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Bolivian Aymara Natives with Chronic Mountain Sickness Have Autonomous BFU-E Growth

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ABSTRACT

Background

Erythrocytosis / polycythemia is divided into *primary* and *secondary*. Primary polycythemia can be either acquired; i.e. polycythemia vera (PV) due to somatic J*AK2* mutation, or congenital due to germ-line DNA changes (erythropoietin (EPO*)* receptor and *VHL*mutations in Chuvash polycythemia). These mutations are expressed within erythroid progenitors, drive increased erythropoiesis and are detected by hypersensitive or autonomous EPO BFU-E responses. In contrast, secondary erythrocytosis (SE), such as seen with cardiopulmonary pathologies, is driven by the circulating EPO.

Chronic mountain sickness (CMS) is characterized by high altitude pathological erythrocytosis and by cognitive and neurological impairments. CMS is found in subjects living in high altitude (2500 meters and higher). In La Paz, Bolivia, (3600m) there is 7% incidence of CMS erythrocytosis.

Some human populations (Tibetans, Andean Quechuas and Aymaras, and Ethiopians) are adapted to very high altitudes and their adapted phenotypes and, in some instances, evolutionarily selected haplotypes, have been reported. Whole genome was evaluated in Andeans and two genes, *SENP1* and *ANP32D*were found to be evolutionarily selected and correlated with presence or absence of erythrocytosis. The genes down-regulation in hypoxia had survival benefit in *Drosophila*ortholog (1).*SENP1* desumoylate GATA-1 and other regulatory proteins and is critical for definitive erythropoiesis (2,3).

Here we evaluated native Aymara La Paz dwellers with three types of polycythemia: CMS, SE secondary to cardiopulmonary disease, and PV, by clinical studies and by *in vitro* evaluation of erythroid progenitors, and compared them to non-polycythemic subjects.

Patients and Methods

Complete blood count was performed by automatic hematologic counter (Micro 60, USA). Serum EPO was measured by Elisa (R&D System, USA) and *JAK2*^{V617F} mutation analysis by PCR assay. Erythroid progenitors were isolated by density gradient centrifugation and cultured in methylcellulose medium with and without EPO (Stem Cell technologies, Canada) at 37^0 C and 5 % CO_2. BFU-E colonies reading was carried out according to standardized criteria at 7 and 14 days.

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Results

Table.

	Normal Control (n=10)	CMS (n=15)	Secondary Erythrocytosis (n=10)	Polycythemia Vera (n=5)
1.Gender M/F	10/0	15/0	10/0	3/2
Age (range)	42 (40-47)	48 (29-58)	53 (34-72)	67 (42-74)
Hb g/dl (SD)	16.2 (+ 0.9)	20.3 (+ 0.9)	22.8 (+ 1.4)	20.0 (+ 2.5)
Ret % (SD)	1.3 (+ 0.1)	2.9 (+ 1.3)	3.6 (+ 1.2)	2.1 (+ 0.3)
WBC /ul (SD)	6300 (+ 1600)	7200 (+ 1900)	6600 (+ 1700)	16600 (+ 4800)
PLT 10^3ul (SD)	273 (+ 80)	229 (+ 58)	193 (+ 54)	604 (+ 177)
sEPO mUI/ml (SD)	10.0 (+ 3.9)	10.5 (+ 2.2)	82.9 (+ 30.4)	3.0 (+ 1.2)
JAK2^{V617F}, No. (%)	0 (0)	0 (0)	0 (0)	100
Apoptosis	Normal	Delayed	Normal	Delayed
BFU-E: EEC	0 (0-0)	10 (2-25)	0 (0-0)	45 (25-70)

Conclusions

a) Endogenous erythroid colony (EEC) are present in Aymaras with CMS, indicating primary polycythemia.
b) Endogenous EECs are higher in PV than in CMS.
c) CMS subjects have normal serum EPO levels.
d) The role of *SENP1*, and hypoxia-regulated RUNX1 and NF-E2 (4) that promote erythropoiesis, is being interrogated in native erythroid cells.
e) It remains to be determined if the autonomous BFU-E growth is specific for Aymara's CMS or present in CMS individuals of other ethnicities.

References:

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Disclosures No relevant conflicts of interest to declare.

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