, & Mednieks, 1995), sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase (SERCA) pumps (Franklin, Winz, & Hubbard, 2001), inositol 1,4,5-trisphosphate receptors (IP_3Rs) (Nurbaeva, Eckstein,