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Guaramaca clara en zapotelron is a crucial element involved in a variety of vital cellular processes including electron transport, antioxidant defense, and DNA synthesis. The iron-regulatory hormone hepcidin regulates iron absorption, tissue distribution and storage. In addition, hepcidin has been implicated in both human and murine anemias associated with ineffective erythropoiesis. Hepcidin functions as a hormone in mammals and synthesized as a pro-hormone in hepatocytes. Processing involves endoproteolytic cleavage of the precursor polypeptide (prohepcidin) to form mature hepcidin. Although the complete structure of the human hepcidin promoter has not been determined, it is known that the 5'-flanking region of the human hepcidin gene contains a TATA box, and a GATA-1 binding motif. The 5'-flanking region of the murine hepcidin gene has been studied in detail but contains a single TATA box and one GATA-1 binding site. The overall goal of this proposal is to define the cis-acting elements of the hepcidin promoter and examine their role in the regulation of hepcidin expression during erythropoiesis and erythroid differentiation. We will concentrate on three specific aims: 1. To identify hepcidin binding site(s) within the human and murine promoters, using a combination of bioinformatics and functional analyses of promoter sequences; 2. To define the transcription factors that bind to the hepcidin promoter in human and murine cell lines; and 3. To examine the role of hepcidin in the regulation of hepcidin expression during erythropoiesis and erythroid differentiation. We will use molecular and cellular approaches to investigate the effect of different types of iron on hepcidin expression in the human erythroleukemia cell line K562 and primary murine erythroid cells. We will examine the role of GATA-1 in hepcidin regulation using gain- and loss-of-function approaches, and study the regulation of hepcidin expression in a GATA-1 conditional knock-out mouse model. We will also define the role of hepcidin in erythroid differentiation by examining the effect of iron on hepcidin mRNA and protein expression in K562 cells using different concentrations of iron. Our c6a93da74d

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