Environmental Control of Gene Regulation

Introduction: The expression of genes in an organism can be influenced by the environment, including the external world in which the organism is located or develops, as well as the organism's internal world, which includes such factors as its hormones and metabolism. One major internal environmental influence that affects gene expression is gender, as is the case with sex-influenced and sex-limited traits. Similarly, drugs, chemicals, temperature, and light are among the external environmental factors that can determine which genes remain switched on and off, thereby influencing the way an organism develops and functions.

Some evidences are as follows:

1. ***Effect of environmental chemicals:***
   a) The presence of drugs or chemicals in an organism's environment can also influence gene expression in the organism. Cyclops fish are a dramatic example of the way in which an environmental chemical can affect development. In 1907, researcher C. R. Stockard created cyclopean fish embryos by placing fertilized *Fundulus heteroclitus* eggs in 100 mL of seawater mixed with approximately 6 g of magnesium chloride. Normally, *F. heteroclitus* embryos feature two eyes; however, in this experiment, half of the eggs placed in the magnesium chloride mixture gave rise to one-eyed embryos.
   b) A second example of how chemical environments affect gene expression is the case of supplemental oxygen administration causing blindness in premature infants. In the 1940s, supplemental oxygen administration became a popular practice when doctors noticed that increasing oxygen levels converted the breathing pattern of premature infants to a "normal" rhythm. Unfortunately, there is a causal relationship between oxygen administration and retinopathy of prematurity (ROP), although this relationship was unknown at the time; thus, by 1953, ROP had blinded approximately 10,000 infants worldwide. Finally, in 1954, a randomized clinical trial identified supplemental oxygen as the factor causing blindness. Complicating the issue is the fact that too little oxygen results in a higher rate of brain damage and mortality in premature infants. Unfortunately, even today, the optimal amount of oxygenation

necessary to treat premature infants while completely avoiding these complications is still not clear.

2. ***Effect of Drugs:***

Thalidomide is a potent teratogen that induces a range of birth defects, most commonly of the developing limbs. Half a century ago, thalidomide was used for its antiemetic properties by pregnant women worldwide. It caused an increase in miscarriage and still birth rates and a 40% increase in infant mortality and up to 10,000 children around the world were born with severe limb malformations, as well as other much less common congenital defects. Children with such defects are still being born today, particularly in Africa and South America, where thalidomide is now increasingly used in treating leprosy. Over 80% of children born to mothers who took thalidomide had limb defects. These defects ranged from absence of the limb (amelia) or proximal limb elements (phocomelia) to loss of the thumb or digit tip and are induced in a small time-sensitive developmental window. The genetic processes that control limb development are complicated and still not fully understood, but several gene families are known to be involved in the spatially and temporally coordinated growth and differentiation of the developing limb. Some of these genes are involved in the initiation and patterning of both the upper and the lower limbs, and others are differentially expressed in the developing forelimb and hindlimb. Regarding phocomelia, retinoic acid (RA) signaling may be important since it affects the expression of *Meis1/2*, which expands distally on RA treatment. On the other hand, the distal expression of *Hox* genes is reduced, revealing that exogenous RA proximalizes the limb-bud mesenchyme RA is synthesized in the proximal mesenchyme and spreads into the distal limb bud, in which it is actively degraded so that high levels of RA would specify proximal cell fates and inhibit distal ones. In fact, the genetic inactivation of CYP26B1, an enzyme involved in the degradation of RA may play a role. Genes encoding many other secreted signaling molecules are expressed in the limb, for example, insulin-like growth factor (IGF), platelet-derived growth factor (PDGF), etc., and diffusible signaling molecules, such as retinoic acid, have also been shown to contribute to generating the pattern of the limb buds. Genes that encode molecules involved in direct cell–cell signaling such as the

Notch/Delta system, and Ephrins/Ephrin receptors are expressed in the developing limb and these interactions may fine-tune the limb bud pattern and/or govern local cell behaviour. Several genes encoding transcription factors have been identified that are expressed in specific domains in the developing limb in response to signaling along antero-posterior, proximodistal, and dorso-ventral axes. These include the 5' genes of the *Hox A* and *D* clusters, *LIM, Tbx, Sall*, and *Shox* genes. Functional inactivation of these genes in mice and/or their mutations, such as in *SHOX* , in human patients, lead to limb defects indicating that these genes play a role in the generation of limb bud pattern.

