Transcriptional regulation of granulopoiesis

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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references


Reactome database release: 71

This document contains 1 pathway and 27 reactions (see Table of Contents)
Neutrophilic granulocytes (hereafter called granulocytes) are distinguished by multilobulated nuclei and presence of cytoplasmic granules containing antipathogenic proteins (reviewed in Cowland and Borregaard 2016, Yin and Heit 2018). Granulocytes comprise eosinophils, basophils, mast cells, and neutrophils, all of which are ultimately derived from hemopoietic stem cells (HSCs), a self-renewing population of stem cells located in the bone marrow. A portion of HSCs exit self-renewing proliferation and differentiate to form multipotent progenitors (MPPs). MPPs then differentiate to form common myeloid progenitors (CMPs) as well as the erythrocyte lineage. CMPs further differentiate into granulocyte-monocyte progenitors (GMPs) which can then differentiate into monocytes or any of the types of granulocytes (reviewed in Fiedler and Brunner 2012). Granulocytes are the most abundant leukocytes in peripheral blood.

For early granulopoiesis the CEBPA, SPI1 (PU.1), RAR, CBF, and MYB transcription factors are essential. CEBPE, SPI1, SP1, CDP, and HOXA10 transcription factors initiate terminal neutrophil differentiation.

Initially, RUNX1 activates SPI1 (PU.1), which is believed to be the key transcription factor driving the formation of MPPs and CMPs (reviewed in Friedman 2007, Fiedler and Brunner 2012). SPI1, in turn, activates expression of CEBPA, an indispensable transcription factor for granulopoiesis especially important in the transition from CMP to GMP (inferred from mouse homologs in Wilson et al. 2010, Guo et al. 2012, Guo et al. 2014, Cooper et al. 2015). CEBPA, in turn, activates the expression of several transcription factors and receptors characteristic of granulocytes, including CEBPA (autoregulation), CEBPE (Loke et al. 2018, and inferred from mouse homologs in Wang and Friedman 2002, Friedman et al. 2003), GFI1 (inferred from mouse homologs in Lidonnici et al. 2010), KLF5 (Federzoni et al. 2014), IL6R (inferred from mouse homologs in Zhang et al. 1998), and CSF3R (Smith et al. 1996). Importantly, CEBPA dimers repress transcription of MYC (c-Myc) (Johansen et al. 2001, and inferred from mouse homologs in Slomiany et al. 2000, Porse et al. 2001). CEBPA binds CDK2 and CDK4 (Wang et al. 2001) which inhibits their kinase activ-
ity by disrupting their association with cyclins thereby limiting proliferation and favoring differentiation of granulocyte progenitors during regular ("steady-state") granulopoiesis (reviewed in Friedman 2015). The transcription factor GFI1 regulates G-CSF signaling and neutrophil development through the Ras activator RasGRP1 (de la Luz Sierra et al. 2010).

Inhibitors of DNA binding (ID) proteins ID1 and ID2 regulate granulopoiesis and eosinophil production such that ID1 induces neutrophil development and inhibits eosinophil differentiation, whereas ID2 induces both eosinophil and neutrophil development (Buitenhuis et al. 2005, Skokowa et al. 2009).

Major infection activates emergency granulopoiesis (reviewed in Manz and Boettcher 2014, Hirai et al. 2015), the production of large numbers of granulocytes in a relatively short period of time. Emergency granulopoiesis is activated by cytokines, CSF2 (GM-CSF) and especially CSF3 (G-CSF, reviewed in Panopoulos and Watowich 2008, Liongue et al. 2009) which bind receptors, CSF2R and CSF3R, respectively, resulting in expression of CEBPB, which interferes with repression of MYC by CEBPA (inferred from mouse homologs in Zhang et al. 2010) and represses MYC less than CEBPA does (Hirai et al. 2006), leading to proliferation of granulocyte progenitors prior to final differentiation. Both, emergency and steady-state granulopoiesis are regulated by direct interaction of CEBPA (steady-state) or CEBPB (emergency) proteins with NAD+-dependent protein deacetylases, SIRT1 and SIRT2 (Skokowa et al. 2009). G-CSF induces the NAD+-generating enzyme, Nicotinamide phosphoribosyltransferase (NAMPT, or PBEF), that in turn activates sirtuins (Skokowa et al. 2009).

GADD45A and GADD45B proteins are essential for stress-induced granulopoiesis and granulocyte chemotaxis by activation of p38 kinase (Gupta et al. 2006, Salerno et al. 2012). SHP2 is required for induction of CEBPA expression and granulopoiesis in response to CSF3 (G-CSF) or other cytokines independent of SHP2-mediated ERK activation (Zhang et al. 2011).

Transcription of neutrophil granule proteins (e.g. ELANE, MPO, AZU1, DEFA4), that play an essential role in bacterial killing are regulated by CEBPE and SPI1 (PU.1) transcription factors (Gombart et al. 2003, Nakajima et al. 2006). RUNX1 and LEF1 also regulate ELANE (ELA2) mRNA expression by binding to its promoter (Li et al. 2003).

**Literature references**


**Editions**

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<td>Authored, Edited</td>
<td>Skokowa, J.</td>
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<td>2019-03-10</td>
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https://reactome.org
SPI1 (PU.1) gene transcription is stimulated by RUNX1:CBFB:KMT2A

Location: Transcriptional regulation of granulopoiesis

Stable identifier: R-HSA-8865505

Type: omitted

Compartments: nucleoplasm

Inferred from: Spi1 gene transcription is stimulated by RUNX1:Cbfb:KMT2A (Homo sapiens)