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Transformation by the v-*fms* Oncogene Product: An Analog of the CSF-1 Receptor

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The product of the c-*fms* proto-oncogene is related to, and possibly identical with, the receptor for the macrophage colony-stimulating factor, M-CSF (CSF-1). Unlike the product of the v-*erb*B oncogene, which is a truncated version of the EGF receptor, the glycoprotein encoded by the v-*fms* oncogene retains an intact extracellular ligand-binding domain so that cells transformed by v-*fms* express CSF-1 receptors at their surface. Although fibroblasts susceptible to transformation by v-*fms* generally produce CSF-1, v-*fms*-mediated transformation does not depend on an exogenous source of the growth factor, and neutralizing antibodies to CSF-1 do not affect the transformed phenotype. An alteration of the v-*fms* gene product at its extreme carboxyl-terminus represents the major structural difference between it and the c-*fms*-coded glycoprotein and may affect the tyrosine kinase activity of the v-*fms*-coded receptor. Consistent with this interpretation, tyrosine phosphorylation of the v-*fms* products in membranes was observed in the absence of CSF-1 and was not enhanced by addition of the murine growth factor. Cells transformed by v-*fms* have a constitutively elevated specific activity of a guanine nucleotide-dependent, phosphatidylinositol-4,5-diphosphate-specific phospholipase C. We speculate that the tyrosine kinase activity of the v-*fms*/c-*fms* gene products may be coupled to this phospholipase C, possibly through a G regulatory protein, thereby increasing phosphatidylinositol turnover and generating the intracellular second messengers diacylglycerol and inositol triphosphate.

Key words: growth factors, tyrosine-specific protein kinase, phospholipase C, second messengers

THE v-*fms* ONCOGENE PRODUCTS

Transforming oncogenes of retroviruses (v-*onc* genes) are generated by recombination between replicating viral vectors and cellular proto-oncogenes (c-*onc* genes) that are presumed to play pivotal roles in controlling normal growth and differentiation [1]. Structural alterations in v-*onc* genes and their inappropriate expression owing

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to retroviral transduction are responsible for the ability of the recombined genes to cause neoplastic tumors in animals and to transform cultured cells. The study of viral transforming genes and their proto-oncogene progenitors has therefore begun to provide insights into the mechanisms by which normal cells are transformed into their malignant counterparts.

The v-*fms* oncogene of the Susan McDonough strain of feline sarcoma virus (SM-FeSV) was isolated from a spontaneously arising fibrosarcoma of a domestic cat [2]. The virus is able to transform fibroblast cell lines from several mammalian species [3], and, similarly, the molecularly cloned SM-FeSV provirus is biologically active in transforming mouse NIH/3T3 fibroblasts after DNA-mediated transfection [4]. Nucleotide sequencing of the SM-FeSV genome revealed that v-*fms* coding sequences were transduced into the viral *gag* gene in the same reading frame [5]. The primary translation product was predicted to be a *gag-fms* fusion polyprotein consisting of 536 amino-terminal *gag*-coded residues and 975 carboxyl-terminal v-*fms*-coded amino acids. Addition of carbohydrate to the polypeptide chain yields a 180-kilodalton (kDa) glycoprotein (gP180$^{gag\text{-}fms}$) containing asparagine (N)-linked oligosaccharide chains. Some of the gP180$^{gag\text{-}fms}$ molecules are cotranslationally cleaved at a site near the *gag-fms* junction to generate two distinct products: an unglycosylated 55-kDa fragment that is precipitated by antibodies to *gag*-coded determinants and a 120-kDa v-*fms*-coded glycoprotein (gp120$^{v\text{-}fms}$) [6,7]. Both gP180$^{gag\text{-}fms}$ and gp120$^{v\text{-}fms}$ contain oligosaccharides of the high-mannose type typical of immature glycoproteins. Some gp120$^{v\text{-}fms}$ molecules are transported through the Golgi compartment, where their N-linked oligosaccharides are processed to complex carhbohydrate chains, and on to the plasma membrane, where they are detected as glycoproteins of greater apparent molecular weight (gp140$^{v\text{-}fms}$) [8,9]. Once expressed at the cell surface, the gp140$^{v\text{-}fms}$ molecules become associated with clathrin-coated pits and are returned in endocytic vesicles to the interior of the cell, where they are probably degraded [10].

