ABSTRACT

Cyclooxygenase-2 (COX-2), a member of the Cyclooxygenase family, is an enzyme that plays a crucial role in initiating the biosynthesis of prostanoids, including Prostaglandin E2 (PGE2). Prostanoids are lipid mediators that regulate various cellular functions and physiological processes. COX-2 is known to be involved in inflammation and tissue repair, but its role in embryonic development is less understood. To investigate the impact of COX-2 on embryonic development, we conducted experiments using chick embryos and a specific COX-2 inhibitor called etoricoxib. The inhibition of COX-2 was found to lead to abnormal development in several structures, particularly in the cranial vault, craniofacial region, jaw, eye, and heart.

To understand the underlying molecular mechanisms responsible for these developmental abnormalities, the researchers focused on cranial neural crest cells (CNCCs). CNCCs are a group of migratory cells derived from the neural crest that play a crucial role in the formation of craniofacial structures. The expression patterns of factors influencing CNCC migration were analysed after inhibiting COX-2 with etoricoxib. The results showed that COX-2, through its downstream effector PGE2, regulates the expression of cell adhesion molecules (CDH1, CDH2), their upstream regulators (MSX1, TGF-β), and other factors involved in CNCC migration. The compromised levels of these molecules in etoricoxib-treated embryos suggested that COX-2 is essential for CNCC proliferation and migration during craniofacial development.

Furthermore, the role of COX-2 in heart development was investigated. The gene and protein expression patterns of major mediators of heart development were analysed on specific days (HH12 and HH20) of chick embryo development. Inhibition of COX-2 activity resulted in deranged expression of upstream regulators of cardiac organogenesis (Wnt11, BMP4, SHH) and downstream regulators of myocardial patterning (MYOCD, HAND2, GATA4, GATA5, and GATA6). The reduction in COX-2 activity also hampered cardiomyocyte proliferation and led to an increase in the rate of apoptosis. These molecular changes likely contributed to the observed heart looping defects in etoricoxib-treated chick embryos.

In addition to its impact on craniofacial structures and heart development, COX-2 was also found to play a significant role in eye development. Neural crest cells are crucial in the process of eye development, wherein the embryonic tissues (ectoderm and mesoderm) differentiate into the optic cup, forming the lens and retina. Inhibition of COX-2 resulted in unilateral anophthalmia, reduced eye size, and pigmentation. These abnormalities were associated with

decreased COX-2 activity and PGE2 synthesis. Restoring COX-2 activity by providing DM-PGE2 partially rescued the eye developmental defects. Inhibition of COX-2 also affected the expression of key regulators of early eye development (Wnt11, Bmp7, Snail1, Frzd, Fgf8, and Pax6), further supporting the involvement of COX-2 in eye formation.

In conclusion, this study provides valuable insights into the role of COX-2 during embryogenesis. Inhibiting COX-2 in chick embryos caused multiple developmental defects, primarily affecting vital organs such as craniofacial structures, heart, and the eye. The findings highlight the significance of COX-2 in regulating key developmental processes and shed light on the molecular mechanisms underlying its impact on embryonic development. Further research in this area may lead to a better understanding the role of COX-2 in embryogenesis.