Monocyte chemoattractant protein 1 in luteolysis

Lesley A. Penny*

Department of Veterinary Clinical Studies, University of Edinburgh, Easter Bush Veterinary Centre, Easter Bush, Roslin, Midlothian EH25 9RG, UK

Monocyte chemoattractant protein 1 (MCP-1) is a member of the chemokine family of cytokines which are involved in leukocyte physiology and trafficking. Interest in the role of inflammatory cells and their cytokine products in luteolysis has been increasing and there is mounting evidence demonstrating that MCP-1 is involved in luteolysis. Cell sources of MCP-1, such as endothelial cells, are abundant in late stage luteal tissue. Increased amounts of mRNA encoding MCP-1 are found after luteolysis in sheep, pigs, cows and women and its up-regulation is associated with an increase in macrophages within the corpus luteum, indicating that MCP-1 may act as an inflammatory mediator during luteal regression. Luteolytic substances (prolactin in rats and prostaglandin F2α in ruminants) appear to be involved in increased expression of MCP-1 within the corpus luteum, although it is unclear whether this is a direct or indirect effect. Cytokines produced within the corpus luteum around luteolysis may also be involved in regulating MCP-1 expression. The field of chemokine biology is expanding rapidly and MCP-1, as well as other chemokines yet to be investigated, may prove to be an important link between the hormonal and cellular events within the corpus luteum around the time of luteolysis.

Chemokines are a family of low molecular weight cytokines that have been widely investigated (for review, see Rollins, 1997) and it has become apparent that their function is not restricted to leukocyte chemotaxis and activation but that they are also involved in physiological processes including angiogenesis, haematopoiesis and various diseases such as rheumatoid arthritis and multiple sclerosis (Bacon and Oppenheim, 1999; Gale and McColl, 1999). Research into chemokines increased when it was discovered in 1996 that some of their receptors act as binding sites for the human immunodeficiency virus (HIV).

Four chemokine families have been defined, and the total number of chemokines identified has expanded markedly (for a review of new chemokines and receptors, see Zlotnik et al., 1999). The majority of chemokines belong to two subfamilies, CXC chemokines (α) and CC chemokines (β), on the basis of the arrangement of four cysteine molecules in their structure. Different chemokines have different functions; however, in broad terms, CXC chemokines are associated with neutrophil chemotaxis, whereas CC chemokines attract monocytes. Chemokines from both families are involved in regulating T lymphocyte function and trafficking (Hedrick and Zlotnik, 1996).

MCP-1 is a CC chemokine (known previously as monocyte chemotactic and activating factor, MCAF) that has a potent chemoattractant effect on monocytes. It is also a chemoattractant for CD4+ and CD8+ T lymphocytes. There is some debate over the ability of MCP-1 to attract natural killer cells, as results vary depending on the assay system used. MCP-1 is produced by a variety of cell types including endothelial cells, fibroblasts, monocytes and T lymphocytes. Early studies concentrated on the effect of MCP-1 in vitro but more recent studies have used MCP-1-deficient mice to confirm similar effects in vivo (Lu et al., 1998). MCP-1 has been investigated in diseases in which inflammation and monocyte infiltration are significant. In human medicine, a role for MCP-1 has been identified in rheumatoid arthritis, multiple sclerosis, atherosclerosis and HIV, as well as in tumour growth (Negus, 1997; Bacon and Oppenheim, 1998).

Four other monocyte chemoattractant proteins have been identified, each with slightly different effects on monocytes, T lymphocytes, eosinophils and basophils. Other chemokines in the group include macrophage inhibitory protein 1 (MIP-1α) and MIP-1β, which also attract monocytes. RANTES (regulated upon activation normal T expressed and secreted) attracts monocytes but is also the most effective chemokine at attracting CD8+ T lymphocytes.

Chemokine receptors belong to the seven-transmembrane spanning G-protein-coupled receptor family. They are unusual in that they generally lack specificity and many are shared among chemokines. MCP-1 binds to two receptors, CCR2 and CCR4, sharing these receptors with MCP-3, MCP-5, MIP-1α and RANTES. It has been suggested that this lack of specificity makes a distinctive role for each chemokine unlikely, but it may be that different combinations of receptor activation have different effects or that individual chemokines are expressed specifically in an individual setting (Rollins, 1997).

Role of MCP-1 in luteolysis

Leukocytes have been recorded in luteal tissue for over 30 years. However, it is only recently, as the field of immunology has expanded and techniques have advanced, that a significant functional role has been attributed to these cells within the

*Present address: The Roslin Institute, Roslin, Midlothian EH25 9PS, UK.
corpus luteum. Leukocyte populations change throughout the oestrous cycle and their cytokine products have also been detected within luteal tissue, providing further evidence that these cells play an active role in the corpus luteum (Brannstrom and Norman, 1993; Pate, 1995; Suzuki et al., 1998; Penny et al., 1999).

Macrophages have been recorded within the corpus luteum, particularly in late stage luteal tissue when an increase in their numbers has been observed in many species. The presence of large numbers of macrophages at this time is consistent with their role in the rapid destruction of the corpus luteum during structural luteolysis. There are many systemic and local influences on the corpus luteum around the time of luteolysis that could be involved in this influx of macrophages. Changing concentrations of progesterone, oestrogen or luteolysins, as well as local ovarian production of oxytocin and prostaglandin, may all be significant (Niswender and Nett, 1994). Cytokines produced by resident leukocyte populations may also have marked local effects within the corpus luteum and have been investigated in some detail (for review, see Terranova and Montgomery Rice, 1997).

