Distinct Impacts of Eda and Edar Loss of Function on the Mouse Dentition

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Abstract

Background: The Eda-A1-Edar signaling pathway is involved in the development of organs with an ectodermal origin, including teeth. In mouse, mutants are known for both the ligand, Eda-A1 (Tabby), and the receptor, Edar (Dowless). The adult dentitions of these two mutants have classically been considered to be similar. However, previous studies mentioned differences in embryonic dental development between EdaΔTa and EdarΔβγ mutants. A detailed study of tooth morphology in mutants bearing loss-of-function mutations of these two genes thus appears necessary to test the pattern variability induced by the developmental modifications.

Methodology/Principal Findings: 3D-reconstructions of the cheek teeth have been performed at the ESRF (Grenoble, France) by X-ray synchrotron microtomography to assess dental morphology. The morphological variability observed in EdaΔTa and EdarΔβγ mutants have then been compared in detail. Despite patchy similarities, our detailed work on cheek teeth in EdaΔTa and EdarΔβγ mice show that all dental morphotypes defined in EdarΔβγ mice resolutely differ from those of EdaΔTa mice. This study reveals that losses of function of Eda and Edar have distinct impacts on the tooth size and morphology, contrary to what has previously been thought.

Conclusion/Significance: The results indicate that unknown mechanisms of the Eda pathway are implicated in tooth morphogenesis. Three hypotheses could explain our results; an unexpected role of the Xedar pathway (which is influenced by the Eda gene product but not that of Edar), a more complex connection than has been appreciated between Edar and another protein, or a ligand-independent activity for Edar. Further work is necessary to test these hypotheses and improve our understanding of the mechanisms of development.

Introduction

Genes of the Eda-A1/Edar signaling pathway are involved in the development of organs with an ectodermal origin, such as hair, glands, teeth [1–3] and palatal rugae [4]. The Eda gene, carried by the X chromosome, encodes the ligand (Eda-A1), and the Edar gene encodes its receptor (Edar). EdaΔTa (Tabby) and EdarΔβγ (Downless) mutant mice bear loss-of-function mutations for the Eda (ectodysplasinA) and the Edar (ectodysplasinA-receptor) genes, respectively [5,6]. Consistent with their operation in a linear signalling pathway, the ectodermal organs of these mutants display similar gross phenotypes. However, differences between Eda and Edar mutants in the histological structure of the submandibular salivary gland have been reported [7]. Concerning dental morphology, only the dentition of Eda mutants has been deeply investigated. These studies revealed a high morphological diversity of the cheek dentition, characterized by modifications in the number of teeth and in the number and arrangement of cusps for homozygous and heterozygous mice [1,8–13]. In contrast, no study has described the EdaΔTa dental phenotype, which is usually supposed to display the same dental defects as in EdarΔβγ mice [14]. However, differences between these mutants have been detected in the enamel knots, which are transient signalling centres that define the cusp pattern of the mature tooth [15]. The enamel knots of EdaΔTa embryonic teeth are simply smaller in than those of WT mice [16], while EdarΔβγ mutant molars have a structure termed the ‘enamel rope’ which is composed of enamel knot cells that are extended across the tooth primordium due to a failure of cell condensation [17]. This may indicate that Eda and Edar losses of function are likely to have different consequences on mature dental morphology. This prompted us to study the cheek dentition in EdaΔTa and...
Materials and Methods

Downless+ and Tabby mice

The Eda<sup>blj</sup> mice (FVB background) have been bred at the PBES of IFR 128 (Lyon). These mice carry a G to A transition mutation causing a glutamate to lysine substitution in the death domain of the Eda protein (E379K) [6]. Old studies on Eda<sup>blj</sup> mutant mice used either Eda<sup>blj</sup> [1,9] or Eda<sup>bleck</sup> [3] mice. Eda<sup>blj</sup> mice have been used in more recent studies comparing the dental development and functional morphology of Eda and Edar mutant mice [17]. Comparison of Eda<sup>blj</sup> and Eda<sup>bleck</sup> dental morphology showed no differences [17]. Homozygous Eda and Edar mutant mice were identified according to external morphological criteria, such as the bald spot behind ears. Heterozygous Eda (female) mice were identified morphologically by the distinctive striping of the coat that gave these mutants their original name, ‘Tabby’. Heterozygous and wild-type Eda<sup>blj</sup> specimens exhibit similar external traits and were genotyped through PCR amplification of a 306 bp fragment covering the point mutation (primers: 5’ GTCTCAGCCCGACCGAGTTG and 3’ GTGGGGAGG-GAGGTGTTACA), followed by sequencing. The Eda<sup>blj</sup> sample was composed of 20 heterozygous (Eda<sup>blj/+</sup>), 47 homozygous (Eda<sup>blj/blj</sup>) and 5 control (WT) specimens. The Tabby sample used in comparison overlaps the sample studied by Kristenova et al. [10]. They carry the Eda<sup>Ta</sup> null allele of the Eda gene, carried by the X-chromosome. Eda<sup>Ta</sup> mice are on a mixed background (C57Bl6J+CB6), the sample included 60 heterozygous females (Eda<sup>Ta/+</sup>), 23 homozygous (Eda<sup>Ta/Ta</sup>) or hemizygous females (Eda<sup>Ta/0</sup>) which have a single X chromosome and display the same phenotype as homozygous [10]; 57 hemizygous males (Eda<sup>Ta/0</sup>) and 40 WT mice. Mice were killed by cervical dislocation. The experimental protocol was designed in compliance with recommendations of the EEC (86/609/CEE) for the care and use of laboratory animals.

