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NEGATIVE MODULATORS OF THE HAEMATOPOIESIS AND MARROW FAILURE IN FA

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Marrow failure is so far the most important cause of morbidity and mortality in FA. The mechanism by which failure occurs have not been fully elucidated as yet. Over the last years studies conducted on cell lines, mice models, and patients' marrow primary cells have shown that the myelosuppressive cytokines TNF-α and IFN-γ have an important role in causing marrow failure by inducing apoptosis.

Although this issue is based on a number of solid evidence, some aspects are obviously under investigation. One of these, is the mechanism of production of these effectors. Recent evidence supported that the in vitro secretion of the TNF-α from FANCC cells is dependent on the FANCC gene since TNF-α was restored to wild type levels after over-expression of the C gene in the cells.

In he same cell line it has also been shown that TNF-α over-secretion was due to over activity of MMP7 that cleaved an increased amount of trans-membrane TNF-α in the extracellular milieu. Another hot topic is whether or not there is a true overproduction of TNF-α and IFN-γ in the marrow of FA patients.

Classical data obtained from the serum of the patients indicate that FA patients tend to have higher amount of TNF-α respect to normal subjects. TNF-α and IFN-γ were found to be over-expressed in marrow cells of the patients after stimulation and the in vitro blockade of TNF-α improved the growth of erythroid colonies of FA patients. Marrow content of TNF-α of FA patients was found to equal that seen in normal individuals.

This finding is in keeping with the hypothesis that FA cells are hypersensitive to suppressive cytokines which are able to induce apoptosis even at low concentrations due to the "constitutional" fragility of the cells.

Regarding the mechanism through which myelosuppressive cytokines cause apoptosis, recent data derived from murine embrionic fibroblasts and mice haematopoietic progenitors indicate that TNF-α-induced apoptosis is ROS mediated and ASK1 and p38 dependent.

Other effectors have been studied. MIP 1 -α was shown to have myelosuppressive effect at very low concentrations in FANCC mice but was not over-expressed in stimulated marrow cells of FA patients and so was FasL.

TRAIL(TNF Related Apoptosis Inducing Ligand) has been found not to induce apoptosis on FANCC cells whereas some apoptotic effect was seen by our group on FANCA cells.

In summary, although multiple cytokines can be involved, most of the current evidence point to a role for IFN-γ, and mainly TNF-α as the effectors of the haematopoietic damage in FA patients.

This opens the door to possible future treatments of marrow failure in FA patients with agents antagonizing the effect of these cytokines.