The mechanisms by which neutrophil leucocytes show oriented movement towards attractant sources are still unclear. It has been suggested that they use either a temporal or a spatial sensing system to "read" gradients.

Temporal gradient sensing requires that a moving cell perceives changes in concentration with time and requires some sort of memory; spatial sensing requires a cell to compare receptor occupancy over its length and coordinate this into a directed response. The terms were first applied in describing the behaviour of bacteria, whose mode of swimming alters with changing concentrations of attractant, resulting in random changes in direction. Bacteria adapt to changes in the concentration of attractant: the response, a change in the mode of swimming, is transient and returns to a baseline in the continued presence of the attractant (Hazelbauer, 1980). Thus, adaptive responses in bacteria allow great sensitivity to changes in concentration rather than to absolute concentration.

Although neutrophils are very different from bacteria, it has nevertheless been argued that they use similar mechanisms to read gradients of attractant. Zigmond (1974) suggested that neutrophils did not use a temporal mechanism because stationary cells oriented towards a gradient source before they moved. Gerisch & Keller (1981) showed that attractant delivered by micropipette stimulated local extension of a pseudopod and suggested that both spatial and temporal sensing might be occurring, because the latter requires only part of a cell to move in order to sample changes of concentration with time. In such experiments cells are not exposed to stable spatial gradients but to developing gradients in which a stationary cell experiences rapid changes in concentration with time (Vicker et al. 1986).

If neutrophils do use a temporal sensing mechanism to read gradients, they can maintain sensitivity to changes in concentration only by adapting to the absolute concentration, as bacteria do. Neutrophils, unlike bacteria, move only when stimulated by an attractant (Zigmond & Sullivan, 1979; Shields & Haston, 1985). In uniform concentrations of attractant they continue to move for several hours. If the attractant is removed, they stop. If the concentration is increased, they round up, ruffle, spread and then begin to move again (Zigmond & Sullivan, 1979). These transient morphological changes may represent an adaptive response to concentration changes. However, neutrophils do not adapt fully. Cells exposed to optimal uniform concentrations of a chemotactic peptide show persistent locomotion with narrow turning angles. Sudden increases in concentration cause the transient ruffling described by Zigmond & Sullivan (1979), but when locomotion resumes it is slower and less persistent (Shields & Haston, 1985).

Unstimulated neutrophils are spherical. The first morphological change after stimulation is the development of a polarized morphology. This requires reorganization of both the cytoskeleton and membrane receptors (Zigmond et al. 1981; Davis et al. 1982; Sullivan & Zigmond, 1985; Shields & Haston, 1985). Morphological polarity is accompanied by functional polarity in that the front of a polarized cell, probably because it has more receptors for chemoattractants (Sullivan et al. 1984), is much more responsive to stimulation than the back (Zigmond et al. 1981). Polarization and receptor redistribution do not require the presence of a chemotactic gradient. Both occur equally well while the cells are floating in suspension in uniform attractant concentration (Shields & Haston, 1985). Polarization is dependent on the concentration of attractant and the optimal concentration, which induces maximal polarity in the most cells, is close to the $K_d$ for the attractant (Shields & Haston, 1985). Supraoptimal concentrations stimulate contraction and ruffling but prevent the development of polarity. At suboptimal concentrations fewer cells respond, though those that do are well polarized. Calculations indicate that one molecule of attractant per cell is probably capable of initiating a polarizing response (I. C. McKay, personal communication). The simplest explanation for these findings is that the cell responds by polarizing towards the site where a ligand first binds to...
a receptor. Contraction waves propagated from this site of 'first hit' determine initial polarity and the concomitant redistribution of receptors towards this region establishes the front of the cell. The redistribution of receptors would increase the sensitivity of the anterior pole and thus amplify the polarizing response (Shields & Haston, 1985). When the ligand concentration is above the $K_d$, ligand molecules bind synchronously at multiple sites, preventing formation of an anterior pole.

Since neutrophils develop such asymmetries in uniform concentrations of attractants, polarization cannot involve 'reading' of a gradient. If neutrophils respond by polarizing towards the site of first hit, then no comparisons in time or space are necessary and gradient 'perception' can be regarded as a stochastic rather than a 'cognitive' process. In a gradient the chance of hits on the up-gradient side will be high and most cells will polarize towards the gradient source. Since polarity and locomotion are interdependent (Haston & Shields, 1984) the cells will move towards the gradient source.

This model predicts that cells orient in both stable 'spatial' gradients and developing 'temporal' ones. However, recently Vicker et al. (1986) reported that neutrophils did not accumulate in preformed and stable spatial gradients, though they accumulated in temporally developing gradients of similar amplitude. They therefore suggested that neutrophils accumulate only when exposed to a sharp temporal increase in concentration. A first-hit mechanism similar to that described above is suggested for the directional response. However, the first-hit hypothesis predicts that a cell's first experience of a stable spatial gradient is a temporal change in receptor occupancy. At the midpoint of the gradients described by Vicker et al. (1986) (about 20% over a cell's dimensions) the occupancy would be anisotropic, sufficiently so to impose polarity and subsequent accumulation. The cells would thus experience a temporal change although the gradient was spatial.

An effective way of testing whether neutrophils can respond to a stable spatial gradient is to bind attractant gradients to a substratum. Gradients of substratum-bound denatured proteins induce directional responses (Wilkinson & Bradley, 1981). Webster et al. (1980) showed chemotactic responses to C5a bound to micropore filters. Our unpublished observations show that neutrophils orient and move in response to surface-bound C5a and that this is not due to cell-release products or to an increase in cell speed up-gradient (J. M. Lackie, personal communication). This confirms that neutrophils can respond to spatial gradients.

Some major questions are raised by the stochastic model suggested here. Is receptor redistribution to the front of polarized cells enough to overcome signal 'noise' or are additional mechanisms involved? By what mechanisms do unrelated receptors such as those for Fc, C5a, formyl-peptides and Thy1.2 (in lymphocytes) become asymmetrically distributed to the front of moving leucocytes?

References


