RELEVANCE TO MUSCULOSKELETAL CONDITIONS: The mechanisms regulating the development of articular cartilage are largely unclear. This study describes for the first time the involvement and roles of members of the ets transcription factor family in establishing and maintaining the phenotype of articular chondrocytes, information which may lead to the design of therapeutic means to restore function in diseased articular cartilage.

INTRODUCTION: Articular chondrocytes form at specific sites and times in the early cartilaginous skeleton, and acquire the ability to persist throughout life, to avoid the endo- and endochondral ossification process, to form joints, organize and maintain articular cartilage and its unique matrix. The mechanisms regulating the genesis of articular chondrocytes as well as those by which the cells retain a stable and functional phenotype throughout life are largely unclear, particularly at the molecular level. Recent studies have indicated that members of the ets family of transcription factors participate in skeletogenesis (1). Here we describe  the identification of 3 members of the ets family that are expressed in articular chondrocytes, and the preferential expression of another member in the pre-hypertrophic chondrocyte population. We term this alternative form C-1-1.

METHODS: In situ hybridization on longitudinal sections of 17-day-old chick embryo tibiae was performed using cDNA probes specific for ERG-3 and C-1-1 and a 81-bp probe specific for ERG-3. Using the embryo tibia, a “general” 473-bp probe (that does not distinguish between ERG-3 and C-1-1) was used in control insert-less viruses. Embryos were reincubated and examined at day 21 of development. To extend these observations to the in situ conditions, C-1-1-positive and ERG-3-negative significant signals were found in the pre-hypertrophic zone of the growth plate and in the post-hypertrophic zone, and strong promoter activity. Interestingly, virally-driven expression of C-1-1 in chick embryo chondrocyte cultures induced strong tenascin-C gene expression and strongly reduced APase activity. Interestingly, virally-driven expression of ERG-3 did not result in any significant effects.

DISCUSSION: The results of the study show for the first time that the ets family factors C-1-1 and ERG-3 participate and play distinct roles in skeletal development. We showed that C-1-1 is normally expressed in epiphyseal chondrocytes and when overexpressed in cultured chondrocytes or in vivo, it maintains the cells in a differentiated state but blocks their development into hypertrophic cells and their subsequent functions. C-1-1 can also induce strong gene expression of tenascin-C gene, a matrix protein that characterizes articular chondrocytes, and strong activation of a tenasin-C gene promoter reporter construct. We have shown that ERG-3 is instead expressed in the pre-hypertrophic zone of growth plate and when overexpressed in vitro, it actually favors the development of chondrocytes into mature hypertrophic and mineralizing cartilage, which is enriched in type X collagen, APase activity and apatitic crystals. Our knowledge, C-1-1 is the first transcription factor identified to date which is involved in the genesis of articular chondrocytes and which maintains chondrocytes in a stable differentiated unique phenotype while preventing their maturation. C-1-1 may thus have a key role in establishing and maintaining articular cartilage for life. Its family member ERG-3 displays opposite properties and promotes completion of chondrocyte development and maturation. ERG-3 is thus likely to have roles in the normal replacement of hypertrophic cartilage with endochondral bone.