An in vitro Model of Chemotherapeutic Damage to Mesenchymal Stem Cells
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Mesenchymal Stem Cells/Stromal Cells (MSC) form the bone marrow microenvironment and are essential in supporting haemopoiesis. Following stem cell transplantation (SCT), whilst haemopoietic cells are replaced, MSC remain of recipient origin. However, MSC have previously been shown to be damaged by chemotherapeutic treatment, administered prior to SCT. If damage is severe it may be implicated in lack of engraftment following some SCT, a major cause of mortality, occurring in 10% of allogeneic peripheral blood transplants. To elucidate this damage, a physiologically relevant in-vitro model is needed as many chemotherapeutic agents are extensively metabolised by hepatic cytochrome P450 enzymes.

An in-vitro co-culture model utilising HepG2 liver spheroids as a source of metabolic enzymes has been developed, enabling study of chemotherapeutic damage. Several cytotoxic effects in MSC have been observed in-vitro following chemotherapy treatment with alkylating prodrugs such as cyclophosphamide using this model. These include altered morphology, decreased expansion (p<0.01), and reduced expression of CD44 (p<0.05), an adhesion molecule involved in haemopoiesis. Similarly, treatment with active chemotherapeutics e.g. vincristine leads to grossly altered morphology, reduced CD44 expression (p<0.01) and decreased expansion (p<0.001). In the presence of liver spheroids, however, these effects are reduced (p<0.05 and p<0.001 respectively), indicating detoxification, as would occur in-vivo.

These results are comparable with effects seen in patients previously treated with chemotherapy, where CD44 expression is decreased (p<0.05), MSC survival in-vitro is reduced (p<0.01) and ability to support haemopoiesis in-vitro is diminished (p<0.05).

Using this co-culture model and age- and sex-matched untreated and chemotherapeutically-treated patient samples, genotoxic damage to MSC in-vitro and in-vivo is currently under investigation, using ³²P post-labelling to separate and identify DNA adducts.

In conclusion, a physiologically relevant model has been developed to study cytotoxic and genotoxic chemotherapeutic damage, with results comparable with effects seen in patients who have undergone chemotherapy treatment for malignancy.