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Role of embryonic hypoxia and effect of prolyl-hydroxyrase inhibitors in development of craniofacial structures

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During embryogenesis, neural crest cells (NCCs) arise from the neural tube by epithelial-mesenchymal transition (EMT) and differentiate into various cell types. In the cranial region, many NCCs contribute towards facial bones and cartilages, providing the skeletal basis for mandibular and neck structures. A deficit of cranial NCCs results in congenital craniofacial hypoplasia such as Treacher Collins syndrome. In adult tissue hypoxia, Hypoxia-Inducible Factor-1α (HIF-1α) permits cell adaptation to a hypoxic environment by promoting angiogenesis and anaerobic glycolysis, thus aiding tissue recovery. In the normoxic condition, on the other hand, HIF-1α is readily degraded via oxygen-dependent prolyl-hydroxyrases (PHDs). Because of this, chemical compounds that stabilize HIF-1α, such as PHD inhibitors, are used for stroke and heart attack therapies. Other functions of HIF-1α include promotion of EMT and metastasis in tumor and up-regulation of chondrogenesis, both of which are promoted in hypoxic microenvironment. Given that embryos are naturally hypoxic; my group has recently shown that induction of NCCs by EMT is up-regulated by HIF-1α-stabilising PHD inhibitors in chick embryos cultured ex ovo and in ovo. We currently investigate the effect of PHD inhibitors at later stages of embryogenesis, as to whether specific cell fate is particularly increased and whether there is any negative impact on the development of other structures. W found advanced development in some cartilage structures such as bony labyrinth, presumably due to hyperplasia caused by the increase of EMT and promoted chondrogenesis by PHD inhibitors. This is currently under detailed investigation.

Biography

Akshay Kumar has completed his BSc in University of Bristol.

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