

# The Embryological Basis of Juvenile Angiofibroma: A Unifying Hypothesis for Tumor Pathogenesis

Bernhard Schick, Lukas Pillong, and Silke Wemmert \*

Department of Otorhinolaryngology, Head and Neck Surgery; Saarland University, Homburg, Germany.

**\*Corresponding Author:** Silke Wemmert, Department of Otorhinolaryngology Kirrberger Strasse 10066421 Homburg, Germany.

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## Abstract

Juvenile angiofibroma (JA) is a rare tumor, primarily affecting adolescent males, with an unclear etiology. This study reviews clinical and molecular data to assess an embryological hypothesis explaining JA's key features: its origin near the sphenopalatine foramen, vascular supply from the maxillary artery, sex-specific incidence, and fibrovascular composition. Findings support the hypothesis that JA arises from remnants of the first branchial arch plexus and persisting neural crest cells, which accounts for its location, blood supply, and growth. The hormonal surge during puberty, acting via the luteinizing hormone receptor, likely triggers tumor development. Epithelial-mesenchymal transition (EMT) is involved in its fibrous component. This hypothesis integrates JA's clinical, histopathological, and rare variant characteristics, suggesting an embryologically derived pathology.

**Keywords:** juvenile angiofibroma; embryology; first branchial arch; neural crest cell; LH/LHR; epithelial-mesenchymal transition

## Introduction

Juvenile angiofibroma (JA) is a rare yet fascinating fibrovascular tumor defined by four distinct features: [1] an origin near the sphenopalatine foramen, [2] a primary blood supply from the maxillary/sphenopalatine artery with potential additional feeders from the internal carotid artery, [3] an almost exclusive manifestation in male adolescents, and [4] a fibrovascular architecture characterized by irregular vascular spaces - often lined solely by endothelial cells - embedded within a fibrous stroma (Schick & Kahle, 2000). These unique characteristics have spurred numerous theories regarding the tumor's nature since the 19th century (Schick & Urbschat, 2004). However, most of these hypotheses have focused on only one aspect of JA, thereby neglecting the full spectrum of its features and ultimately failing to achieve general acceptance.

Historically, many proposed theories have concentrated on either the vascular or fibrous components of JA. This piecemeal approach risks an incomplete understanding of the tumor's etiology, as it overlooks the interplay between both tissue components. In parallel, extensive genetic and molecular investigations - such as the frequent detection of beta-catenin mutations in JA - have identified various alterations without providing decisive insights into tumor etiology (Abraham et al., 2001; Calanca et al., 2021; Schick et al., 2011).

Moreover, these genetic and molecular studies have not identified a definitive tumor cell of origin, a crucial step for establishing a convincing etiological model. The absence of a clear explanation for the tumor's

almost exclusive occurrence in adolescent males further underscores the limitations of previous approaches; hormone studies, for instance, have yielded conflicting results (Kumagami, 1993; Liu et al., 2015; Schick et al., 2014).

In response to these challenges, a strong impetus is to adopt a unifying theory of JA nature. Here, we present an embryological perspective that, for the first time, simultaneously accounts for all four characteristic features of JA. This model integrates the vascular and fibrous elements of the tumor and offers a comprehensive explanation for its pathogenesis, thus holding the promise of achieving general acceptance.

## Start of Embryological Thoughts in JAs

Two key developments initiated the embryological perspective on juvenile angiofibroma:

1. **Anatomical Insights:** A landmark study (Beham et al., 2000) provided a detailed examination of the irregular vascular structures in JAs. The findings from this investigation led to the hypothesis that JA may represent a vascular malformation.
2. **Embryological Considerations:** Independent of the anatomical study, researchers questioned whether a vascular embryological origin could simultaneously account for the tumor's specific site of origin and its characteristic blood supply. To explore this possibility, the development of normal

embryological vessels was analyzed to determine if they establish a connection between the future region of the sphenopalatine foramen (and its associated arteries) and the segment of the internal carotid artery that occasionally contributes to JA vascularization. This line of inquiry highlighted the first branchial arch as a structure of interest (Schick & Urbschat, 2004).

### First Branchial Arch Artery

The first branchial arch artery is transiently present during embryonic development (days 22 to 24). It provides the essential blood supply to the developing brain during this period, while the later needed arteries are not yet fully established (Bertulli & Robert, 2021; Schick & Urbschat, 2004). Notably, the first branchial arch artery forms a temporary connection between the tissues surrounding the future sphenopalatine foramen and the segment of the internal carotid artery from which internal carotid feeders in JA are sometimes observed. As development proceeds, this artery regresses via the formation of a vascular plexus, with remnants of this plexus subsequently being incorporated into the arteries around the sphenopalatine foramen (Schick & Urbschat, 2004). Figure 1 a-d illustrates the normal development of the first branchial arch artery, along with the potential remnants of its plexus.

