

Adenosine in the Bone Marrow Myeloma Niche: Immune Checkpoint and Key Player in the Progression of Myeloma Disease

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Commentary

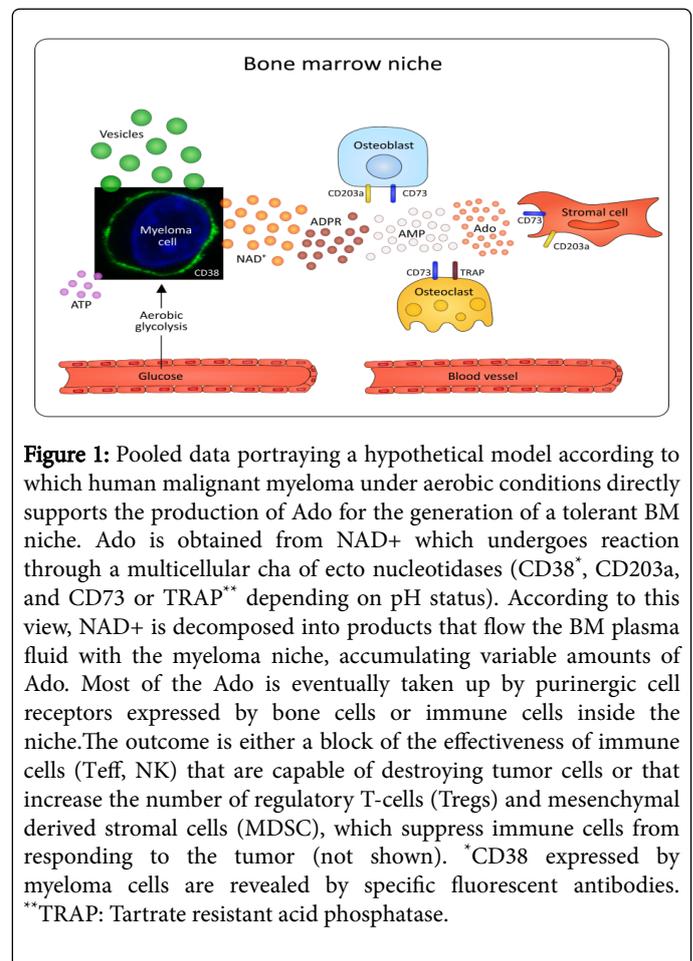
The tumor microenvironment is rich extracellular mono- and dinucleotides (ATP, NAD⁺), which are metabolized by cell surface ectoenzymes to produce increased local concentrations of adenosine (Ado), a nucleoside involved the control of inflammation and immune responses [1]. A recent study by our group demonstrated that adenosinergic pathways contribute to customize the immune homeostasis of multiple myeloma (MM) [2]. A plasma cell malignancy, MM prevalently develops and expands with bone marrow (BM) niches [3]. Malignant plasma cells at all stages of the disease overexpress CD38 [4], a molecule with widespread tissue distribution and complex functions not yet fully elucidated. CD38 is a 45-kDa type II (or III) trans membrane glycoprote expressed by several immune and non-immune cell types, and it plays a dual role as a receptor and as an ectoenzyme [5]. As a nucleotide-metabolizing ectoenzyme, CD38 catalyzes at neutral pH the extracellular conversion of a dinucleotide of adenine (NAD⁺) to cADPR and ADPR. At acidic pH, CD38 can also catalyze the exchange of the nicotinamide group of NADP⁺ with nicotinic acid and produce NAADP⁺ and ADPRP.

All of the final products are basic regulators of calcium signaling [6]. The initial disassembly of NAD⁺ is followed by adenosinergic activity, provided that CD38 is operating the presence of other ectoenzymes (ectonucleotide pyrophosphatase/phosphodiesterase CD203a and 5'-nucleotidase CD73). These findings point to the existence of an alternative axis for extracellular production of the immunosuppressive Ado. Such a pathway would be able to flank and, some instances, to bypass the canonical pathway based on the conversion of ATP by the ecto-nucleoside triphosphate diphosphohydrolase CD39 [7,8]. These coordinated networks may be hijacked by the tumour for its own purposes.

These observations are relevant to myeloma homeostasis the BM. For energy production and the synthesis of nucleotides and other macromolecules, malignant plasma cells favour glycolysis over oxidative phosphorylation (the Warburg effect), thus sacrificing efficiency for speed. This metabolic shift is hallmarked by hypoxic conditions, and leads to a decrease ATP concentrations and a concurrent increase NAD⁺ levels to susta high-rate glycolysis. this context, extracellular Ado may originates and be released from tumor cells depleted of ATP, or it may derive from extracellular ATP and NAD⁺ leaked from damaged tumor tissues.

As a consequence, Ado may assume the role of a local hormone, adjusting cellular metabolism either *via* low or high affinity specific receptors expressed by normal and tumor cells [5]. Evidence for this is our finding that CD56^{bright} CD16⁺ NK cells produce Ado through a CD38-mediated pathway [9]. The functional relevance is that these NK

cells operate as activated immune effector/regulatory cells inhibiting autologous CD4⁺ T cell proliferation. This strategy of immune escape has already been observed: melanoma cells produce Ado through a CD38/CD203a/CD73 pathway and suppress CD4⁺ T cell proliferation [10].



These actions can ultimately lead to immune suppression. Ado is thus seen to contribute to the failure of immune surveillance cancer. It is reasonable to hypothesize that a similar metabolic strategy is deployed to silence immune effectors during the progression of MM from indolent monoclonal gammopathies to symptomatic overt disease [2]. Now clinical application is a therapeutic anti-CD38 antibody used to deplete immune-regulatory CD38+ cell populations;

this is accompanied by expansion of CD4+ T-helper cells and CD8+ cytotoxic T-cells MM [11].

As expected, elevated levels of extracellular Ado were detected plasma obtained from the myeloma BM niche for diagnostic purposes [2]. We showed that NAD⁺ with the BM niche is able to activate a discontinuous (i.e., multicellular) pathway for Ado production that relies upon CD38, CD203a and CD73 (or TRAP) ectonucleotidases, depending on the environmental pH. Observed variations of the Ado concentrations BM plasma aspirates were likely due to interactions taking place between myeloma and other cells lining the niche (Figure 1).

The results of a pilot study revealed a parallel between Ado levels and disease progression, and patients with symptomatic MM usually have high Ado. This is reflected statistically the International Staging System (ISS) for MM [2]. While these observations may only be correlative and a reflection of the tumor burden, Ado levels the BM plasma may prove to be a useful marker of myeloma progression. Another aspect of the dynamics of available anti-CD38 antibodies for MM therapy is the role of polarization and release of micro vesicles (MV). These plasma membrane structures are known to express several molecules clustered lipid domains [12]. The MV deriving from MM are peculiar that they are rich CD38, CD203a and CD73 and can therefore generate Ado [13]. Meanwhile, the adenosinergic pathways have become new immune checkpoint targets for improving the efficacy of immunotherapies designed with the aim of re-engaging the depressed immune system [14,15].

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