The location of hydrophobic segments within gP180$^{gag\text{-}fms}$ suggested a model for the transmembrane orientation of the v-*fms*-coded glycoprotein during translocation [11,12]. Vectorial transfer of newly synthesized molecules into the lumen of the endoplasmic reticulum (ER) proceeds until a segment of 26 hydrophobic amino acids is encountered near the middle of the v-*fms*-coded sequence. This hydrophobic peptide was predicted to stop translocation and to anchor the v-*fms*-coded glycoprotein in the membrane with its amino-terminal portion in the lumen of the ER and its carboxyl-terminal 406 amino acids in the cytoplasm. Canonical sites for addition of N-linked oligosaccharides (Asn-X-Ser/Thr) are clustered in the v-*fms*-coded sequence on the amino-terminal side of the transmembrane segment where they are accessible to glycosyl transferases within the ER cisternae. Intracellular transport via membrane vesicles would be expected to orient gp140$^{v\text{-}fms}$ at the cell surface with its glycosylated amino-terminal domain outside the cell and its carboxyl-terminal domain at the cytoplasmic face of the plasma membrane. This transmembrane orientation of the v-*fms*-coded glycoproteins was confirmed experimentally [12].

The cytoplasmic carboxyl-terminal domain of the v-*fms* gene product shares amino acid sequence homology with the products of other oncogenes that code for tyrosine-specific protein kinases [5]. When the v-*fms*-coded glycoproteins are precipitated with appropriate antisera and incubated with radiolabeled ATP in the presence of Mn^{++} ions, an associated kinase activity transfers the γ-phosphate from the

nucleotide onto tyrosyl residues of the oncogene product itself or to exogenously added protein substrates [13]. A series of v-*fms* mutants encoding products that lack the associated kinase activity do not transform cells, suggesting that this enzymatic function is required for transformation. However, unlike prototypic members of the tyrosine kinase family of retroviral oncogenes, the v-*fms* products themselves are not extensively phosphorylated on tyrosine residues in vivo, and cells transformed by SM-FeSV do not exhibit an increase of the phosphotyrosine detected in total cellular proteins.

Intracellular transport of the v-*fms* oncogene product positions the carboxyl-terminal kinase domain of gp140$^{v\text{-}fms}$ at the inner surface of the plasma membrane. This subcellular localization is shared by the products of several other oncogenes [14–19], suggesting that the intracellular targets for transforming signals generated by these proteins are at or near the plasma membrane. Indeed, transformation is blocked by mutations in the polypeptide chain [20] or by inhibitors of glycosylational processing [21] that prevent cell surface expression of the v-*fms* gene product. The topological features of the v-*fms*-coded glycoprotein are similar to those of a family of cell surface receptors for polypeptide growth factors that exhibit a ligand-stimulated tyrosine-specific protein kinase activity. The glycosylated amino-terminal portion is analogous to the extracellular ligand-binding domain of a receptor linked by the transmembrane segment to an intracellular signal-transducing function (the kinase domain). A relationship between oncogenes and growth factors or their receptors is also evident from the findings that the v-*sis* oncogene product is homologous to a chain of the platelet-derived growth factor (PDGF) [22,23], and the v-*erb* B oncogene product represents a truncated form of the receptor for epidermal growth factor (EGF) [24].