Previous findings have further illuminated the presence of exclusively endothelial-lined vascular spaces in fetal tissues adjacent to the sphenopalatine foramen in both sexes (Harrison, 1987). These spaces are hypothesized to represent regression remnants of the first branchial arch artery plexus, which may, in rare instances, persist and provide the anatomical basis for later JA development.

### Verification of Embryological Tissue

Based on the embryological hypothesis, specific markers indicative of an embryological origin should be detectable in JA tissues. Molecular analyses have primarily focused on the pathological JA vessels. Notably, laminin alpha2 expression was identified in these vessels (Starlinger et al., 2007), a marker typically expressed in embryonic vessels associated with the brain. This finding strongly supports the embryological origin hypothesis for JA. Additionally, an embryological collagen I texture has been observed in the fibrous component of JA (Gramann et al., 2009), further reinforcing this notion.

Moreover, the detection of TSHZ1 in JA vessels (Schick et al., 2011) has provided additional support for the involvement of the first branchial arch artery in JA pathogenesis. TSHZ1 is known to play a role in the formation of the first and second branchial arch arteries in mice (Coré et al., 2007), thereby renewing interest in its potential role in JA.

### Cell of Tumor Origin

For many years, attempts to define the tumor cell of origin in JA have been unsuccessful. The embryological hypothesis offers a new perspective, guided by two key considerations: a) the persistence of neural crest cells in pathologies of embryological origin, and b) the critical role of neural crest cells in vascular development (Ponzoni et al., 2022; Schussler et al., 2021).

A particularly compelling observation is the consistent detection of CD271-positive cells in all examined JA samples, localized near the irregular vascular structures. These CD271-positive cells were interpreted as persisting neural crest cells, further supporting the concept that JA originates from embryological remnants (Schick et al., 2022).

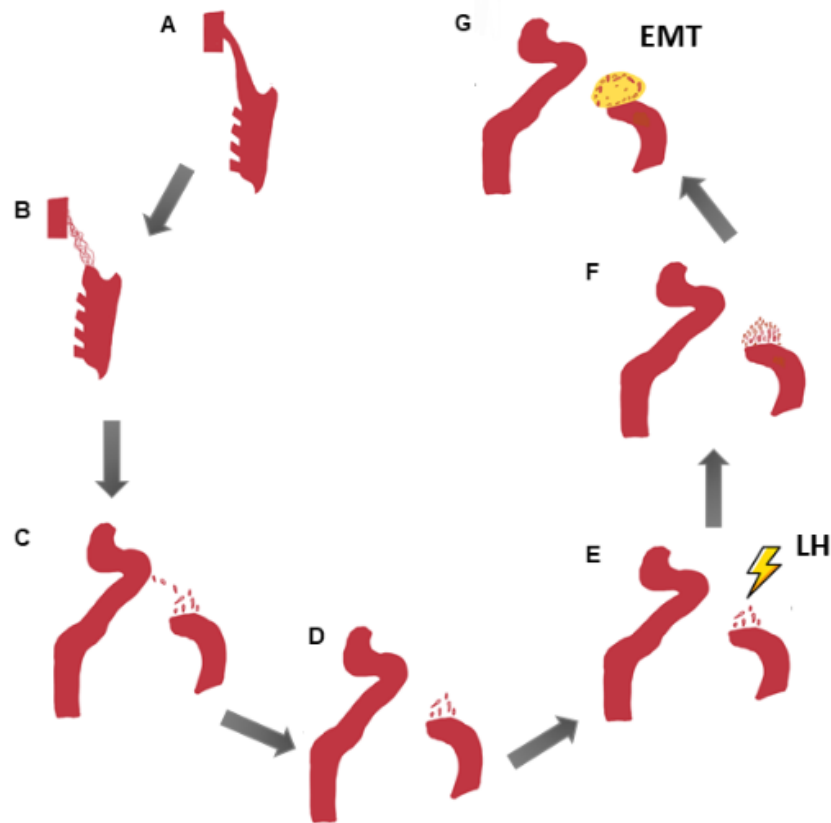
### Tumor Initiation

The almost exclusive manifestation of JA in adolescent males has long suggested a hormonal influence in its initiation. Initial studies, however, did not find altered hormone levels in affected individuals (Kumagami, 1993). Consequently, research shifted to investigating hormone receptors -primarily androgen, estrogen, and progesterone receptors (Liu et al., 2015; Schick et al., 2014). Yet, these studies yielded contradictory results, leaving the explanation for the tumor's sex specificity unresolved.

