GRANULOCYTE DEVELOPMENT

Vitamin B3: a neutrophil supplement

Neutropenia in individuals with a congenital defect or patients with cancer who are undergoing chemotherapy is generally treated with granulocyte colony-stimulating factor (G-CSF) to restore normal granulopoiesis. Now, Skokowa *et al.* describe a new pathway involving vitamin B3 (nicotinamide) metabolism to explain how G-CSF triggers granulopoiesis.

When searching for factors that are activated by G-CSF during myeloid-cell differentiation, the authors found that levels of the enzyme nicotinamide phosphoribosyltransferase (NAMPT) were markedly increased in haematopoietic-cell precursors and in the plasma of G-CSF-treated healthy volunteers and patients with congenital neutropenia. NAMPT is involved in the conversion of nicotinamide to nicotinamide adenine dinucleotide (NAD^+), which has key roles in numerous biological processes through regulating the expression and transcriptional function of the sirtuin family of deacetylases. Accordingly, NAMPT upregulation by G-CSF treatment was accompanied by increased levels of NAD^+ and sirtuins. In addition, the key granulocyte-specific transcription factors CCAAT/enhancer-binding protein-α (C/EBPα) and C/EBPβ also showed G-CSF-dependent expression.

In support of the idea that the G-CSF-dependent increase in NAMPT expression promotes neutrophil differentiation, exogenously added NAMPT or lentivirally transduced *NAMPT* were shown to promote the differentiation of haematopoietic precursors into myeloid-lineage cells *in vitro*. Conversely, treatment of haematopoietic precursors with a small molecule inhibitor of NAMPT abrogated the G-CSF-triggered increase in NAD^+, C/EBPα and C/EBPβ expression and the concomitant granulocytic differentiation.

Given that C/EBPs are known to activate the transcription of genes encoding G-CSF and the G-CSF receptor (G-CSFR), the authors proposed that NAMPT activates an autoregulatory loop, whereby upregulation of NAMPT expression by G-CSF increases NAD^+ production, which promotes the overexpression and activation of sirtuins. These, in turn, act on C/EBPs to induce G-CSF and G-CSFR transcription. This proposed mechanism was supported by the findings that sirtuin 1 co-precipitated with C/EBPα and C/EBPβ and that knockdown of sirtuin 1 expression abolished NAMPT-induced G-CSF and G-CSFR transcription.

Finally, based on these *in vitro* findings, the authors investigated whether vitamin B3 could be used instead of G-CSF as a treatment to boost neutrophil numbers in neutropenic subjects. Treatment of healthy individuals with vitamin B3 resulted in significant increases in neutrophil numbers, which declined following discontinuation of treatment. Similar to G-CSF-treated cells, neutrophils from individuals taking oral vitamin B3 showed increased expression of NAD^+, C/EBPα, C/EBPβ and G-CSFR.

So, although it has not yet been tested in individuals with congenital neutropenia, vitamin B3 could prove to be an inexpensive and safe treatment option for this disease.

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ORIGINAL RESEARCH PAPER Skokowa, J. *et al.* NAMPT is essential for the G-CSF–induced myeloid differentiation via a NAD^+–sirtuin-1–dependent pathway. *Nature Med.* **15**, 151–158 (2009)

FURTHER READING Khanna-Gupta, A. & Berliner, N. Vitamin B3 boosts neutrophil counts. *Nature Med.* **15**, 139–141 (2009)