In-Class Activity

Using a grid to summarize research findings across multiple papers

Penrose & Katz recommend a process to find similarities and differences among a group of papers reporting on related research. This activity will give you an opportunity to practice that process on four papers on the fibroblast growth factor receptor-3 (FGFR-3), which is implicated in achondroplasia, a hereditary form of dwarfism. The abstracts for the three papers are reproduced below. The papers are concerned with related issues having to do with the molecular basis of the role of mutations affecting FGFR-3 in this disease.

In this activity you will create a grid (table, really) with four columns representing the four papers and rows for as many topics as you would like (use the paper in the wide—landscape—orientation). These topics will represent findings described in the abstracts. In reality, in doing this process for yourself, you will want to read the abstract, introduction and discussion portions of the papers, but we haven't enough time in class to cover that much information.

The abstracts have specialized vocabulary; you may have to Google terms you don't know.

Hopefully, this activity will provide skills you can use in analyzing the papers you are considering as references for your writing project.

1. Rousseau F, Bonaventure J, Legeai-Mallet L, Pelet A, Rozet JM, Maroteaux P, Le Merrer M, Munnich A. Mutations in the gene encoding fibroblast growth factor receptor-3 in achondroplasia. Nature. 1994 371:252-4.

   Achondroplasia, the most common cause of chondrodysplasia in man (1 in 15,000 live births), is a condition of unknown origin characterized by short-limbed dwarfism and macrocephaly. More than 90% of cases are sporadic and there is an increased paternal age at the time of conception of affected individuals, suggesting that de novo mutations are of paternal origin. Affected individuals are fertile and achondroplasia is transmitted as a fully penetrant autosomal dominant trait, accounting for rare familial forms of the disease (10%). In contrast, homozygous achondroplasia is usually lethal in the neonatal period and affects 25% of the offspring of matings between heterozygous achondroplasia parents. The gene responsible for achondroplasia has been mapped to chromosome 4p16.3 (refs 7, 8); the genetic interval encompassing the disease gene contains a member of the fibroblast-growth-factor receptor (FGFR3) family which is expressed in articular chondrocytes. Here we report the finding of recurrent missense mutations in a CpG doublet of the transmembrane domain of the FGFR3 protein (glycine substituted with arginine at residue 380, G380R) in 17 sporadic cases and 6 unrelated familial forms of achondroplasia. We show that the mutant genotype segregates with the disease in these families. Thus it appears that recurrent mutations of a single amino acid in the transmembrane domain of the FGFR3 protein account for all cases (23/23) of achondroplasia in our series.

2. Sahni M(1), Ambrosetti DC, Mansukhani A, Gertner R, Levy D, Basilico C.FGF signaling inhibits chondrocyte proliferation and regulates bone development through the STAT-1 pathway. Genes Dev. 1999 13:1361-6.

   Several genetic forms of human dwarfism have been linked to activating mutations in FGF receptor 3, indicating that FGF signaling has a critical role in chondrocyte maturation and skeletal development. However, the mechanisms through which FGFs affect chondrocyte proliferation and differentiation remain poorly understood. We show here that activation of FGF signaling inhibits chondrocyte proliferation both in a rat chondrosarcoma (RCS) cell line and in primary murine chondrocytes. FGF treatment of RCS cells induces phosphorylation of STAT-1, its translocation to the nucleus, and an increase in the expression of the cell-cycle

inhibitor p21WAF1/CIP1. We have used primary chondrocytes from STAT-1 knock-out mice to provide genetic evidence that STAT-1 function is required for the FGF mediated growth inhibition. Furthermore, FGF treatment of metatarsal rudiments from wild-type and STAT-1(-/-) murine embryos produces a drastic impairment of chondrocyte proliferation and bone development in wild-type, but not in STAT-1(-/-) rudiments. We propose that STAT-1 mediated down regulation of chondrocyte proliferation by FGF signaling is an homeostatic mechanism which ensures harmonious bone development and morphogenesis.

3. Cho JY, Guo C, Torello M, Lunstrum GP, Iwata T, Deng C, Horton WA. Defective lysosomal targeting of activated fibroblast growth factor receptor 3 in achondroplasia. Proc Natl Acad Sci U S A. 2004 101:609-14.

   Mutations of fibroblast growth factor receptor 3 (FGFR3) are responsible for achondroplasia (ACH) nd related dwarfing conditions in humans. The pathogenesis involves constitutive activation of FGFR3, which inhibits proliferation and differentiation of growth plate chondrocytes. Here we report that activating mutations in FGFR3 increase the stability of the receptor. Our results suggest that the mutations disrupt c-Cbl-mediated ubiquitination that serves as a targeting signal for lysosomal degradation and termination of receptor signaling. The defect allows diversion of actively signaling receptors from lysosomes to a recycling pathway where their survival is prolonged, and, as a result, their signaling capacity is increased. The lysosomal targeting defect is additive to other mechanisms proposed to explain the pathogenesis of ACH.

4. de Frutos CA, Vega S, Manzanares M, Flores JM, Huertas H, Martínez-Frías ML, Nieto MA. Snail1 is a transcriptional effector of FGFR3 signaling during chondrogenesis and achondroplasias. Dev Cell. 2007 13:872-83.

   Achondroplasias are the most common genetic forms of dwarfism in humans. They are associated with activating mutations in FGFR3, which signal through the Stat and MAPK pathways in a ligand-independent manner to impair chondrocyte proliferation and differentiation. Snail1 has been implicated in chondrocyte differentiation as it represses Collagen II and aggrecan transcription in vitro. Here we demonstrate that Snail1 overexpression in the developing bone leads to achondroplasia in mice. Snail1 acts downstream of FGFR3 signaling in chondrocytes, regulating both Stat and MAPK pathways. Moreover, FGFR3 requires Snail1 during bone development and disease as the inhibition of Snail1 abolishes its signaling even through achondroplastic- and thanatophoric-activating FGFR3 forms. Significantly, Snail1 is aberrantly upregulated in thanatophoric versus normal cartilages from stillborns. Thus, Snail activity may likely be considered a target for achondroplasia therapies.