The subsequent detection of luteinizing hormone receptor (LHR) mRNA in JA (Schick et al., 2014) expanded the perspective. Although LHR expression is typically limited to a few tissues, its presence in JA was striking. A closer examination revealed that the pubertal surge in luteinizing hormone (LH) - which marks the onset of puberty - could serve as a potent stimulus for tumor growth in male adolescents. Further investigations visualizing both LHR mRNA and protein in JA tissue sections consistently demonstrated LHR expression in proximity to the pathological vessels (Wemmert et al., 2024), supporting the hypothesis that the pubertal LH surge plays a critical role in JA initiation (**Figure 1e**).

### Fibrovascular Tissue Architecture

The distinctive fibrovascular architecture of JA demands an explanation that integrates both its vascular and fibrous components. Within the context of an embryological vascular origin, the process of epithelial-to-mesenchymal transition (EMT) - a key embryological mechanism - emerges as a compelling candidate (Ang et al., 2023; Calanca et al., 2021; Serrano-Gomez et al., 2016). EMT provides a plausible mechanism by which the vascular component transitions into the fibrous tissue observed in JA (**Figure 1g**). This hypothesis is further supported by the expression of EMT-associated markers such as MMP3, PDGFR $\beta$ , NG2, and vimentin (Boewe et al., 2022; Schick et al., 2022), as well as transcription factors like Snail and Twist (own unpublished data).



**Figure 1: Embryological explanation for the characteristic vascular and fibrous features of JA.** The first branchial arch artery ensures in embryology between day 22 and 24 blood supply for the developing brain in a still not completely developed internal carotid artery (a). The only temporarily present first branchial arch artery recedes via plexus formation in further development (b). The plexus remnants are found along the first branchial arch artery (c). Finally, they are only observed close to the area of the later sphenopalatine foramen (d) and incorporated partially into the arising vessels in this region. LHR-expressing remnants of the first branchial arch artery plexus are sensitive to an LH increase during puberty (e), resulting in vascular growth at this time (f) and tumor occurrence. Fibrous tissue arises (yellow) from the vascular component of the tumor by epithelial-mesenchymal transition (EMT)(g).

## Clinical Aspects

### Tumor Localization

The endonasal approach is highly effective for resecting JA because it provides direct access to the sphenopalatine foramen and the altered vascular structures in this region. Complete tumor removal should include potential plexus remnants near the sphenoid foramen, the pterygoid plate, and the basissphenoid, thereby reducing the risk of recurrence (Howard et al., 2001).

### Vascular Supply

In regard to JA embryological origin, it is essential to perform comprehensive angiographic evaluations of both the external and internal carotid arteries. Such assessments help to delineate the entire tumor blood supply and are critical in avoiding cerebral complications during embolization procedures. Moreover, the embryological perspective may also account for scarce, atypical JA locations (Windfuhr & Vent, 2018) where persistent vascular structures, akin to first branchial arch artery remnants, might be the origin.

### Sex Specificity

The proposed involvement of LH in JA initiation not only explains the tumor's prevalence in adolescent males but also provides insight into its occasional occurrence in early childhood (Newman et al., 2023). Known minor LH peak during early childhood could stimulate sensitive vascular

remnants leading to JA formation. Additionally, clinical observations indicate that anti-androgen therapy results in some tumor shrinkage in post-pubertal patients but not during puberty at the time of elevated LH levels, supporting the idea that LH is the dominant hormonal driver during puberty.

### Fibrovascular Tissue

Histological analyses of JA reveal a transition from densely vascularized areas beneath a pseudo-capsule to regions dominated by fibrous tissue - a pattern consistent with EMT. This observation substantiates the clinical recommendation to avoid biopsies (due to the risk of abundant bleeding) and instead perform resection along the pseudo-capsule. In some cases, tumor involution may occur if the vascular remnants cease proliferating (Tosun et al., 2008), which aligns with the proposed EMT-based mechanisms.

### Embryological JA Nature

The embryological hypothesis for JA is robustly supported by multiple lines of evidence that collectively address its unique features. The detection of persisting neural crest cells and TSHZ1 in JA tissues (Schick et al., 2022; Schick et al., 2011) strongly supports the notion that the tumor arises from remnants of the first branchial arch plexus, thereby explaining its site of origin and characteristic blood supply. Furthermore, the identification of LHR in JA provides a plausible explanation for the near-exclusive manifestation in adolescent males, correlating with the pubertal LH surge (Schick et al., 2014; Wemmert et al., 2024). Finally,

the transformation of vascular tissue into fibrous tissue via EMT accounts for the tumor's dual histological components. Together, these findings offer a comprehensive and unifying explanation for JA pathogenesis. Basically, the embryological model "takes it all."

**Conflict of Interest Disclosures:** The authors declare no conflicts of interest.

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