Chemokines are a relatively new group of cytokines and have only recently been studied within the corpus luteum. The majority of research relating to MCP-1 has focussed on its role in disease processes. However, MCP-1 production has also been studied within the physiology of reproduction and, in particular, the corpus luteum (Simon et al., 1998).

Evidence so far
Molecular techniques, including RT–PCR and in situ hybridization, have been used to locate mRNA encoding MCP-1 in the corpus luteum of pigs (Hosang et al., 1994), cows (Tsai et al., 1997, Penny et al., 1998) and sheep (Haworth et al., 1998). In addition, immunoreactive protein for MCP-1 has been identified by immunohistochemistry in the rat and human corpus luteum (Townson et al., 1996; Senturk et al., 1999).

In view of the populations of leukocytes and the significant proportion of fibroblasts and endothelial cells within luteal tissue, all of which are potential sources of MCP-1, it is not surprising that mRNA encoding MCP-1 is found. The more significant question is whether MCP-1 plays an active role in luteal physiology. In rats, luteolysis was induced using prolactin, and MCP-1 expression and influx of macrophages (Fig. 1). In other species, the stimulus for MCP-1 production is less clear. It is possible that the products of steroidogenic cells in the corpus luteum may be involved directly (Senturk et al., 1998) or that other intraluteal cytokines may play a central role (Oppenheim, 1991).

Upregulation of mRNA encoding MCP-1 may be a direct or a convoluted process. MCP-1 is not found in sheep large luteal cells, which are the primary site of action for PGF$_{2\alpha}$ in the sheep corpus luteum (Haworth et al., 1998). This finding indicates a more indirect process. It is likely that the residing populations of leukocytes, in particular T lymphocytes and macrophages, are involved in the fine control of the whole process through cytokine production. Various cytokine products of T lymphocytes, in particular tumour necrosis factor $\alpha$, have been shown to upregulate MCP-1 production (Oppenheim et al., 1991). Cytokines may also be significant in activating incoming populations of macrophages, as MCP-1 acts only as a chemoattractant and does not activate these cells (Fig. 1). In the cow corpus luteum, there is an influx of CD8$^+$ T lymphocytes before functional luteolysis (Penny et al., 1999). The role of these cells is unclear but they may act, through cytokine release, as local regulators of MCP-1 production and macrophage activation.

The cellular sources of MCP-1 within the corpus luteum are unclear. Hosang et al. (1994) suggested that, in pigs, luteal cells are the primary source of MCP-1. However, the tissue samples used in their study could not be guaranteed to be free of non-luteal cells. Another study failed to co-localize tissue inhibitor of metalloproteinase and MCP-1 in large luteal cells, demonstrating that large luteal cells are not a source of MCP-1 in sheep (Haworth et al., 1998). Serial staining of sections of luteal tissue in cows has indicated that T lymphocytes (in particular CD8$^+$) may be a source of MCP-1 in the cow corpus luteum (Penny et al., 1998). However, in view of the abundance of other MCP-1-producing cell types in the corpus luteum, further studies will be required to clarify the situation and it is possible that multiple cell types are involved.

Future developments
Studies of the role of MCP-1 in the corpus luteum are still in their infancy, with many avenues for further investigation still open. The significance of MCP-1 in the whole process of luteolysis is of interest. For example, in rats, MCP-1 expression and the accumulation of macrophages are not sufficient to cause luteolysis (Gaytan et al., 1998). In addition, the fine control of MCP-1 expression has yet to be investigated. If MCP-1 is involved, how does the luteolytic substance act to increase its production, and what limits its production, or is it self-limiting through destruction of MCP-1-producing cells in luteolysis? The downregulation of MCP-1 expression may be due to relative hypoxia from a combination of dead and dying cells and...
failure of vascular supply (Negus et al., 1998). Other studies have demonstrated that oestradiol downregulates MCP-1 production in rabbits (Pervin et al., 1998). Therefore, it is possible that increasing concentrations of oestradiol from the developing preovulatory follicle are involved.

In addition to MCP-1, there are other chemokines that could affect development and function of the corpus luteum. For example, CXC chemokines have been shown to have a role in angiogenesis (Rollins, 1997), which is a significant process in the formation of the corpus luteum as well as during luteolysis. In comparison with cytokines such as tumour necrosis factor α and interleukin 1β, which have been studied in some detail in corpus luteum function, the chemokines have received little attention. An understanding of the role of chemokines in the normal physiology of reproductive function will allow further investigation of their significance in reproductive disease and dysfunction. A role for MCP-1 has already been suggested in the pathology of endometriosis and ovarian tumours in women (Simon et al., 1998, Negus et al., 1997).

In many fields, including reproduction, chemokines are providing exciting new avenues for investigation and are a focus for novel treatments in immune-mediated diseases. Reproductive events are being redefined to include a rising tide of information about chemokines, as well as other cytokines and growth factors. Events such as luteolysis, once described in comparatively simple hormonal and cellular terms, are now thought to involve complex local and systemic interactions. Chemokines may well prove to be one of the major missing links between hormonal and cellular events within the corpus luteum.

Fig. 1. Proposed order of events around luteolysis in cows: prostaglandin F2α (PGF2α) is released from the uterus and initiates luteolysis at about day 18 of the oestrous cycle. PGF2α acts on various cell types in the corpus luteum (CL) to promote monocyte chemoattractant protein 1 (MCP-1) production directly or indirectly, possibly through production of other cytokines such as tumour necrosis factor α (TNF-α) or interleukin 1β (IL-1β). An influx of macrophages takes place within the corpus luteum in response to MCP-1 release, and these cells play a major role in the structural regression of luteal tissue and are also a further source of MCP-1.

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