Structural analysis and functional exploration of a leukemia-associated protein, IQCG

Supported financially by the National Natural Science Foundation of China, Prof. Chen Saijuan and Chen Zhu's laboratory at Shanghai Institute of Hematology, Rui Jin Hospital affiliated to Shanghai Jiao Tong University (SJTU) School of Medicine, published a research article in *Nature Communications* (**2014**, 5: 3811), entitled "Functional and molecular features of the calmodulin-interacting protein IQCG required for haematopoiesis in zebrafish".

This research group had previously reported a fusion protein NUP98-IQCG associated with an acute leukaemia, which functioned as an aberrant regulator of transcriptional expression, but remained to be characterized for its structure and function . In this study, the researchers investigated the role of *iqcg* in haematopoietic development by using zebrafish as a model system. They found that the numbers of haematopoietic stem cells and multilineage-differentiated cells were reduced in *iqcg*-deficient embryos. To further elucidate the function of IQCG, they combined structural analysis with biochemical assays, and mechanistically showed that IQCG bound to calmodulin (CaM) and acted as a molecule upstream of CaM-dependent kinase IV (CaMKIV). Crystal structures of IQCG IQ motif in the complex with CaM revealed dual CaM-binding footprints in this motif, and provided a structural basis for a higher CaM-IQCG affinity when deprived of calcium. Collectively, this work has allowed a better understanding of the IQCG-mediated calcium signalling in haematopoiesis, and proposed a model of IQCG-modulated activity of CaMKIV. In this model, IQCG stores CaM at low cytoplasmic calcium concentrations, and releases CaM to activate CaMKIV when calcium level rises.

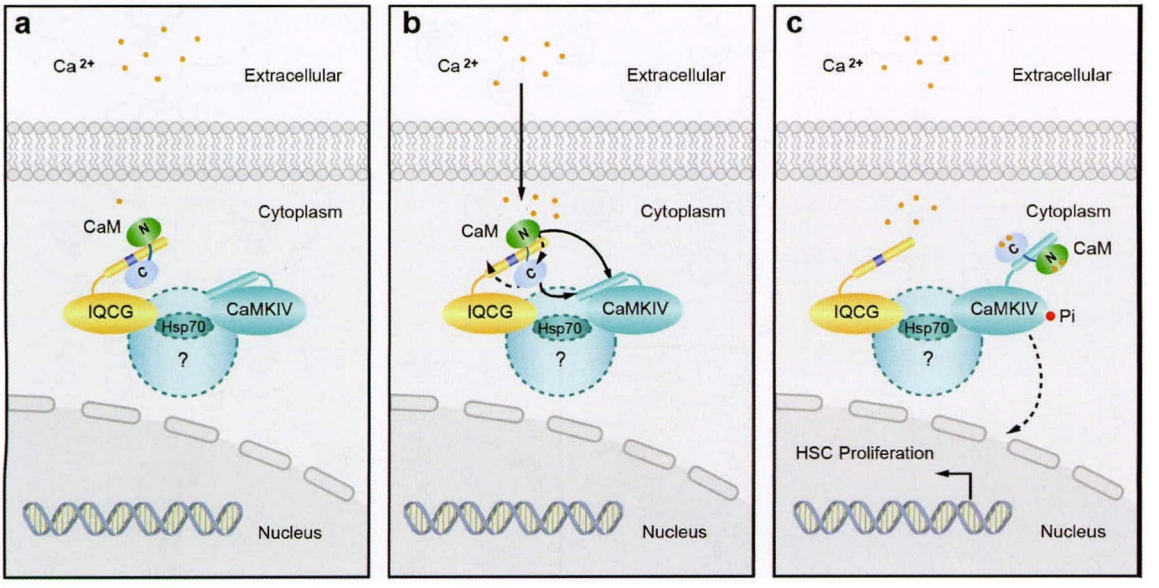

Figure Proposed mechanism of IQCG in calcium/CaM signalling. a, When the cytoplasmic Ca^{2+} level is low, IQCG binds to Ca^{2+}-free CaM via the IQ motif. b, Elevation of the cytoplasmic Ca^{2+} concentration decreases the affinity between CaM and IQ motif. As IQCG and CaMKIV are hypothetically bound by scaffold proteins including HSP70, both lobes of CaM may subsequently bind CaMKIV (indicated by solid line) instead of re-associating to the new sites of IQCG (indicated by dotted line). c, The binding of CaM activates CaMKIV and its downstream pathway, and promotes the proliferation of haematopoietic stem cells.