THE c-*fms* PROTO-ONCOGENE PRODUCT AND CSF-1 RECEPTOR

Although the properties of the v-*fms* product strongly suggested that it was derived from a proto-oncogene coding for a cell surface receptor, the identity of that receptor was unknown. To deduce the function of the c-*fms* proto-oncogene product, expression of the c-*fms* gene was assayed in different tissues of the domestic cat. High levels of a polyadenylated c-*fms* RNA about 4 kilobases in length were detected in spleen, whereas significantly lower levels of transcripts were found in liver, lymph nodes, bone marrow, and brain [25]. When monoclonal antibodies to v-*fms*-coded epitopes [8] and the immune complex kinase reaction were used, c-*fms*-coded glycoproteins of 130 kDa and 170 kDa were detected in cat splenocytes and were phosphorylated on tyrosine residues by an associated enzymatic activity. The patterns of glycosylation of the c-*fms*-coded products were analogous to those of the glycoproteins encoded by v-*fms*, suggesting that feline gp130$^{c\text{-}fms}$ is a precursor of the mature cell surface form, gp170$^{c\text{-}fms}$ [25]. Fluorescence-activated flow cytometry performed with the same monoclonal antibodies demonstrated that expression of the cat c-*fms* gene product was primarily restricted to macrophages [26]. Although these monoclonal antibodies to feline v-*fms*-coded epitopes do not react with c-*fms*-coded glycoproteins in species other than the domestic cat, antisera to a recombinant v-*fms*-coded polypeptide expressed in bacteria precipitated c-*fms*-coded molecules from mouse [26] and man [27,28]. Again, the expression of the c-*fms* gene product in somatic

tissues from these other species was primarily restricted to cells of the mononuclear phagocyte series, including peripheral blood monocytes and tissue macrophages.

Since the only known growth factor specific in its action for mononuclear phagocytes is the macrophage colony-stimulating factor CSF-1 (M-CSF) [29], a possible relationship between the c-*fms* gene product and CSF-1 receptor was investigated. Purified CSF-1 from mouse L cells was found to bind with high affinity to the murine c-*fms* gene product, and, in membrane preparations, it enhanced tyrosine-specific phosphorylation of the c-*fms*-coded glycoprotein [26]. The viral oncogene product, gp140$^{v\text{-}fms}$, was also found to specifically bind murine CSF-1, so that cells transformed by SM-FeSV acquire CSF-1 binding sites on their surface [30]. These results suggest that the c-*fms* proto-oncogene is closely related to, and possibly identical with, the gene encoding the receptor for CSF-1. However, because the amino acid sequence of the purified CSF-1 receptor has not yet been determined, there is as yet no formal proof that these are identical genes.

MECHANISMS OF TRANSFORMATION

An implication of these findings is that the mechanism of viral transformation may involve the transduction of a competent receptor gene into cells that synthesize the corresponding growth factor. Indeed, CSF-1 is normally produced by mesenchymal cells in the bone marrow [29] and also by fibroblast cell lines susceptible to transformation by SM-FeSV [30]. SM-FeSV-mediated transformation does not depend on an exogenous source of CSF-1, and neutralizing antibodies to CSF-1 do not affect the transformed phenotype [30]. It remains formally possible that an interaction between the colony-stimulating factor and the v-*fms*-coded receptor might occur intracellularly within the secretory compartment. However, it seems more likely that rearrangement of the v-*fms* gene product at its extreme carboxyl-terminus [31] or more subtle mutations at other positions within the polypeptide affect the kinase activity of the viral-coded receptor so that the enzyme either acts constitutively, has enhanced activity in the presence of ligand, or phosphorylates substrates not recognized by its normal cellular counterpart.

It is intriguing that deletions of the long arm of human chromosome 5 at bands q33.2–q34, the site of the c-*fms* locus [32,33], are associated with a variety of hematopoietic disorders including refractory anemia, myelodysplastic syndromes, and therapy-related acute nonlymphocytic leukemias (ANNL) [34–37]. This raises the possibility that rearrangements at or near the c-*fms* locus may contribute in some way to the altered hematopoiesis seen in these disorders. Deletion of c-*fms* has been demonstrated both in cases of the 5q− refractory anemia syndrome and in ANNL [38,39], although the locations of the precise breakpoints in the long arm of chromosome 5 remain unknown. Moreover, the genes coding for both CSF-1 [39] and for the granulocyte-macrophage colony-stimulating factor (GM-CSF) [40,41] map to a neighboring region of chromosome 5q implying that the observed deletions may affect any of these genes or, perhaps, additional genes regulating hematopoiesis that cluster within this region. Although rearrangements of c-*fms*, GM-CSF, and the CSF-1 genes have not yet been documented in ANNL, a search for such alterations now seems warranted.