The uncertain homology of teeth between WT and mutant mice led us to adopt a nomenclature using T<sub>x</sub> and T<sub>y</sub> where T and x respectively symbolize the tooth and its rank within the row (e.g. T<sub>1</sub> for the first upper cheek tooth, T<sub>1</sub> for the first lower cheek tooth).

3D-data acquisition

Cheek teeth were examined using a Leica MZ16 stereomicroscope. Morphotypes have been defined for lower and upper tooth rows on the basis of the number and arrangement of cusps. Occlusal surface areas of cheek teeth were measured from digitized pictures using Optimas software. It has been demonstrated that X-ray synchrotron microtomography brings very high quality results for accurate imaging of small teeth [10]. Thus, tooth rows of a representative panel which covers the totality of observed morphologies were imaged using X-ray-synchrotron microtomography at the European Synchrotron Radiation Facility (ESRF, Grenoble, France). 3D-renderings were performed using VGStudioMax software.

Statistical tests

Statistical tests have been performed to compare tooth size. The Kruskal-Wallis analysis of variance was used to verify the significance of observed differences between Eda<sup>Ta</sup> and Eda<sup>blj</sup> mice. This is a non-parametric method, which tests equality of population medians among groups. The non-parametric Wilcoxon rank-test is used to indicate which groups are statistically different from the others.

Results

Wild-type mice

WT specimens from Eda<sup>Ta</sup> and Eda<sup>blj</sup> breeding colonies all display the normal dental morphology, without anomalies, and measurements show similar tooth size (ANOVA test at p = 0.05 threshold value). Thus, molars from WT from both genetic backgrounds were included in a single WT sample.

Heterozygous Eda<sup>Ta/+</sup> and Eda<sup>blj/+</sup> mice

As Eda is located on the X chromosome while Edar is on an autosome, morphological differences linked to the X-inactivation process were predictable. Accordingly, in both the upper and lower cheek dentitions, heterozygous Eda<sup>Ta/+</sup> mice display dental morphologies very close to WT specimens (Fig. 1A–B, Fig. 2A–B) whereas Eda<sup>Ta/+</sup> mice dentitions exhibit highly variable patterns (Fig. 1C–G, Fig. 2I–K). Eda<sup>Ta/+</sup> upper tooth rows differ from the WT morphology by the occurrence of a supplementary centro-
vestibular cusp at the T1 (arrow on Fig. 1B). This pattern approaches the morphotype \(\text{He}1\) of \(\text{Eda}^{Ta/+}\) mice (arrow on Fig. 1D) [13]. The size of the upper teeth only differs between WT, \(\text{Eda}^{Ta/He1}\) and \(\text{Edar}^{dl-J}\) by a smaller T2 in \(\text{Edar}^{dl-J}\) (Fig. 3A). Upper tooth size is similar for \(\text{Edar}^{dl-J/+}\) and \(\text{Eda}^{Ta/+}\) He0, defined as the Tabby heterozygous morphotype exhibiting the wild-type morphology (presented Fig. 1C).

\(\text{Eda}^{Ta/+}\) mice sometimes exhibit a small mesial lower tooth (Fig. 2J–K) which is never found in \(\text{Edar}^{dl-J/+}\) mice. Moreover, \(\text{Edar}^{dl-J/+}\) lower teeth are all smaller than those of the WT. They also differ from the \(\text{Eda}^{Ta/He1}\) major morphotype by a smaller T1 (Fig. 3B). The almost normal morphology of upper and lower cheek dentitions of \(\text{Edar}^{dl-J/+}\) is thus far from the morphological diversity observed in \(\text{Eda}^{Ta/+}\).

