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Iron down-regulates macrophage anti-tumour activity by blocking nitric oxide production.

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Abstract

Although the inhibitory effect of iron on macrophage production of tumoricidal free radical nitric oxide (NO) has been reported, its possible influence on macrophage anti-tumour activity has not been established. In the present study, FeSO4 markedly reduced IFN-gamma + LPS-induced NO synthesis in mouse and rat macrophages. The effect of iron coincided with the loss of macrophage cytotoxic activity against NO-sensitive C6 rat astrocytoma and L929 mouse fibrosarcoma cell lines, as measured by MTT assay for cellular respiration and the crystal violet test for cell viability. Tumour cell survival did not improve further in the presence of FeSO4 if macrophage NO release and cytotoxicity were already blocked by aminoguanidine. In accordance with the results obtained with exogenous iron, cell membrane permeable iron chelator o-phenanthroline enhanced both macrophage NO release and anti-tumour activity. Iron also down-regulated NO production and increased the viability of L929 fibrosarcoma cells stimulated with IFN-gamma + LPS in the absence of macrophages. However, neither NO release nor cell viability was affected by iron addition to cultures of the C6 astrocytoma cell line. Iron was unable to prevent L929 and C6 cell death induced by the NO releasing chemicals SNP and SIN-1, indicating that iron-mediated inhibition of NO synthesis, rather than interference with its cytotoxic action, was responsible for the protection of tumour cells. Collectively, these results indicate that iron might protect tumour cells by reducing both macrophage and tumour cell-derived NO release.

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