Putting the DOT on IL1A

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IL-1α is an upstream component of the senescence-associated secretory phenotype. In this issue, Leon et al. (2021. J. Cell Biol. https://doi.org/10.1083/jcb.202008101) show that DOT1L-mediated H3K79 methylation at the IL1A gene plays a key role in its induction during oncogene-induced senescence.

Senescence is a heterogeneous phenotype, often characterized by the ability to secrete diverse functional molecules (senescence-associated secretory phenotype [SASP]). The quantity and quality of those SASP components are key determinants of the short-term and long-term impacts of senescent cells in vivo (1). The inflammatory SASP is cooperatively mediated by two transcription factors (TFs), nuclear factor-κB (NF-κB) and CCAAT/enhancer-binding protein β (C/EBPβ), which target inflammatory cytokines (including IL-1, IL-6, and IL-8) that can, in turn, activate those TFs.

Thus, the overall signal is amplified both cell autonomously and noncell autonomously (1), and depletion of some individual factors can lead to the collapse of the entire inflammatory SASP (3). In particular, IL-1α is proposed to be an upstream cytokine in this feed-forward SASP network (3).

Located in the IL1 cluster, the IL1A gene is a product of IL1B gene duplication, and consequently IL-1α and IL-1β share a receptor, IL-1R1, and its downstream signaling (4). Yet, they have distinct regulatory mechanisms for their activities at multiple levels. While both are produced as pro-forms, IL-1β, but not IL-1α, is a well-established substrate of the inflammasome/Caspase-1 complexes (5). Unlike IL-1β, IL-1α has additional functions, represented by the presence of a nuclear localization signal within its pro-domain (4).

In the senescence context, IL-1α–specific regulatory mechanisms have also been proposed: Mammalian target of rapamycin (mTOR) preferentially facilitates IL-1α translation and GATA4 can, probably indirectly, promote IL-1α induction upstream of NF-κB (1). In contrast to IL-1β, IL-1α is a substrate of noncanonical inflammatory caspases (5). Functionally, expression of downstream SASP components, IL-6 and IL-8, depends on IL-1α, but not IL-1β (3). Compared with the differential regulation through the mostly post-transcriptional steps listed above, studies directly comparing IL1 transcriptional regulation appear limited. This is perhaps, in part, because transcriptional regulation of IL1A is less explored compared with that of IL1B and other SASP genes. Transcription at the IL1 locus is mainly driven by NF-κB and C/EBPβ, and both IL1A and IL1B have been linked to “super-enhancers” or de novo enhancers in the senescence context (6). However, evidence suggesting differential regulatory mechanisms for these IL1 genes is now emerging. Olan et al. (7) recently showed that, while IL1A and IL1B share enhancers upon acute induction by TNFα in fibroblasts, the enhancer utilization at the IL1 locus becomes more specialized through 3D chromatin reorganization during oncogene-induced senescence (OIS), distinguishing the transcriptional activation of IL1A and IL1B.

In this issue, Leon et al. (8) introduce a new mechanism for how IL1A expression is distinctly regulated. In their epiproteomics survey of OIS culture models, they focus on an increase in histone H3K79me2/3, among others. H3K79 methylation is associated with gene activation, and DOT1L is the only known H3K79 methyltransferase (9). DOT1L and H3K79me2/3 are involved in diverse biological processes, including development, reprogramming, and cell cycle (9), but their role in senescence was unknown.

Besides a global increase in H3K79me2/3 level during OIS, the authors also showed a focal increase in DOT1L binding and DOT1L-dependent H3K79me2/3 deposition at the IL1A locus. Curiously, in contrast to IL1A, H3K79me2/3 levels were even reduced at other major SASP gene loci (IL1B, IL16, and CXCL8) in OIS cells (Fig. 1). This preferential H3K79me2/3 deposition at the IL1A locus also occurs when DOT1L is ectopically expressed, supporting the specific association between DOT1L and IL1A, at least among the SASP genes tested. In addition, the authors showed a close correlation between IL1A expression and H3K79me2/3 accumulation at this locus. Notably, DOT1L knockdown resulted in the down-regulation of IL1A, as well as other SASP genes. This is consistent with the idea that IL-1α is an upstream regulator of the SASP network (8). Indeed, ectopic expression of IL1α in DOT1L-depleted OIS cells restored expression of IL1B and other SASP genes. DOT1L also appears necessary for CEBPβ (encoding C/EBPβ) up-regulation during OIS. While ectopic DOT1L can induce CEBPβ and the SASP genes without the obvious senescence phenotype, only IL1A is associated with H3K79me2/3 alteration. The authors also demonstrated that DOT1L itself is up-regulated during OIS and acts downstream of stimulator of interferon genes.
ties, exemplificative environment affects DOT1L/Dot1 activity and IL1 and IL-1β are differentially regulated at several stages during OIS: transcriptionally, both genes are regulated by the TFs C/EBPβ and NF-κB but, unlike in the context of acute inflammation, they use distinct enhancers (Enh) during OIS. Now DOT1L/H3K79me2/3 is proposed to be a direct mediator of IL1A, but not IL1B or other SASP components. Note, GATA4 is a transcription factor, but it appears indirectly involved in the IL-1α induction during senescence: post-transcriptionally, IL1A mRNA is preferentially translated via mTOR, and IL-1α is a substrate of the noncanonical inflammation, whereas IL-1β is processed by the canonical inflammation. (b) SASP regulation during OIS. DOT1L plays a key role in coordinating the entire inflammatory SASP through IL1A induction. It also can induce C/EBPβ, but it is unknown whether this is through IL-1α and/or other targets. Note, DOT1L itself is transcriptionally up-regulated during OIS downstream of STING, where the cyclic GMP-AMP synthase–STING–NF-κB pathway is the cytoplasmic DNA sensing effector implicated in triggering the inflammatory SASP.

This possibility is exciting, particularly considering that, while DOT1L activity is modulated by preexisting epigenetic marks, DOT1L can also modulate the local and global epigenetic landscape through inhibition of local histone deacetylation and heterochromatinization (11), as well as potentially through global heterochromatin redistribution (12). Finally, although the authors showed a positive correlation between DOT1L and IL1A in 7,12-dimethylbenz[a]anthracene/12-O-tetradecanoylphorbol-13-acetate–induced murine papillomas, which contain OIS pro-neoplastic lesions, further validation is required to determine the physiological relevance of this study. Interestingly, unlike directly targeting SASP components (2), the senescence arrest is preserved after DOT1L depletion, hinting at a “senomorphic” potential of targeting DOT1L.

Leon et al. (8) indeed show that the treatment with pinometostat (EPZ-5676), the first selective DOT1L inhibitor used in clinical trials in leukemia (9), leads to a decrease in H3K79me2/3 and reduction of the SASP. The mechanism of how DOT1L inhibition blocks the SASP without senescence reversal is unknown, but it is conceivable that other DOT1L/H3K79me2/3-controlled genes may, directly or indirectly, contribute to the maintenance of the arrest. It has been shown that a reduced level of DOT1L leads to growth arrest and cell death (13). Indeed, it was also reported that DOT1L depletion promotes senescence induction in endothelial cells (14). Comprehensive genome-wide analysis of DOT1L/H3K79me2/3 and their crosstalk with other chromatin features might reveal a new epigenetic landscape in senescence, potentially relevant for considering new therapeutic targets.

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