CONFERÊNCIA **2023**

LEADING INNOVATION CHANGING LIVES

O FUTURO DA CARREIRA MÉDICA

PRÉMIO MSD
INVESTIGAÇÃO EM SAÚDE
5ª EDIÇÃO

MSD

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- Interna de Formação Específica em Hematologia Clínica
- Colaboradora do grupo Hematopoiese e Microambiente do Dr. Delfim Duarte no i3S
- Mestre em Medicina pela Universidade do Porto (2009)
- Doutorada em Biologia Básica e Aplicada pela mesma universidade (2018)
- Ano comum do Internato Médico no Centro Hospitalar Universitário de Santo António
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PROJETO

INVESTIGATING THE ROLE OF NRF2 AND IRON OVERLOAD IN BONE MARROW TRANSPLANTATION PATIENTS

Patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT) often have iron overload. This has been shown to increase, in as much as doubling, non-relapse mortality after transplant. Whether one can detect a subgroup of patients at higher risk for worse outcomes has not been addressed.

Iron is a required redox co-factor for many enzymes, but in its free form is also detrimental for cells as it generates free radicals. One of the means to limit iron´s toxicity is the production of antioxidants. NRF2 is a master regulator of this process: upon oxidative stress, it drives the transcription of antioxidant and cytoprotective enzymes. We hypothesize that NRF2 may impact HSCT outcomes when iron overload is present.

To study the role of NRF2 in the bone marrow (BM), we used WT, Nrf2-KO and Hamp1-KO (iron overload model) mice as transplant recipients. WT BM cells were transplanted into these mice and engraftment and survival assessed. Unlike single Hamp1-KO or Nrf2-KO recipient mice, Nrf2/Hamp1 double KO recipient mice had a very short survival after BM transplant when compared to WT animals. Treatment of Nrf2-KO mice with Iron Dextran prior to transplant recapitulated the phenotype of double KO mice. These results show that when increased iron is accompanied by decreased NRF2 activity survival after transplant is much decreased, suggesting that iron overload and the lack of antioxidant response act synergistically. It is unknown if NRF2 function in patients is also required to overcome iron toxicity after HSCT.

We propose to investigate the role of NRF2 in iron overloaded allogeneic HSCT recipients. To do so, we will classify patients based on the NRF2 polymorphism rs35652124, which is located in the promoter region of the gene and affects its expression level and activity. Survival after HSCT will be compared.

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- Mestrado Integrado em Medicina pela Faculdade de Medicina da Universidade de Lisboa (2020)
- Membro da Comissão de Internos do SESARAM EPE (Jan 2021 – Dez 2021)
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PROJETO

PREDICTING EFFICACY AND TOXICITY OF IMMUNE CHECKPOINT INHIBITORS: A ROLE FOR INTERLEUKIN 7

Immune checkpoint inhibitors (ICIs) have been increasingly used as a therapeutic weapon against cancer and have proven efficacy, being approved for at least 90 different indications. Nevertheless, not all patients are responders. Moreover, this novel immunotherapy has an unique spectrum of side effects related to activation of the immune system leading to immune-related adverse events (irAEs) (Boutros et al.). These irAEs are unpredictable and can lead to hospitalization, discontinuation of treatment, or death. Identification of biomarkers that help predict which patients (pts) are more likely to benefit from ICIs and those more predisposed to irAEs is an unmet clinical need.

Two recent studies (Groha et al. and Taylor et al.) have identified genetic markers associated with the occurrence of irAEs in patients with melanoma under ICIs. A polymorphism in the interleukin 7 (IL7) gene (rs16906115), was associated with irAEs. This variant was associated with increased expression of IL7 and its receptor (IL7R) in B cells and CD4+ T cells in patients that develop irAEs.

Taylor et al. confirmed the relationship between this variant of the IL7 gene and irAEs in patients with melanoma that received treatment with ICIs. In this study, the increase of IL7 in B cells was associated with irAES independently of the genotype.

These findings hold promise for identifying subgroups of cancer patients at higher risk of irAEs and those who may benefit the most from ICI.

In our current study, we will evaluate a cohort of patients under ICIs for analysis of genetic and phenotypic factors that might influence response and toxicity to ICIs as it has been proven in the aforementioned studies. We expect to extrapolate the data seen in melanoma patients to patients with other types of cancer under ICIs.

In upcoming studies, we intend to further investigate other factors that might influence drug response to ICIs, an emerging therapy.

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- Mestrado Integrado em Medicina pela Faculdade de Medicina da Universidade de Lisboa (2020)
- Participação ativa em diversos projetos de investigação nas áreas de Neurociência e Doença Cerebrovascular
- Colaboração nas disciplinas de Fisiopatologia da FMUL e Fundamentos de Neurociências da NOVA *Medical School*
- Prémio de Mérito do Mestrado Integrado em Medicina 2020
- Prémio Melhor Projeto de Investigação GAPIC 2018

PROJETO

PREDICTING EFFICACY AND TOXICITY OF IMMUNE CHECKPOINT INHIBITORS: A ROLE FOR INTERLEUKIN 7

Cerebral venous thrombosis (CVT) predominantly affects young adults, especially women at fertile age, and can cause severe brain damage, leading to long-term disability and death. Early venous recanalization is crucial for both brain lesion recovery and preventing further progression, but predicting these outcomes is challenging. Invasive interventions, particularly endovascular treatment, are promising but have shown limited success due to the lack of robust patient selection criteria. The use of validated markers of potential brain tissue evolution could enhance the precision and effectiveness of selecting patients for invasive interventions. Perfusion, which refers to the delivery of oxygen and nutrients to tissues through blood flow, is a fundamental biological function. Perfusion magnetic resonance imaging (MRI) has been used to select patients with ischemic stroke for endovascular treatment, using metrics such as Relative Cerebral Blood Flow (rCBF) and Mean Transit Time (MTT), as well as to estimate blood-brain barrier (BBB) permeability through BBB leakage rates. This study proposes using perfusion metrics as predictors of brain tissue fate in CVT patients. A prospective, multicenter, observational cohort study of 70 adult patients with CVT will define perfusion characteristics associated with early imaging deterioration and progression towards established infarction. Dynamic susceptibility contrast perfusion MRI will assess perfusion values and BBB leakage rates for each outcome group. The study aims to define a perfusion and BBB leakage rates thresholds for predicting the risk of further brain damage and the evolution of baseline lesions. The expected results will provide a rapid method to analyze tissue viability and predict the risk of imaging worsening, which will be crucial in developing a model for patient selection in future clinical trials involving recanalization therapies.

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