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**Effects of chronic inflammation on megakaryocyte and platelet function in a conditional mouse model**

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| (max. 2000 characters with space; line spacing: 1.2; Arial 11pt):  BACKGROUND: Megakaryocytes can sense inflammatory signals via TLRs but little is known how this might change platelets, which can contribute to cardiovascular diseases via immune-modulatory processes. Most inflammatory signalling pathways converge at the kinase IKK2 (inhibitor of NF-κB kinase 2) activating the transcription factor NF-κB. Our aim was to determine the effect of chronic inflammation on megakaryocytes and platelets by using conditional transgenic mouse models that alter NF-κB activity in megakaryocytes.  METHODS: Mice with a megakaryocyte-specific constitutively active IKK2 or IKK2 knock-out were compared to littermate controls, thereby studying different inflammatory states in megakaryocytes. Megakaryocytes were analysed with respect to their ploidy and ability to form pro-platelets. Blood platelets were analysed for size, number and granule content. Moreover, platelet functions were determined in vitro by testing for agonist-induced degranulation and aggregation.  RESULTS: We could not observe significant differences in megakaryocyte maturation and differentiation. Platelets of mice with megakaryocyte-specific constitutive active IKK2 though, showed an increased volume and contained more RNA as compared to controls. Basal surface P-selectin expression was increased indicating constitutive degranulation, whereas platelet aggregation capability in vitro was significantly decreased.  CONCLUSIONS: Our results suggest that platelets from megakaryocytes under persistent inflammatory stimulation have a higher basal activation, while reactivity is decreased. This may imply an “exhausted” phenotype and might represent a feedback mechanism that reduces thrombotic tendencies in states of chronic inflammation. |