Although the CSF-1 receptor has been defined through its role in hematopoiesis, c-*fms* transcripts are also detected at high levels in placental trophoblasts and in

malignant choriocarcinoma cell lines [42]. As predicted, the human c-*fms* gene product was detected in several independently derived human choriocarcinoma cell lines and was identical in its biochemical properties with the c-*fms*-coded glycoprotein precipitated from monocytes and macrophages [27,28]. Thus, the CSF-1 receptor may play some additional role in placental development that differs from its function in adult tissues.

GUANINE-NUCLEOTIDE-DEPENDENT PHOSPHOLIPASE C IN v-*fms* TRANSFORMANTS

The identity of the intracellular target(s) of the CSF-1 receptor kinase and the v-*fms*-coded transforming glycoprotein is unknown, but the generation of phosphatidylinositol(PtdIns)-derived second messengers may be physiologically important. The catalytic component of this signaling system is a hormone-responsive, PtdIns 4,5-diphosphate (PtdIns-P_2) phospholipase C that hydrolyzes PtdIns-P_2, giving rise to inositol 1,4,5-triphosphate (Ins(1,4,5)-P_3) and diacylglycerol. The liberated Ins(1,4,5)-P_3 mobilizes calcium from intracellular stores, thereby activating a host of calcium-regulated functions, and the diacylglycerol stimulates the phosphorylation of a number of proteins via the activation of protein kinase C [43–45]. These two intracellular effector molecules are capable of eliciting a wide range of biological responses, and their production is stimulated following the exposure of cells to many growth-promoting polypeptide hormones [46–58].

Enhanced PtdIns turnover is also associated with cell transformation induced by a variety of oncogenes and chemical agents [59–67]. Our recent observations that cells transformed by the v-*fms* or v-*fes* oncogenes have elevated specific activities of guanine-nucleotide-dependent PtdIns-P_2 phospholipase C suggest that an increase in this enzymatic activity may be responsible for the higher rates of PtdIns turnover exhibited by these cells [67]. The levels of PtdIns turnover and membrane-associated PtdIns-P_2 phospholipase C activity were higher in v-*fes* transformants than in v-*fms* transformants, correlating with the relative activities of these transforming proteins as tyrosine-specific protein kinases in vivo [13,68]. It is therefore tempting to speculate that the tyrosine kinase activities of these oncogene products are responsible for the increased PtdIns-P_2 phospholipase C activity. The tyrosine kinases may directly activate the phospholipase C or may alter the properties of an intermediate transducing protein (G-protein) that mediates the interaction of receptors and catalytic units. The removal of an endogenous phospholipase C inhibitor could also account for these results.

If the v-*fms*-coded glycoprotein activates PtdIns metabolism, we would anticipate that CSF-1 would also fall within the class of polypeptide growth factors that mediate a rapid PtdIns response. In Balb/c 3T3 fibroblasts, growth factors act synergistically in stimulating DNA synthesis and have been classified according to their biological effects by "order of addition" experiments. For example, PDGF does not need to be continually present during the cell cycle, but exerts its action in the GO/G1 transition and renders 3T3 fibroblasts "competent" to begin traversing the cell cycle [69]. PDGF-primed cells require a second hormone (ie, EGF or insulin) to initiate a round of division, and these latter "progression" factors must be present throughout the G1 phase of the cell cycle to exert their effects [70]. In contrast to PDGF, EGF and insulin apparently do not stimulate PtdIns hydrolysis in Balb/c 3T3

fibroblasts [71]. Thus, competence factors in these cells are associated with the activation of PtdIns metabolism, whereas progression factors do not elicit a PtdIns response. Other fibroblast cell lines do not obey these rules [72,73], and whether the action of CSF-1 can be classified by an analogous scheme remains unclear. CSF-1 stimulates mouse bone marrow-derived macrophages to enter S phase and appears to be necessary throughout the duration of G1 [74]. However, recent experiments demonstrating that the human c-*fms* gene product and the mouse PDGF receptor are closely related to one another [75] suggest that the PDGF and the CSF-1 receptor kinases might phosphorylate a similar class of physiologic target molecules.

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