The Biology Behind


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The protein now known as OPN\(^2\) was first identified and characterized in two contexts: (a) in bone as a phosphorylated sialoglycoprotein \(^1\); and (b) in cultures of transformed cells as transformation-related phosphoprotein \(^2\). The rat cDNA encoding the bone protein was cloned from an osteosarcoma cell line and named OPN because of its ability to form a bridge between bone cells and bone matrix \(^3\). Mouse OPN was cloned as 2ar, a cDNA clone identified in a differential screen as corresponding to a mRNA that was strongly induced in mouse JB6 epidermal cells by the tumor promoter 12-O-tetradecanoylphorbol-13-acetate \(^4\). Thus from the time it was first discovered, both as a protein and as a cDNA, there was the implication that OPN might be important in cancer biology. It is interesting that at about the same time a number of laboratories cloned OPN in a number of different contexts, for example as Eta-1 (early T-lymphocyte activation gene 1; Ref. 5) and as 2B7, a rat smooth muscle cell mRNA elevated in hypertension \(^6\). The human cDNA was cloned and characterized by Young et al. \(^7\). Why was this gene identified at about the same time in such different contexts? One answer is that as a secreted protein, OPN mRNA levels must be substantially induced in a short time to produce sufficient protein to impact significantly on the extracellular environment.

OPN was subsequently discovered to be a ras-responsive gene; it was ras responsive in that its mRNA levels were substantially increased in Ras-transformed cells or after Ras activation \(^8–10\). Furger et al. \(^11\) have reviewed the involvement of OPN in malignant processes, with a focus on human breast cancer. Le et al. \(^12\) now report in this issue of Clinical Cancer Research that OPN is a prognostic plasma marker for HNSCCs. This is an exciting development because it provides a new diagnostic for solid tumors that have been notoriously difficult to relate to a plasma marker. HNSCC is unfortunately a rather common malignancy that is subject to tumor recurrence and a negative outcome.

Why OPN? How does hypoxia enhance its expression, and what is its role in tumor progression? It was noted as early as 1994 \(^22\) that hypoxia (and subsequent reoxygenation) can increase
OPN expression in proximal tubule epithelial cells. More recently, sodhi et al. (23) have reported that exposure of cultured rat aortic vascular smooth muscle cells to hypoxia results in a biphasic enhancement of OPN mRNA levels, with peaks at about 2 and 24 h. The basis for increased OPN expression under hypoxic conditions is not known. With regard to its role in tumor progression, a number of possibilities have been suggested (24). OPN is both a cell attachment molecule and a cell signaling molecule, able to engage a number of receptors including several integrins and CD44 variants. Genes whose expression has been reported to be affected include inducible nitric oxide synthase, nuclear factor-kB, vascular endothelial growth factor, urokinase-type plasminogen activator, and Met, the receptor for hepatocyte growth factor (11, 24). OPN, which is strongly up-regulated in many inflammatory processes, can support cell survival, stimulate cell migration, and increase expression of other genes involved in invasive events, notably matrix metalloproteinases, and promote tumor angiogenesis (25–27). In short, the evidence is overwhelming that OPN contributes to tumor progression and aggressiveness in many circumstances. This is the significance of the finding by Le et al. (12) that the elevated OPN levels accompanying hypoxic HNSCC are indicative of a poor prognosis.

References


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