Syndromes or Defined Phenotypes Presenting With Phocomelia [Winter and Baraitser, 2010; OMIM, 2011]

Syndrome or defined phenotype	***OMIM number, or reference***	***Location***	***Gene/locus***
Acrofacial dysostosis-type Rodríguez	201170	—	—
Alveolar capillary dysplasia with misalignment of pulmonary veins.	265380	2q35; 16q24	*CPS1; FOXF1*
Baraitser-brachyphalangia-polydactyly	609945	—	—
Cornelia de Lange syndrome 1 (Brachmann-de Lange syndrome)	122470	5p13.2	*NIPBL*

3. Effect of temperature:

a) Temperature and light are external environmental factors that may influence gene expression in certain organisms. For example, Himalayan rabbits carry the C gene, which is required for the development of pigments in the fur, skin, and eyes, and whose expression is regulated by temperature. Specifically, the C gene is inactive above 35°C, and it is maximally active from 15°C to 25°C. This temperature regulation of gene expression produces rabbits with a distinctive coat coloring. In the warm, central parts of the rabbit's body, the gene is inactive, and no pigments are produced, causing the fur color to be white. Meanwhile, in the rabbit's extremities (i.e., the ears, tip of the nose, and feet), where the temperature is much lower than 35°C, the C gene actively produces pigment, making these parts of the animal black.

b) One of the best-studied reptiles is the European pond turtle, *Emys obicularis.* In laboratory studies, incubating *Emys* eggs at temperatures above 30°C produces all females, while temperatures below 25°C produce all-male broods. The threshold temperature (at which the sex ratio is even) is 28.5°C. The developmental period during which sex determination occurs can be discovered by incubating eggs at the male-producing temperature for a certain amount of time and then shifting the eggs to an incubator at the female-producing temperature (and vice versa). In *Emys*, the last third of development appears to be the most critical for sex determination. It is not thought that turtles can reverse their sex after this period. It appears that the enzyme **aromatase** (which can convert testosterone into estrogen) is important in temperaturedependent sex determination. The estrogen synthesis inhibitors used in the experiments mentioned above worked by blocking the aromatase enzyme, showing that experimentally low aromatase conditions yield male offspring. This correlation is seen to hold under natural conditions as well. The aromatase activity of *Emys* is very low at the male-promoting temperature of 25°C. At the female-promoting temperature of 30°C, aromatase activity increases dramatically during the critical period for sex determination. Temperature-dependent aromatase activity is also seen in diamondback terrapins, and its inhibition masculinizes their gonads. One

remarkable finding is that the injection of an aromatase inhibitor into the eggs of an all-female parthenogenetic species of lizards causes the formation of males. It is not known whether the temperature sensitivity resides in the aromatase gene or protein itself or in other proteins that regulate it. One hypothesis is that the temperature is sensed by neurons in the central nervous system and transduced to the bipotential gonad by nerve fibers. Another hypothesis is that aromatase activity may be regulated by *Sox9*. This sex-determining gene is seen throughout the vertebrates, where its expression in gonads correlates extremely well with the production of testes. When two species of turtles were raised at female-promoting temperatures, *Sox9* expression was down-regulated during the critical time for sex determination. However, in the bipotential gonads of those turtles raised at male-promoting temperatures, *Sox9* expression was retained in the medullary sex cords destined to become Sertoli cell.

4. ***Effect of light:***

Light can also influence gene expression, as in the case of butterfly wing development and growth. For example, in 1917, biologist Thomas Hunt Morgan conducted studies in which he placed *Vanessa urtica* and *Vanessa io* caterpillars under red, green, or blue light, while other caterpillars were kept in the dark. When the caterpillars developed into butterflies, their wings showed dramatic differences. Exposure to red light resulted in intensely colored wings, while exposure to green light resulted in dusky wings. Blue light and darkness led to paler colored wings. In addition, the *V. urtica* butterflies reared under blue light and *V. io* butterflies reared in the dark were larger than the other butterflies.

General discussion:

The environment can play a significant role in the production of phenotypes. However, the developmental mechanisms by which the environment can affect normal development are only now being elucidated. At least three paths have been found through which the environment can modify gene expression. The first is the neuroendocrine route, wherein the nervous system

transmits signals from the environment to the endocrine system and the hormones alter gene expression. The second pathway involves environmental agents that change the methylation pattern of genes, thereby altering their transcriptional capacities. The third route involves the direct induction of gene expression in the host by its microbial symbionts. The normal environmental regulation of phenotype production should be considered a normal component of development and developmental biology and further detailed studies are required on the environmental regulation of gene expression during developmental phases.

References:

- **Christina Therapontos *et al.*, 2009.**
- **Eva Bermejo-Sánchez *et al.*, 2011.**
- **Gilbert 2004.**
- **Lobo, I. 2008.**