Chapter 6

EPIGENETIC DYSREGULATION OF MASPIN (SERPINB5) IN CANCER INVASION AND METASTASIS

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Abstract: The goal of this chapter is to promote the value of studying maspin regulation as a paradigm for loss of transcriptional control during cancer progression and to highlight the importance of this endeavor in developing a comprehensive picture of the epigenetics of the malignant phenotype. We will attempt to do this through a discussion of the structure and functions of the serpin superfamily of proteins, with an emphasis on maspin, its discovery as a tumor suppressor, and its functional role in cancer. The control of maspin expression in normal tissue by epigenetic mechanisms will be described and how this underlying mechanism is compromised in cancer leading to the inappropriate silencing of maspin in cancers derived from maspin-positive cell types, as well as the activation of maspin in cancers derived from normally maspin-negative cell types. Finally, we will close with speculation that maspin may represent an inaugural member of a class of cell-type restricted genes involved in cancer cause and progression that are controlled by epigenetic mechanisms. During transformation, epigenetic instability and mischief results in a loss of control in the expression of these genes. We propose that these genes, through metastable epigenetic switching mechanisms, can be turned off and on in response to environmental stresses and cues in the cancer cell, thereby allowing tumor cells a phenotypic plasticity that appears necessary for the challenges a tumor cell and its progeny must undertake to migrate from primary tumor site to distant metastatic site. It is proposed that this epigenetic switch can be targeted by therapeutics designed to transcriptional reprogram tumor cells and flip the switch back to non-malignant behavior.

Key words: maspin, methylation, histone, chromatin, tissue-specific, expression, p53

1. SERPINS AND MASPIN

Serpins (Serine Proteinase Inhibitors) are a super family of proteins with hundreds of members distributed through the Animal and Plant kingdoms (1). Examples of serpins are also found in viruses, but homologs have not been identified in prokaryotes or fungi. Additionally, serpins are found in some model organisms (D. Melanogaster, C. Elegans, and A. Thaliana), but not others (S. Pombe, Cerevisiae). Serpins are important to human health and disease because of their roles in disparate biochemical pathways, which include blood homeostasis, hormone transport, and neuronal function (2). As such, disruption of normal serpin function through mutation or loss of expression contributes to a wide range of human diseases that include cirrhosis, emphysema, dementia, and cancer (3).

Serpins are variable glycosylated proteins that are monomers in their active state. The typical serpin is 350 to 500 amino acids and folds into 3 beta sheets, 9 alpha helices, and a reactive site loop (RSL) necessary for cognate proteinase recognition and subsequent suicide substrate-like inhibition (2). Most serpins inhibit serine proteinases of the chymotrypsinogen family; however, some serpins are able to inhibit cysteine proteinases, such as cathepsins. Not all serpins are protease inhibitors, however, with one example being cortisol binding globulin. While still not fully resolved, maspin appears to be another example of a non-inhibitory serpin, or at least a serine protease inhibitor with additional functions (4-7).

Analysis of 219 serpin sequences from animals, plants and viruses produced a phylogenetic tree that divides the serpins into 16 branches or clades (families) (1). These 16 clades are categorized A through P and are named based on their prototypical member. Maspin is a member of clade B and is named the ovalbumin, intracellular family of serpins (ov-serpins). The ov-serpins can be found in gene clusters on chromosomes 6 and 18 (8). Maspin, whose RefSeq name is SerpinB5 (clade B, member 5), is found on chromosome 18.q21.33 along with many other serpins of the ov-serpin class that are from centromere to telomere serpin B5 (Maspin), B12, B13 (Hurpin), B4 (SCCA2), B3 (SCCA1), B11, B7 (Mgsin), B2 (PAl2), B10 (Bomapin), and B8 – the names in parentheses refer to the gene’s common name.

2. MASPIN DISCOVERY

Maspin or mammary serpin was one of the first tumor suppressor genes cloned using expression genetics, which followed the idea that investigation of heredity at the level of RNA and gene expression would reveal many new