Homozygous \(\text{Eda}^{Ta}\) and \(\text{Edar}^{dl-J}\) mice

Upper and lower cheek teeth clearly differ between \(\text{Eda}^{Ta}\) and \(\text{Edar}^{dl-J}\) mice in terms of morphology and size. \(\text{Edar}^{dl-J}\) upper dentition is characterised by: (i) a T1 with a single lingual cusp (asterisk in Fig. 1H) linked by a crest to the mesial-most cusp, (ii) a T2 with a lingual interconnection between mesial and distal cusps (arrows in Fig 1H). T1 of \(\text{Eda}^{dl-J}\) are similar to those of \(\text{Eda}^{Ta/He1}\) (Fig. 1H–I). T1 of \(\text{Eda}^{dl-J}\) and \(\text{Eda}^{Ta/He1}\) statistically have the same size (Fig. 3A). However, T2 are statistically smaller in \(\text{Eda}^{dl-J}\) (Fig. 3A) and the lingual ridge of \(\text{Eda}^{dl-J}\) T2 does not occur in \(\text{Eda}^{Ta/T2}\). The morphological differences between \(\text{Eda}^{Ta}\) and \(\text{Eda}^{dl-J}\) T2 can be explained by their crown size differences referring to the ‘patterning cascade mode of cusp development’ [19] in which the signalling centre succession, and consequently the number and position of cusps, is linked to the crown size.

The lower cheek dentition of \(\text{Eda}^{dl-J}\) is more variable than the upper. Four morphotypes can be defined (Fig. 2C–G), specimens can exhibit two different morphotypes on left and right sides, none of the four morphotypes occurs in \(\text{Eda}^{Ta}\) dentition. (i) The first morphotype, Dl1 (for Downless1), includes 45% of the studied material. It is characterized by a three-toothed row and a four-cusp T1. The three mesial cusps form a three-leaf clover shape, while the fourth cusp is either isolated in the distal part of the tooth (85% of Dl1 tooth rows, arrowed in Fig. 2C) or connected to the others by a longitudinal crest (15% of Dl1 tooth rows, arrowed in Fig. 2D). No \(\text{Eda}^{Ta}\) morphotype is similar to this Dl1 morphotype. (ii) The Dl2 morphotype (12% of examined tooth rows) also exhibits three cheek teeth, but the fourth cusp is either isolated in the distal part of the tooth (85% of Dl1 tooth rows, arrowed in Fig. 2C) or connected to the others by a longitudinal crest (15% of Dl1 tooth rows, arrowed in Fig. 2D). No \(\text{Eda}^{Ta}\) morphotype is similar to this Dl1 morphotype. (iii) The Dl3 morphotype (31% of tooth rows) is characterized by rows with two lower cheek teeth (Fig. 2F). The most mesial element varies from a large rounded cusp (arrowed in Fig. 2F) to a highly reduced, almost absent, element (arrow in Fig. 2G). This latter

![Figure 2. Lower tooth rows; wild-type morphology and morphotypes defined among EdaTa and Edarl-J mutant mice. A: WT morphology; B: Edardl-J/+ morphology; C–D: Edarl-J morphotype Dl1, E: Edarl-J morphotype Dl2, F–G: Edarl-J morphotype Dl3, H: Edarl-J morphotype Dl4, I–K: EdaTa morphotypes, L: EdaTa morphotype la, M: EdaTa morphotype lb, N: EdaTa morphotype lc, O: EdaTa morphotype lla, P: EdaTa morphotype llb. The proportions indicated below the morphotypes are the occurrence frequency of the morphotypes. Images of EdaTa mice are obtained by photography and are taken from Kristenova et al. [10] and Peterkova et al. [30]. Same orientation as in Fig. 1. The structures indicated by arrows are discussed in the main text. doi:10.1371/journal.pone.0004985.g002](image-url)
morphology is alike the EdaTa IIb morphotype (Fig. 2P). The Dl3 morphotype displays the same tooth size as EdaTa IIa and IIb morphotypes (Fig. 3B).

(iv) The Dl4 morphotype (7% of tooth rows) is characterized by a small T1 (arrow in Fig. 2H), 57% of the Dl4 tooth rows encompass three teeth, while 43% have a tiny T4. The T2 encompasses four cusps, three mesial interconnected and an isolated distal one. The presence of the reduced T1 is reminiscent of the EdaTa Ic morphotype (Fig. 2N). However, the morphology of the T1 is highly different as it encompasses a higher number of cusps than that of the EdaTa Ic morphotype, which moreover never exhibits 4 teeth.

**Discussion**

X-inactivation might explain differences between heterozygous EdaTa/+ and Edardl-J/+ mice

The many observed differences, and the higher variability of tooth rows, between EdaTa/+ and Edardl-J/+ mice can be explained...
by the fact that the \textit{Eda} gene is X-linked and that Edar is carried by an autosome. Due to the X-inactivation effect in females [20,21], \textit{Eda}\textsuperscript{Ta/\textit{Ta}} and \textit{Edar}\textsuperscript{dl-J} mice are mosaicos of cells with expression of a wild-type or a null \textit{Eda} gene. This might induce a strong and random variability in the amount of Ectodysplasin-A1 protein available for dental development, explaining the higher morphological variability recorded in \textit{Eda}\textsuperscript{Ta/\textit{Ta}}. This phenomenon does not occur in the \textit{Edar}\textsuperscript{dl-J} teeth since the gene is located on an autosome (chromosome 10).

**Differences between homozygous \textit{Eda}\textsuperscript{Ta} and \textit{Edar}\textsuperscript{dl-J} mice imply other mechanisms**

The same general trends in the reduction of the cusp number and tooth size are observed in both \textit{Eda}\textsuperscript{Ta} and \textit{Edar}\textsuperscript{dl-J} mutants. However, none of the \textit{Eda}\textsuperscript{Ta} and \textit{Edar}\textsuperscript{dl-J} tooth rows are identical. The two mutants are supposed to display total losses of function of the ligand and the receptor of the \textit{Eda} pathway, respectively. According to Tucker et al. [17], \textit{Eda} mice have small enamel knots while \textit{Edar}\textsuperscript{dl-J} mice have disorganised “enamel ropes”. As enamel knots are orchestrating the final mineralized crown pattern, differences of size and morphology, differences in enamel knots are likely to explain differences of size and morphology between \textit{Eda}\textsuperscript{Ta} and \textit{Edar}\textsuperscript{dl-J} dentitions.

Various hypotheses could explain these differences: (i) They could be linked to epistatic differences between the two different backgrounds of \textit{Eda}\textsuperscript{Ta} and \textit{Edar}\textsuperscript{dl-J} mice (respectively mixed C57Bl6J-CBA and FVB); However we consider this possibility to be unlikely to be the only explanation. Indeed, suppression of \textit{Eda} action in embryonic CD-1 mice by addition of soluble forms of Edar to tooth explants results in the same phenotype as seen in \textit{Eda}\textsuperscript{Ta} mice on NMRI and mixed CBAT6T6xNMRI backgrounds but differs from the \textit{Eda}\textsuperscript{dl-J} on CD-1 background [17]. This indicates that differences observed between enamel knots in \textit{Eda}\textsuperscript{Ta} and \textit{Edar}\textsuperscript{dl-J} mice are not due to a difference in background but rather to an intrinsic difference between loss of \textit{Edar} function and alteration of \textit{Eda} function in \textit{Eda}\textsuperscript{dl-J}. (ii) \textit{Eda} codes for two proteins, \textit{Eda}-A1, which binds to Edar, and \textit{Eda}-A2, which binds to Xedar [22]. The Xedar pathway is thus lost in \textit{Eda}\textsuperscript{Ta} mice but still present in \textit{Eda}\textsuperscript{dl-J} mice. An effect on tooth development of the loss of the Xedar pathway in the case of \textit{Eda} loss of function and not in the \textit{Edar} one might explain some of the differences that we report. Though a study of Xedar-null mice indicated no requirement for this gene in the normal development of ectodermal organs [23], dominant negative and constitutively active forms of this protein have been shown to have effects similar to those of Edar in developing chicken skin [24] and a compensatory action of Xedar that is revealed only in the amount of Ectodysplasin-A1 protein available for dental development, explaining the higher morphological variability recorded in \textit{Eda}\textsuperscript{Ta/\textit{Ta}}. These differences indicate unknown mechanisms of the \textit{Eda} pathway involved in tooth morphogenesis. These unknown mechanisms we hypothesize to be based on an unexpected role of the Xedar pathway in tooth development, a more complex connection than thought between Edar and Edaradd, or on a ligand-independent activity for Edar.

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**Author Contributions**

Conceived and designed the experiments: VL LV. Performed the experiments: CC PT LV. Analyzed the data: CC SP. Contributed reagents/materials/analysis tools: SP DJH. Wrote the paper: CC SP PT DJH VL LV.

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